AstraZeneca

Statistical Analysis Plan

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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 Subjects with Extensive Stage Small-Cell Lung Cancer

Study Statistician PPD

Global Product Statistician PPD

Version 2, 05 May 2022

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AEPI	Adverse event of potential interest
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
APFxx	Proportion of subjects alive and progression free at xx months from start of study treatment in the induction phase
AST	Aspartate aminotransferase
BMI	Body mass index
BOR	Best objective response
CCGs	eCRF Completion Guidelines
CI	Confidence interval
CR	Complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CCI	
CTCAE	Common Terminology Criteria for Adverse Events
CCI	
CV	Coefficient of variation
DCO	Data cut-off
DLT	Dose limiting toxicity
DoR	Duration of response
ECD	Early clinical development
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EP	Etoposide and platinum-based chemotherapy
ES-SCLC	Extensive stage small cell lung cancer

Abbreviation or special term	Explanation
CCI	[redacted]
HLR	High level results
imAE	immune-mediated adverse event
INR	International normalized ratio
IP	Investigational product
IPD	Important protocol deviation
KM	Kaplan-Meier
LD	Longest diameter
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NC	Not calculable
NE	Not evaluable
NHP	Non-compliance handling plan
NQ	Not quantifiable
NTL	Non-target lesions
ORR	Objective response rate
OS	Overall survival
OSxx	Proportion of subjects alive at xx months from start of study treatment in induction phase
PD	Progressive disease
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PFS2	Progression-free survival after subsequent anticancer therapy
PK	Pharmacokinetics
PR	Partial response
PRO	Patient-reported outcome
PT	Preferred term
PTT	Partial prothrombin time
Q6W	Every 6 weeks

Abbreviation or special term	Explanation
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
QT	Electrocardiogram QT interval: time from start of the Q wave to end of T wave
QTcB	Bazett's Correction Formula
QTcF	Fridericia's Correction Formula
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
CCI	
RS	Raw score
SAP	Statistical Analysis Plan
SCLC	Small cell lung cancer
SD	Stable disease
SoC	Standard of care
SOC	System organ class
CCI	
TEAE	Treatment emergent adverse event
TL	Target lesion
CCI	
TSH	Thyroidstimulating hormone
TTD	Time to deterioration
ULN	Upper limit of normal
ULOQ	Upper level of quantification
WHODD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Date	Brief description of change
05MAY2022	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. This amendment was driven by this decision, with the following sections impacted: Section 1: Added clarifications for study objectives and final analysis. The CSR will be prepared as an abbreviated report focused on safety aspects, while the efficacy and CCI will be reduced due to limited data available. Section 2: Evaluable analysis sets removed, and summary of outcome variables updated. Section 3: Added clarifications for sample size and time windows. Maintenance period definition updated as for the latest CSP. Efficacy and CCI CCI reduced in accordance with the scope of the final analysis. Subgroup analysis removed. Subset of lab parameters defined for shift tables. Section 4: General summary principles updated. Demographic data presentation, efficacy and CCI reduced according with final analysis scope. Section 5: Clarifications added for final analysis. Section 5: Interim analyses removed. References: Added CSP version 9.0 to the list of references. Appendix A and C: revisited in accordance with the scope of the final analysis. Other changes: Section 2: CCI removed because related analyses will be handled outside the CSR. ECD NHP replaced with Protocol Deviation Plan as for current AZ SOPs. Section 3: Screening period updated including details for rescreened subjects. Induction period definition updated as for CCGs. Added clarifications for imputation rules, baseline characteristic summary, actual treatment duration and

Date	Brief description of change
	dose intensity. Added clarification for AESI, including AEPIs and imAE. Metabolite specified in the PK section. QTcB added as for the latest CSP. Section 4: General principles for assessment on day 1 added as for SAP template. Added reference ranges for vital signs and ECG parameters. Added clarifications for analysis on dosing deviations, laboratory parameters, ECG values, AEs summaries (including AEPIs and imAE). Added geometric mean plots for AZD2811 and metabolite blood concentrations. Log scale applied for all PK graphical presentations. Appendix A: PK figures added. Appendix C: Clarifications added for assessments pre-dose on CCI CCI added for lab and vital signs.

1 STUDY OBJECTIVES

This study was designed as a Phase II, open-label, multicenter, single arm, global study to determine the efficacy, safety and tolerability of AZD2811 + durvalumab maintenance therapy in subjects with extensive stage small cell lung cancer (ES-SCLC) who do not progress during etoposide and platinum-based chemotherapy (EP) combined with durvalumab induction therapy as onset of first-line treatment.

According to the original Clinical Study Protocol (CSP), the global recruitment will be completed when approximately 100 eligible subjects are enrolled at sites worldwide. Treatment will be conducted in 2 phases – an initial induction phase followed by a maintenance phase.

However, from CSP v9.0 onwards, the enrolment has been terminated prematurely 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.

Information on originally planned study objectives and endpoints, as outlined in Section 3 of the CSP are presented in Table 1 for reference. However, it should be noted that due to the decision to terminate enrolment prematurely, 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 as described in this SAP.

In addition, the CCI [redacted] will be handled outside the abbreviated clinical study report (CSR) and thus are not part of this statistical analysis plan (SAP).

Table 1 Study Objectives and endpoints

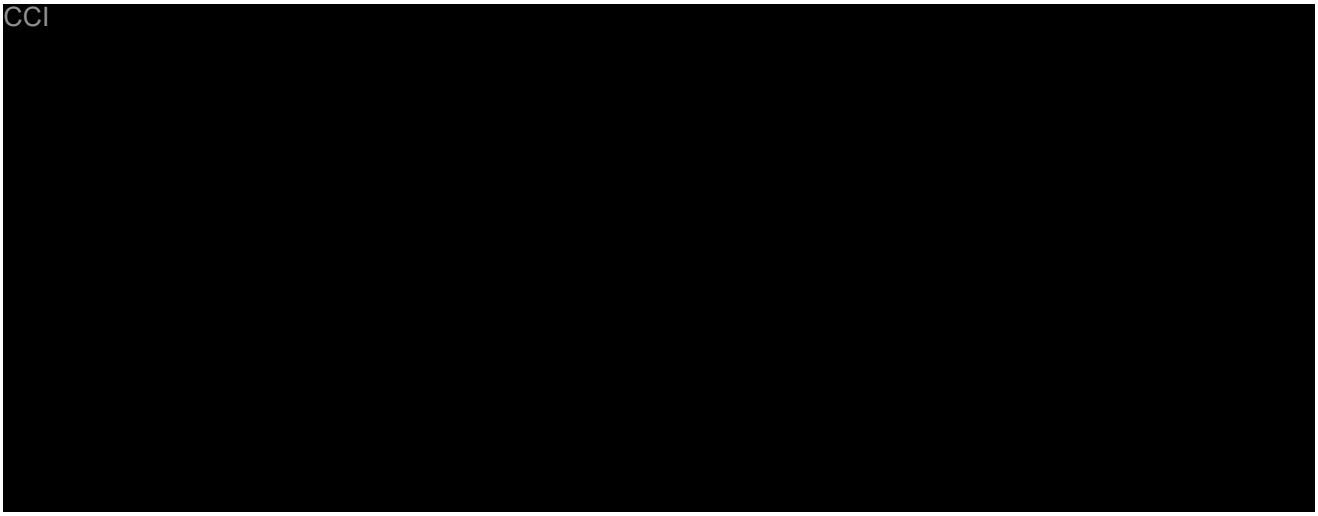
Objectives	Endpoints
Primary	
To evaluate the efficacy of AZD2811 + durvalumab by assessment of the proportion of subjects alive and progression free at 12 months APF12 who have not progressed during EP-durvalumab based induction therapy.	The proportion of subjects alive and progression free at 12 months 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 subjects who enter the maintenance phase.
Secondary	
To evaluate efficacy of AZD2811 + durvalumab by assessment of the proportion of subjects 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 subjects 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 subjects who enter the maintenance phase.

Objectives	Endpoints
To evaluate efficacy of AZD2811 + durvalumab by assessment of the proportion of subjects 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 subjects 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 subjects 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 subjects 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 subjects).
To evaluate efficacy of AZD2811 + durvalumab by assessment of ORR in the subjects who had not progressed during EP-durvalumab based induction therapy.	ORR is defined as the proportion of subjects with measurable disease at baseline who have a confirmed CR or PR, by the investigator at local site per RECIST v1.1, in subjects who enter the maintenance phase.
To evaluate efficacy of AZD2811 + durvalumab by assessment of PFS in subjects 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 subjects who enter the maintenance phase.
To evaluate efficacy of AZD2811 + durvalumab by assessment of OS in subjects 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 subjects 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, prothrombin time/PTT/INR, hematology, ECG, and urinalysis, as well as 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.

Objectives	Endpoints
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]	

CCI

[redacted]



AE Adverse event. APFxx Proportion of subjects alive and progression free at xx months from start of study treatment in the induction phase (e.g., PFS rate at 6 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. OSxx Proportion of subjects alive at xx months from start of study treatment in induction phase (e.g., OS rate at 12 months). PD Progressive disease. PD-L1 Programmed cell death-ligand 1. PFS Progression-free survival. PFS2 Progression-free survival after subsequent anticancer therapy. PK Pharmacokinetics. PR Partial response. PTT Partial prothrombin time. QLQ-C30 30-item Core Quality of Life Questionnaire. QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire. QoL Quality of life. RECIST Response Evaluation Criteria in Solid Tumors. [redacted]. SCLC Small-cell lung cancer. [redacted]. TSH Thyroidstimulating hormone.

2 DEFINITION OF ANALYSIS SETS

2.1 Analysis sets

Details of the analysis sets are presented in Table 2 and Table 3.

Please note that due to the decision to terminate enrolment prior to completion, limited patients received AZD2811 in combination with durvalumab, thus the efficacy evaluations originally planned will no longer be reported in the abbreviated CSR and the 'Evaluable' analysis sets are no longer required.

Table 2 Analysis sets

Analysis set	Definition
Enrolled	All subjects who signed the informed consent
Assigned to study intervention	All subjects assigned a study intervention
Safety	All subjects who received at least one dose/have been exposed to any study intervention
Pharmacokinetics	All subjects who received at least one dose of AZD2811 and/or durvalumab with at least one reportable concentration corresponding to the dosed study intervention (reportable means at least one concentration above lower limit of quantification (LLOQ))

Study interventions/treatments are the following: durvalumab, carboplatin or cisplatin, etoposide and AZD2811. Throughout the SAP, it will be referred to study interventions unless 'treatment' is part of a standard terminology as in 'treatment emergent adverse events'.

Standard of care (SoC) comprises etoposide, carboplatin or cisplatin and durvalumab. Investigational products (IP) are AZD2811 and durvalumab only.

Table 3 Summary of outcome variables and analysis sets

Outcome variable	Analysis sets
General data	
Subject disposition	Enrolled
Important protocol deviations	Safety
Demographics and baseline characteristics	Safety
Baseline disease status	Safety
Medical and surgical history	Safety
Concomitant medications	Safety
Post-discontinuation anticancer therapy	Safety
Substance usage	Safety
Pandemic study disruptions	Safety
Efficacy data (to be listed only)	
Tumor assessment details	Assigned to study intervention
Progression details	Assigned to study intervention
Survival details	Assigned to study intervention
Best objective response (BOR)	Assigned to study intervention
Change in Target lesion size	Assigned to study intervention
Safety data	
Exposure	Safety
Adverse Events	Safety
Laboratory measurements	Safety
Vital Signs/ECG	Safety
Pharmacokinetics (PK)	
Whole blood or serum concentrations	Pharmacokinetics

ECG Electrocardiogram.

2.2 Protocol deviations

Study specific important protocol deviations (IPD) will be defined in the Protocol Deviation Plan. The IPDs occurring during screening period will be summarized in induction phase.

A list of all protocol deviations will be reviewed and decisions regarding how to handle these deviations will be documented by the study team physician, clinical pharmacology scientist and statistician prior to database lock. Important protocol deviations may include, but are not limited to: not meeting eligibility

criteria, non-performance of important assessments, use of prohibited medications, global/country situation related IPDs etc..

3 DESCRIPTION OF VARIABLES

3.1 General principles

3.1.1 Sample size and data cut off

According to the study design, the global recruitment will be complete when approximately 100 subjects have been assigned in the induction phase and a minimum of 80 subjects have entered the maintenance phase and have been exposed to AZD2811. In the event that 100 subjects do not yield the minimum of 80 subjects exposed to AZD2811 in the maintenance phase, additional subjects will be enrolled and assigned into the study.

Note that as of CSP v8.0 the intent was to achieve a minimum of 80 patients at a starting dose of CC[redacted] AZD2811, however this CSP version was not implemented and no patients started the maintenance phase on CCI[redacted].

The data cut-off (DCO) for the final analysis was originally intended to occur approximately 18 months following last participant first dose, unless there were no longer participants receiving AZD2811 + durvalumab.

Nevertheless, the study enrolment was prematurely terminated based on a thorough risk-benefit analysis carried-out in the safety run-in for the maintenance phase.

As a result of the early termination of the study enrolment, no interim and primary analyses will be performed and the DCO for the final analysis planned for 18 June 2022, approximately 5 months after last participant first dose. Main data collection will stop at that point. An abbreviated CSR will be written based on this dataset.

3.1.2 Baseline measurements and change from baseline variables

Baseline will be the last non missing value obtained prior to the first administration of study intervention in induction phase and any information taken after first administration of study intervention will be regarded as post baseline information. All changes from baseline analyses use this definition of baseline regardless of the period being analyzed, e.g. no baseline for maintenance phase will be defined.

If two visits are equally eligible to assess subject status at baseline (e.g., screening or re-screening and baseline assessments both on the same date prior to first administration with no washout or other intervention in the screening period), the average should be taken as the baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on Day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarized over time, study day will be calculated in relation to date of first study intervention in induction phase. If no value exists before the first study intervention, then the baseline value will be treated as missing.

In all summaries change from baseline variables will be calculated as the post treatment value minus the value at baseline. For % change from baseline, calculate:

(Post baseline value – Baseline value)/Baseline value × 100

Study day will be calculated as:

Date of assessment – Date of first dose/administration of study intervention in induction phase + 1

3.1.3 Study periods

This study design consists of four study periods: screening, induction phase, maintenance phase and safety and survival follow-up.

Screening period

A subject enters the screening period at the date of completion of the informed consent. The screening period is scheduled to take up to 21 days (-21 Day to -1 Day). A subject may proceed into the induction phase if they meet all the eligibility criteria for the study otherwise they will be considered as a 'screen failure'. The screening period starts on the date of signed informed consent and ends either on date of screen failure or one day before first administration of study intervention.

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 screen fail date (maximum of 7 weeks between initial consent and Cycle 1 Day 1 or second screen failure). Rescreened participants will receive the same participant number as for the initial screening.

Induction period

The induction phase starts when a subject receives the first administration of study intervention. The induction phase consists of CCI cycles. One cycle equals CCI of therapy given every CCI. In total, the planned duration of the induction phase is CCI. A subject is considered as having completed induction phase treatment, when all CCI cycles of treatment have been administered.

If a subject discontinues induction treatment prior to completing CCI cycles, the end date of the induction period is the day of end of induction treatment as per electronic case report form (eCRF) (as for eCRF completion guidelines (CCGs) this should be the date of last administration). The subject rolls over into safety follow-up period.

If a subject does not discontinue, does not withdraw consent, does not progress during the induction phase (tumor assessment at week 6 or with symptomatic PD) or does not die in the induction phase, subjects will be assessed for disease progression in week CCI which is used to confirm eligibility for maintenance therapy. Subjects who either progress or are not eligible for maintenance for other reasons will have the end date of induction phase at the date of the respective Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 assessment. These subjects roll over into safety follow-up period.

Subjects who do not progress based on RECIST v1.1 or die, and are assessed to be eligible to continue into maintenance phase are considered to have the induction phase completed with end date one day before date of first study intervention in maintenance phase.

Maintenance period

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 or durvalumab monotherapy as maintenance therapy. The maintenance phase starts when a subject receives the first administration of IP (AZD2811+durvalumab or durvalumab monotherapy) in the maintenance phase.

Assessments performed pre-dose on CCI will be considered part of the induction phase unless based on the time collected indicates that the assessment occurred after the first dose in the maintenance phase. Assessments performed on day of dosing where time is not collected are assumed to have been done pre-dose. Maintenance phase end date is the date of end of last treatment during maintenance phase (maximum of end of treatment of AZD2811 and end of treatment of durvalumab). Subjects can discontinue from maintenance phase by withdrawal of consent, progression, death or if other discontinuation criteria are met. A subject who has been treated for a minimum of 2 years of maintenance treatment and continues to experience CR, PR, or SD, as demonstrated by radiographic measures, may be considered for treatment discontinuation.

Safety and survival follow-up period

Safety (concomitant medications and AEs/serious adverse events) will be followed up until 90 days after last dose. Start date of safety follow-up period is one day after end of treatment date in either induction or maintenance phase as per eCRF. The end date is

End date of Safety Follow-up = Date of last dose (regardless of phase) + 90.

Please note, for programming purpose the safety follow-up period duration might be derived as less than 90 days where date of last dose is not equal to date of end of treatment as per eCRF (if a subject discontinues between dose administrations).

For summary presentations, data during safety follow-up will be included in periods from which the subject rolled over to safety follow-up.

For subjects who were treated in maintenance phase, survival follow-up period starts one day after end of treatment date in maintenance phase as per eCRF. Data for overall survival, second progression and information for subsequent anticancer therapy will be collected, every 2 months +/- 1 week until DCO or their end of study.

3.1.4 Time windows

Analysis time windows for safety variables and efficacy will be based on scheduled visits/cycles of the schedule of activities for each phase (see Table 1, Table 2, Table 3 and Table 4 of the CSP).

Time windows will need defining for any presentations that summarize or list values by visit. This will be applicable for RECIST assessments, laboratory, vital signs and ECG parameters. The following conventions should apply, unless otherwise specified:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data should have the potential to be included in the summaries.

- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day.

RECIST assessments with regards to target lesion tumor size will be windowed as well. Whenever TL tumor size data for the week XX (Note: or visit at which progression was documented if before week XX) is available then this should be used in the analysis. A windowing rule will be applied and will follow the protocol allowed visit window; therefore, any RECIST scan performed within +/- 1 week of the protocol scheduled visit will be used for that visit.

Appendix C shows detailed derivation rules for the visit windows assessment for RECIST (target lesions), clinical chemistry, hematology, coagulation, vital signs, urinalysis and ECG parameters. Additionally, the definition of study periods in Section 3.1.3 will be used to ensure that assessments will be mapped to applicable analysis visits only (i.e. an assessment prior to first administration of maintenance treatment will be mapped to CCI but considered part of the induction phase).

- For summaries showing the maximum or minimum values during treatment, the maximum/minimum value recorded after date of first dose of investigational product. will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a subject.
- For visit based summaries
  - If there is more than one value per subject within a time window then the closest value to the scheduled visit date should be summarized, or the earlier, in the event the values are equidistant from the nominal visit date. The listings should highlight the value for the subject that contributed to the summary table, wherever feasible.
    Note: in summaries of extreme values (i.e. maximum on treatment) all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
  - Summary statistics for mean, standard deviation, median, and range will be presented by visits until there are at least 3 subjects with evaluable data. A minimum of 12 cycles will be presented in any case.
- For summaries at a subject level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a subject level statistic such as a maximum.

3.1.5 Imputation rules

In general, there is no imputation of missing data for efficacy analyses.

For RECIST, in case of partially missing target lesion (TL) measurements the results will be scaled up as detailed in section 3.1.6.1.

How to handle not quantifiable data in PK summaries is outlined in section 3.2.3.3.

Imputation of partial dates will be applied only for AEs onset/worsening/stop dates, concomitant medication stop dates, death dates, smoking history and date of first diagnosis.

Unless otherwise specified, imputed dates will not be used to derive durations of events or treatments. In the listings the data will appear as they are reported in the database.

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. Note that 0 should not be used as an imputed value in case the endpoint requires a log transformation.

Imputation of adverse event onset date/adverse event worsening date

Missing onset/worsening dates will be imputed according to the following rules:

- Completely missing dates will not be imputed. AEs will be considered as treatment emergent in maintenance, unless there is evidence to the contrary.

- If day is missing assume 01-MMM-YYYY unless:
  - month and year are the same as the first administration of study intervention in induction phase, then assume first dose date in induction phase.
  - month and year are the same as the date of the first administration of study intervention in maintenance phase, then assume first dose date in maintenance phase.
- If day and month are missing, then assume 01-JAN-YYYY unless:
  - year is the same as first administration of study intervention in induction phase and is different to first administration of study intervention in maintenance phase, then assume first dose date in induction phase.
  - year is the same as both, the year of first administration of study intervention in induction phase and the year of first administration of study intervention in maintenance phase, then assume first dose date in maintenance.

After applying these rules, if the imputed AE onset date is after a complete or imputed AE end date (or date of death), the imputed onset date will be the same as the complete AE end date (or date of death).

Imputation of adverse event / concomitant medication stop date

Adverse event/concomitant medication stop dates will be imputed. It will be used to allow determination of prior or concomitant medications. The imputation of AE end date does not affect definition of treatment emergent, with the exception of cases when it is used for the imputation of the onset date.

Missing stop dates will be imputed according to the following rules:

- Completely missing dates will be not imputed. Medications will be considered to be concomitant for both periods, induction and maintenance, unless there is evidence to the contrary.
- If the day is missing: input day as the earlier of either the DCO or the last day of the month
- If the month is missing: input the day and month as the earlier of either the DCO or the last day of the year (31-DEC-YYYY).

After applying these rules, if the imputed AE or concomitant medication stop date is after the date of death, the imputed stop date will be the same as the date of death.

If the AE/concomitant medication is ongoing, the stop date will remain missing.

Imputation of date of death

If a subject 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.

Imputation of date of substance usage start/stop date

Start dates are only applicable for current and former substance usage. Missing start dates will be imputed according to the following rules:

- Completely missing dates will be not imputed.
- For missing day only - using the 1st of the month
- For missing day and month - using the 1st of January

Stop dates are only applicable for former substance usage. Missing stop dates will be imputed according to the following rules:

- Completely missing dates will be not imputed.
- For missing day only - using the last day of the month
- For missing day and month - using the latest of screening date and 31st of December (screening date is used here to ensure substance usage is former)

Imputed dates will be used in the calculation of smoking history durations. Note: To allow the calculation of the years smoking for current substance usage, the screening date will be considered in the formula as the end date (see further details in Section 3.2.1.1).

Imputation of date of original diagnosis

Missing dates of first diagnosis will be imputed according to the following rules:

- Completely missing dates will be not imputed.
- For missing day only - using the 1st of the month
- For missing day and month - using the 1st of January

Imputed dates will be used in the calculation of time from original diagnosis to first administration of study intervention.

Missing data due to COVID-19

No sensitivity analyses are planned due to the COVID-19 pandemic.

3.1.6 Derivation of RECIST visit responses

For all subjects, the RECIST tumor response data will be used to determine each subject's visit response according to RECIST version 1.1 (see further details in Appendix F in the CSP). It will also be used to

determine if and when a subject has progressed in accordance with RECIST and also their best objective response to study treatment.

Baseline radiological tumor assessments are to be performed no more than 21 days before the first administration of study intervention and ideally as close as possible to the start of study treatment. Tumor assessments are then performed every [redacted]) ± 1 week following start of study treatment for the first 36 weeks, then every [redacted]) ± 1 week thereafter until objective disease progression.

If an unscheduled assessment is performed, and the subject 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 subjects being assessed at a different frequency than other subjects.

From the investigator's review of the imaging scans, the RECIST tumor response data will be used to determine each subject's visit response according to RECIST version 1.1. At each visit, subjects will be programmatically assigned a RECIST v1.1 visit response of complete response (CR), partial response (PR), stable disease (SD) or progressive disease (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 subject has had a tumor assessment which cannot be evaluated, then the subject 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).

Please see below in Section 3.1.6.1 the definitions of CR, PR, SD and PD.

RECIST outcomes will be calculated programmatically for the site investigator data (see Section 3.2) from the overall visit responses.

3.1.6.1 Target lesions (TLs)

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 computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A subject can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as TLs. If more than one baseline scan is recorded, then measurements from the one that is closest and prior to first administration of study intervention will be used to define the baseline sum of TLs. 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.

All other lesions (or sites of disease) not recorded as TL should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Note: For subjects who do not have measurable disease at entry (i.e. 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 (see section Overall visit response for further details). If a subject does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

Please note, that having non-measurable disease at baseline is violating inclusion criteria 8. In consequence, we don't expect any subjects who do not have measurable disease at entry.

Target lesion tumor size will be windowed to map assessments to analysis visits according to Section 3.1.4 and Appendix C.

Table 4 TL visit responses (RECIST v1.1)

Visit Reponses	Description
Complete Response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters, as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not Evaluable (NE)	Only relevant in certain situations (i.e. if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response
Not applicable (NA)	No TLs are recorded at baseline (Not expected, because of inclusion criteria 8)

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a TL response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

If all TL measurements are missing, then the TL visit response is not evaluable (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.

Lymph nodes

For lymph nodes, if the size reduces to < 10mm then these are considered non-pathological. However, a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

A CR can only be followed by CR, PD or NE. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if the sum of diameters for lymph node short axis increases by 20% but all lymph node TL remain < 10mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are also met.
- Step 3: If not all lesions meet the CR criteria and the sum of lesions meets the criteria for PD, then response will be set to PD.
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team, if appropriate blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure, then this will be indicated as such on the case report form and a value of 5mm will be entered into the database and used in TL calculations. However, a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response results in PD, then this will be reviewed by the study team.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation/ palliative surgery/ embolisation), should be handled in the following way and once a lesion has had

intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumors:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the subject would be assigned a TL response of PD.
- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (i.e. if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Subjects with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling

If > 1/3 of TL measurements are missing, then TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥5mm from nadir).

If ≤ 1/3 of the TL measurements are missing, then the results will be scaled up (based on the sizes at the nadir visit) to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of scaling

Lesion 5 is missing at the follow-up visit; it had a BL measure of 29.3 cm. The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at nadir visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4 cm:

$$\frac{26}{26.8} \times 29.3 = 28.4 \text{ cm}$$

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤ 1/3 lesion assessments not recorded, the scaled up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 cm.

Change in method of assessment of TLs

CT, MRI and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing. The TL visit response may still be evaluable if the number of missing TL measurements at a visit is ≤1/3 of the total number of TLs.

3.1.6.2 Non-target lesions (NTLs) and new lesions

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

NTL response will be derived based on the Investigator's overall assessment of NTLs as follows:

Table 5 NTL visit responses

Visit responses	Description
Complete Response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
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 subjects without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline

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 the presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

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: i.e. 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.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present, but should not overtly affect the derivation.

Symptomatic progression 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.

Subjects with 'symptomatic progression' 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.

3.1.6.3 Overall visit response

Table 6 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 6 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**

3.1.7 Subgroups

No subgroups analyses will be performed.

3.2 Outcome variables

3.2.1 General variables

3.2.1.1 Demographics and baseline characteristic data

Demographics and baseline characteristics will be assessed at screening and/or on date of first administration of study intervention in induction phase (necessarily before first administration). For rescreened subjects, data re-entered at the re-screening visit will be used for analysis.

Demographic variables are age in years, sex, ethnicity, race and country. Following age groups will be created: age group 1: ≥18 - <50, ≥50 - <65, ≥65 - <75, ≥75 and age group 2: ≥18 - <65, ≥65 in years. Further subject characteristics include height in cm, weight in kg and body mass index (BMI) in kg/m^2 at baseline. Weight groups of <70, >=70 - <=90, >90 in kg will be derived. The BMI is calculated as weight in kg divided by (height in m)^2. BMI groups of <=25, >25 - <=30, >30 kg/m^2 will be derived.

The BMI will be calculated considering the following formula BMI (kg/m^2) = weight/ (height)^2. To evaluate nicotine, use and consumption, number of pack years as number of pack-years = (number of packs / day) *numbers of years smoking will be calculated. Number of years smoking is calculated as (end date – start date +1)/365.25 (in case of missing or partial dates, imputed dates will be used for this calculation, see section 3.1.5). The end date for current substance usage will be the date of the screening (or re-screening) visit. If subject provides information on number of packs per week instead of per day, number of packs will be divided by 7 to be used in this formula.

Time (weeks) from original diagnosis to first administration in induction phase will be derived as

(date of first administration in induction phase – date of original diagnosis + 1)/7.

In case of missing date of original diagnosis, use imputed date instead, see section 3.1.5.

Subject recruitment will be also presented by region, country and center using the following regional groups: Asia (S. Korea), Europe (Spain, Poland) and North America (United States, Canada).

3.2.1.2 Medical history

The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to code the medical history.

3.2.1.3 Prior/Concomitant medications and post-discontinuation therapy

The latest or current World Health Organization Drug Dictionary (WHODD) at the time of reporting will be used to code any medications.

Any medications taken by the subject at any time between the date of the first administration of study intervention in induction phase (including the date of the first administration) up to the date of last administration of study intervention (regardless of phase) + 90 days in the study will be considered as concomitant medication. Any medication that started prior to the first administration of the study intervention in induction phase and ended after the first administration or is ongoing will be considered as both prior and concomitant medication. In a similar way, medications can be concomitant for both phases, induction and maintenance phase, and will be summarized in both phases accordingly. A flag will be used to identify in the listing breakthrough pain medication and antibiotics.

As per protocol sections 6.5.1 and 6.5.2, concomitant medications will be categorized into permitted (allowed) and prohibited (disallowed) medications. Allowed medication will be summarized including details for G-CSF as prophylaxis or treatment for adverse events. Prohibited medications will be listed only.

Subsequent therapies (chemotherapy or immunotherapy) received after discontinuation of IP will be listed. Radiotherapy received after discontinuation of IP will be listed separately. Therapy received on the same day as discontinuation of study treatment will be considered to be a subsequent therapy.

3.2.1.4 Duration of exposure

Duration of exposure is defined as:

- Total treatment duration (days) = (min(last dose date where dose > 0 [units] + xx days, date of death, date of DCO) − date of first dose +1), where xx days equal the following dependent on treatment:
  - Durvalumab xx days = CCI
  - Etoposide (last dose date on Day 1 of a cycle) xx days =
  - Etoposide (last dose date on Day 2 of a cycle) xx days =
  - Etoposide (last dose date on Day 3 of a cycle) xx days =
  - Carboplatin xx days =
  - Cisplatin xx days =
  - AZD2811 xx days =
- Actual treatment duration = total treatment duration, excluding total duration of dose interruptions and cycle delays. The duration of dose delays/interruptions will be the sum of positive values of [Date of the dose -Date of previous dose –(C +xx) days] where xx is 3 days for induction and 1 day for maintenance (window around visit as for protocol schedule of activities).

To convert treatment duration from days to weeks, the duration will be divided by 7 and from days to years, the duration will be divided by 365.25.

For durvalumab, the total treatment duration and actual treatment duration will be calculated separately for induction and maintenance phase as well; using first/last dose date in the respective phase only in the derivation.
For subjects who continued into maintenance without delay on CCI the cut-off for Durvalumab exposure will be the day before the first dose in maintenance.

Exposure will also be measured by the number of cycles received. A cycle corresponds to a period of C . 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.

A dose modification is either a, dose interruption and/or dose reduction as collected in the eCRF.

For handling exposure and dose interruptions, the following rules will be considered.

Subjects who permanently discontinue during a dose interruption

If a subject permanently discontinues study treatment during a dose interruption, then the date of last administration of study intervention recorded on the appropriate exposure eCRF form will be used in the programming. See further Appendix B.

3.2.1.5 Dose intensity

Dose intensity of investigational products (IP) (AZD2811 and durvalumab only) will be addressed by considering relative dose intensities (RDI).

Relative dose intensity is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. Relative dose intensity will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule (i.e. dose interruptions and/or cycle delays).

When deriving actual dose administered the volume before and after infusion will also be considered.

Subsequent to the review of the safety run-in cohort of the current study (see CSP 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 . This will be considered when defining the intended dose for patients treated with AZD2811 after the 28th September 2021.

3.2.2 Primary outcome variables

The primary outcome variable which addresses the efficacy of AZD2811 is described in Section 9.4.2.1 of the CSP.

3.2.2.1 Progression free survival (PFS)

PFS is defined as the time from first administration of study intervention in the induction phase until the date of the first documented (subsequently confirmed) disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from study therapy or receives another anti-cancer therapy prior to progression (i.e. date of PFS event (progression/death) or censoring – date of first administration of study intervention + 1). Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

However, if the subject progresses or dies immediately after two or more consecutive missed visits, the subject will be censored at the time of the latest evaluable RECIST assessment prior to the two missed visits. Note: A NE visit is not considered as a missed visit.

Given the scheduled visit assessment scheme (i.e. CCI for the first 36 weeks then CCI thereafter) the definition of 2 missed visits will change. If the previous RECIST assessment is less than study day 204 (i.e. week 29: week 30 – 1 week for early assessment) then two missing visits will equate to CCI since the previous RECIST assessment, allowing for early and late visits (i.e., CCI). If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from CCI to CCI this will equate to CCI (i.e., CCI . The time period for the previous RECIST assessment will be from study days 204 to 245 (i.e. week 30 up to week 36). From week 36 onwards (when the scheduling changes to CCI

CCI assessments), two missing visits will equate to CCI (i.e. CCI + 1 week for an early assessment + 1 week for a late assessment = CCI

If the subject has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline (12 weeks plus 1 week allowing for a late assessment within the visit window) in which case, their date of death will be used.

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

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

- For investigational assessments, the date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression
- When censoring a subject for PFS the subject will be censored at the **latest** of the dates contributing to a particular overall visit assessment

  Note: for TLs only the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

Days prior to progression for discontinued subjects will be calculated as date of progression – date of treatment discontinuation + 1.

For days between RECIST assessments, days will be calculated as date from next assessment – date from latest scan date + 1 and averaged for a subject. The first post baseline RECIST assessment is compared to the date of first administration of study intervention in induction phase.

3.2.3 Secondary outcome variables

The secondary outcome variables which address the further efficacy of AZD2811 are described in Section 9.4.2.2 of the CSP. PK concentrations are secondary outcome variables as well.

Safety and tolerability will be evaluated in terms of AEs, vital signs, physical examination, clinical chemistry, TSH, prothrombin time/PTT/INR (coagulation is included in laboratory), hematology, ECG, and urinalysis, as well as infusion interruptions, cycle delays, dose reductions, and dose discontinuations.

Due to the decision to terminate enrolment prior to completion and the limited number of patients who received AZD2811+durvalumab, the efficacy analysis will be reduced to listings and only the outcomes listed in the following sub-sections will be derived.

3.2.3.1 Overall survival (OS)

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 subject withdraws from study therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of first dose + 1).

Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive (SUR_DAT, recorded within the SURVIVE module of the eCRF).

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

The status of ongoing, withdrawn (from the study) and "lost to follow-up" subjects at the time of the final OS analysis should be obtained by the site personnel by checking the subject's notes, hospital records, contacting the subject's general practitioner and checking publicly-available death registries. In the event that the subject has actively withdrawn consent to the processing of their personal data, the vital status of the subject can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3.2.3.2 Best objective response (BOR)

Best objective response (BOR) is calculated based on the overall visit responses from each RECIST assessment, described in Section 3.1.6.3. It is the best response a subject has had following first administration of study intervention but prior to starting any subsequent cancer therapy and up to subsequently confirmed RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorization of BOR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 6 weeks minus 1 week, i.e. at least 35 days (to allow for an early assessment within the assessment window), after first administration of study intervention.

BOR will be determined programmatically based on RECIST using all site investigator data up until the first progression event (i.e. progression or death). For subjects whose progression event is death, BOR will be calculated based upon all evaluable RECIST assessments prior to death. In addition, only the RECIST assessments prior to start of subsequent cancer therapy (note that for this analysis, palliative or adjuvant radiotherapy is not considered a subsequent anticancer therapy) will be included.

For subjects who die with no evaluable RECIST assessments, if the death occurs ≤13 weeks (i.e. 12 weeks + 1 week to allow for a late assessment within the assessment window) after first dose study intervention, then BOR will be assigned to the progression (PD) category. For subjects who die with no evaluable RECIST assessments, if the death occurs >13 weeks after start of first dose of study intervention then BOR will be assigned to the NE category.

3.2.3.3 Pharmacokinetics

Whole blood samples will be collected for measurement of whole blood concentrations of AZD2811 and its metabolite (AZ12102238). Serum samples will be collected for measurement of serum concentrations of durvalumab.

Concentrations below the lower limit of quantification will be reported in the following way:

1. Individual BLQ concentrations are reported as NQ (not quantifiable).
2. For summary data:
    a. If, at a given time point, 50% or less of the concentrations are NQ, the geometric mean, geometric CV, geometric standard deviation, arithmetic mean and standard deviation are calculated by substituting the LLOQ for values which are NQ.
    b. If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric CV, geometric standard deviation, arithmetic mean and standard deviation are reported as not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set as NQ.
    c. If all the concentrations are NQ, the geometric mean and arithmetic mean are reported as NQ and the geometric CV, geometric standard deviation and standard deviation as NC.
    d. The number of values below LLOQ are reported for each time point along with the total number of collected values.
    e. Any concentration record that is reported as not collected or not reported will be regarded as missing and excluded from summary tables and any corresponding figures.

Three values >LLOQ are required as a minimum for a concentration to be summarized. Two values are presented as a minimum and maximum with the other summary statistics as NC. The LLOQ will be reported in the CSR and in PK tables, figures and listings.

Individual concentration data may be excluded from summary tables and graphical presentation for legitimate scientific reasons. Any exclusions will be provided to programming in accordance with AZ Best Practice Guideline for the Study Level Process for Pharmacokinetic Data Analysis v2.0. Any exclusions, together with justification for the exclusion, will be clearly documented in the abbreviated CSR. These individual data will still be presented in the listings, but will be flagged to identify that they are excluded from summary outputs.

3.2.3.4 Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a subject or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. The full definition of AEs and serious AEs (SAEs) can be found in the CSP Appendix B.

AEs and SAEs will be collected throughout the study, from date of informed consent until 90 days after the last dose of study intervention. Events will be defined as treatment emergent if they started after dosing or prior to dosing and worsen following study intervention. AEs which start in induction phase and subsequently worsen in maintenance phase will be defined as treatment emergent for both phases. AEs which start in induction phase and are ongoing, but not worsened, in maintenance phase, will be presented for induction phase only. For dosing days, AE start timing will be collected as well to identify pre- or post-dose AEs. AEs which start on Cycle 1 Day 1 but with start time before dosing are not considered treatment emergent. AEs which start/worsen on [redacted] but with start time before dosing are considered as treatment emergent for induction phase only as long as they do not worsen in maintenance phase afterwards.

AEs with start or worsening date in safety follow-up period (within 90 days after the last dose of study intervention) will be presented along with AEs occurring in the phase from which the subject discontinued.

A flag will be created to indicate AEs which occur within the 90 days safety follow-up period but after initiation of the first subsequent therapy following discontinuation of study intervention.

The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE Version 5.0).

Maximum CTCAE grades on treatment overall and by phase will be derived.

For durvalumab, AEs of special interest (AESI) are defined in CSP Section 8.3.12.2. Preferred terms (PT) of AESIs and adverse events of potential interest (AEPI) are detailed in the AstraZeneca durvalumab AESI/AEPI PTs list. The PTs list (current or latest version at the time of reporting) will be used to identify and distinguish AESIs and AEPIs. The AESIs and AEPIs will also be classified as immune-mediated AEs (imAE) or not imAEs. Further details are provided in an imAE Charter.

If, during the course of the study, AEs will be defined as of special interest for AZD2811, then they will be analyzed in a similar manner as AESI for durvalumab.

3.2.3.5 Laboratory Data

The laboratory variables to be measured are presented in Section 8.2.4 of the CSP: Table 17 (clinical chemistry), Table 18 (hematology), Table 19 (urinalysis), and Table 20 (other safety tests, including coagulation).

White blood cell (WBC) differential counts will be presented as a percentage (relative numbers of each type of WBC in relationship to the total WBC) and as an absolute value (percentage x total WBC).

If the absolute count for a particular type of blood cell (basophils, eosinophils, lymphocytes, neutrophils, monocytes and reticulocytes) is not reported, it will be derived as the total white blood cell count multiplied by the differential percentage for that cell type.

Laboratory variables will be followed-up until end of treatment visit. Data collected during safety follow-up will be presented along with data collected during the period from which the subject discontinued.

Change from baseline in hematology and clinical chemistry will be calculated for a subset of parameters at each post-dose visit, see section 3.1.2. The subset will include the following parameters:

- Hematology
    - Haemoglobin
    - WBC
    - ANC
    - Platelets
- Clinical chemistry
    - Albumin
    - Creatinine
    - Creatinine clearance
    - Total bilirubin

- AST
- ALT
- Amylase
- Lipase

- Coagulation
  - International Ratio (INR)
  - Fibrinogen

CTC grade will be calculated at each visit. Maximum post-baseline CTC by study phase and overall will also be calculated. Clinically important changes are defined as CTCAE grade >= 2 or changes to CTCAE grade 3 or 4 and will be derived by study phase and overall. End of treatment results will be those which are assessed on the latest nominal visit prior or on the date subjects discontinue or complete study intervention. Absolute values will be compared to the local laboratory reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings.

3.2.3.6 Vital Signs Changes

Vital signs include blood pressure (systolic and diastolic), pulse rate, body temperature, respiration rate, body weight and BMI. Body height is assessed only at screening and is part of baseline characteristics only. BMI over time will be derived based on baseline body height. Vital signs data obtained up until the end of treatment visit will be used for reporting.

Change from baseline in vital signs variables will be calculated for each post-dose visit, see section 3.1.2. End of treatment results will be those which are assessed on the latest nominal visit prior or on the date subjects discontinue or complete study intervention.

3.2.3.7 ECG Changes

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

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

For numeric ECG parameters, triplicate ECG assessments will be programmatically derived using the averaged by time point and change from baseline will be calculated for each post-dose visit, see section 3.1.2. End of treatment results will be those which are assessed on the latest nominal visit prior or on the date subjects discontinue or complete study intervention.

The Bazett's Correction Formula (QTcB) may also be derived if it is the local standard.

3.2.4 CCI

CCI [redacted]

3.2.4.1 Change in tumor size

Tumor size is the sum of the longest diameters (or short axis measurements for lymph nodes) of the target lesions. Target lesions are measurable tumor lesions. Baseline for RECIST is defined to be the last evaluable assessment within 28 days prior to first administration of study intervention. The percentage change in target lesion tumor size at each week [redacted] until [redacted] and [redacted] onwards) for which data are available will be obtained for each subject taking the difference between the sum of the target lesions at each week [redacted] and the sum of the target lesions at baseline divided by the sum of the target lesions at baseline multiplied by 100 (i.e. (week [redacted] - baseline)/baseline * 100).

The tumor size and percentage change from baseline in the sum of tumour size at each assessment will be calculated. The best change in tumor size from baseline (i.e. depth of response) is the largest decrease from baseline or the smallest increase from baseline in the absence of a reduction and will include all assessments prior to the earliest of death in the absence of progression, any evidence of progression, the start of subsequent anti-cancer therapy or the last evaluable RECIST assessment is the subject has not died, progressed or started subsequent anti-cancer therapy.

No imputation methods will be considered for missing data in tumor size.

4 ANALYSIS METHODS

The analysis for the study will be descriptive only. There will be no formal statistical hypotheses.

4.1 General principles

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles (as applicable), minimum, and maximum. For log transformed data (in this study only applicable to PK concentrations) it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.
- By visit, data will be presented until at least 3 subjects have evaluable data. A minimum of 12 cycles will be presented in any case. If data are available for less than 3 subjects within the first 12 cycles, no summary statistics other than minimum, maximum and number of observations will be presented.
- Unless otherwise stated, percentages will be calculated out of the analysis set total.
- For continuous data the mean and median (1st quartile and 3rd quartile, if present) will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- SAS® version 9.4 or higher will be used for all analyses.
- For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are

captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

- It is acceptable to present large numerical values in more appropriate units. For example, an AUC value of 123,000 ng·h/mL may be reported as 123 µg·h/mL instead of 123,000 ng·h/mL. It is, however, important to keep the units consistent within the report and the precision consistent with that prior to conversion.

4.2 Description of analysis methods

In general, summaries will be presented by study phase ('Induction Phase', 'Maintenance Phase', 'Overall'), if applicable, and treatment population ('Total', 'SoC', 'AZD2811 + Durva'). The summaries for 'SoC' present results for subjects who withdrew the treatment during induction phase or continued in maintenance with durvalumab monotherapy, whereas 'AZD2811 + Durva' summarizes results for subjects who entered maintenance phase and have been dosed with AZD2811 and durvalumab in maintenance phase. Note that per CSP v8.0 patients in 'AZD2811 + Durva' are planned to be summarized by starting dose of AZD2811, however it should be noted that all patients received the same starting dose and therefore will be summarized together as a single group. In presentations by study phase, the combination of 'Induction Phase' and 'AZD2811 + Durva' is presenting results assessed in induction phase for subjects who entered maintenance phase. The subjects included in 'SoC' who withdrew during induction will be excluded from maintenance phase.

Listings will be sorted by group ('AZD2811 + Durva' first, followed by 'SoC'), if applicable, and by subject. If there are subjects who are assigned to treatment, but didn't receive any study intervention, they will be presented at the end of the listings with missing group.

The full list of planned outputs is provided in Appendix A.

4.2.1 Demographic, safety and tolerability data

There is no formal statistical analysis of demographic, safety and tolerability data required for this study and descriptive statistics will be used.

Tables will present number and percentage of subjects for categorical variables and summary statistics for continuous variables (unit in brackets) for following data (analysis population is Safety unless otherwise specified):

- Subject disposition (Enrolled)
- Important protocol deviations, including information on pandemic related important protocol deviations
- Analysis sets (no analysis population)
- Demographic characteristics, including age (years), age group 1 and 2, sex, race, ethnic group and country
- Subject characteristics, including height (cm), weight (kg), weight group, BMI (kg/m^2) and BMI group
- Subject recruitment by region, country and center
- Nicotine use and consumption, including substance usage categories and consumption (pack-years)
- Medical history by system organ class and preferred term
- Disease characteristics at baseline, including Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor location, site of metastatic disease, tumor laterality, histology

type, tumor grade, AJCC staging (American Joint Committee on Cancer) and time from original diagnosis to first administration in induction phase (weeks)
- All allowed concomitant medications during study by ATC classification and generic term

Subjects affected by the COVID-19 pandemic will be listed including category for study disruption due to the pandemic and details of the disruption.

All data summarized in tables will be included in listings. Disallowed concomitant medications, prior cancer therapy, post-discontinuation disease-related anticancer therapy, radiotherapies and pregnancy data (pregnancy test results and pregnancy reports) will be listed only.

4.2.2 Tumor response

In consideration of the decision to terminate enrolment prior to the completion and the limited number of evaluable patients, the efficacy analysis will be reduced and tumor assessment details will only be listed for all subjects assigned to study intervention. Listings will include the following endpoints:

- Progression free survival (PFS)
- Overall survival (OS)
- Best objective response (BOR)
- Change in TL tumor size

4.2.3 Safety

Unless stated otherwise, all analyses described in following subsections will be based on Safety analysis population.

4.2.3.1 Exposure

Exposure to study intervention (i.e. the total amount of study drug received) and dose modification data will be listed for all subjects.

Total treatment duration (weeks) will be summarized by study interventions by the following: mean, standard deviation, minimum, maximum, median, number of observations and total treatment years.

Number of treatment cycles received will be summarized by study intervention by mean, median and lower and upper quartile. The number and percentages of subjects receiving none and more than x cycles (x=1, 2, 3 …) will be presented.

Actual treatment duration (weeks) and dose intensity of investigational products will be summarized using mean, standard deviation, median, and quartiles as well as the minimum and maximum values.

Dosing deviations for study interventions will be summarized with reasons for deviations for the following categories: treatment interruptions, dose reductions (not applicable for durvalumab administration) and cycle delays.

4.2.3.2 Adverse events

Data from all cycles (of induction and maintenance phase) will be presented separately as well as combined.

The majority of the AE summaries, unless stated otherwise, will be based on TEAEs. See section 3.2.3.3 for definition of treatment emergence. Any AE occurring within the defined 90-day follow-up period after discontinuation of study intervention will be included in the AE summaries. Any AEs in this period that occur after a subject has received further therapy for cancer (following discontinuation of study intervention) will be flagged in the data listings and will be excluded from above summaries. Numbers and percentages of subjects will be presented for all AEs, AEs with grade ≥ 3, AEs grade 5, possibly related AEs, possibly related AEs with grade ≥ 3, possibly related AEs with grade 5, serious AEs and possibly related serious AEs.

AEs occurring prior to first dose of investigational product (i.e. before study Day 1), or after the 90-day follow-up period after discontinuation of investigational product will be listed.

An overall summary table of the number of subjects experiencing each category of AE will be produced. Following categories will be included:

- Any AE
- Any AE of CTCAE grade 3 or higher
- Any AE with outcome = death
- Any SAE (including events with outcome = death)
- Any SAE leading to discontinuation of treatment
- Any AE leading to discontinuation of treatment
- Any AE leading to reduction of treatment
- Any AE leading to dose interruption of treatment
- Any AE leading to modification of treatment (either an interruption and/or a dose reduction)
- Any AESI or AEPI

Except for any AE leading to reduction, dose interruption or modification of treatment and any other significant AE, all categories will be duplicated as applicable to add the condition of being possibly related to treatment (overall and separately for etoposide or cisplatin/carboplatin, etoposide or cisplatin/carboplatin or durvalumab, durvalumab, AZD2811, durvalumab or AZD2811).

Besides the overall summary table, following presentations of number of subjects experiencing TEAEs and of number of AEs will be presented:

- Number of subjects with AEs by SOC and PT
- Number of AEs by SOC and PT
- Number of subjects with AEs, most common (frequency of >10%) by PT
- Number of subjects with AEs by SOC, PT and maximum reported CTCAE grade
- Number of subjects with AEs of CTCAE grade 3 or higher by SOC and PT
- Number of subjects with AEs, assessed by investigator as possibly related to study intervention by SOC, PT and maximum reported CTCAE grade
- Number of subjects with AEs of CTCAE grade 3 or higher, assessed by investigator as possibly related to study intervention by system organ class and preferred term
- Number of subjects with AEs leading to dose reduction by IP by SOC and PT
- Number of subjects with AEs leading to dose interruptions by IP by SOC and PT
- Number of subjects with AEs leading to dose modifications by IP by SOC and PT
- Number of subjects with AEs with outcome of death by SOC and PT
- Number of subjects with SAEs by SOC and PT
- Number of SAEs by SOC and PT

- Number of subjects with SAEs, assessed by investigator as possibly related to study intervention by SOC and PT
- Number of subjects with AEs leading to discontinuation of IP by SOC and PT
- Number of SAEs by SOC and PT

Details of any deaths will be listed for all subjects (Enrolled). For Safety set, the number and percentages of subjects of deaths will be presented by death categories (death related to disease under investigation only, AE with outcome of death only, AE with outcome of death only (AE start date falling after 90 day follow up), number of subjects with death related to disease and an AE with outcome of death, other deaths).

A list of PTs provided by AZ will be used to identify AESIs and AEPIs. Presentations will be provided for AESIs/AEPIs by SOC and PT.

Key subject information will be provided for SAEs, AESIs/ and AEPIs including flag for imAEs, which will be identified as described in Section 3.2.3.4.

In order to distinguish between AESIs and AEPIs, PTs for AEPIs will be flagged in all AESI/AEPI outputs.

A summary for non-serious AEs occurring in greater than 5% of subjects will be prepared for Food and Drug Administration, but will not be part of the CSR.

All AE data will be listed for several populations:

- Safety
- Safety, subjects with subsequent therapy within 90 days after end of study treatment
- Enrolled, subject who were not exposed to treatment

AESIs will be listed (Safety) including flag for AEPI and imAE.

4.2.3.3 Laboratory

Clinical chemistry, coagulation and hematology results and change from baseline will be summarized using descriptive statistics (number of observations, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum) at each scheduled assessment time for continuous laboratory assessments). For a subset of laboratory variables (see Section 3.2.3.5) included in the current version of CTCAE, the CTCAE grade change from baseline to maximum on treatment will be summarized by phase. Urinalysis results will be listed only.

Number and percentages of clinically important changes will be presented by clinical chemistry, coagulation and hematology parameter.

Proportions of subjects with elevated liver test (elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (≥3 ULN), and elevated Total bilirubin (≥2x ULN)) will be summarized and individual subject data for subjects with potential Hy's law will be provided.

Key subject information will be also provided for subjects with treatment-emergent clinical chemistry, coagulation or hematology values outside predefined criteria.

Plots for ALT and AST versus total bilirubin, expressed as multiples of upper limit of normal (ULN) and liver biochemistry test results over time will be created. The reference lines are 3x ULN for ALT, AST, and 2x ULN for Total bilirubin. In each plot, total bilirubin will be in the vertical axis.

Laboratory reference ranges as well as all individual laboratory data will be listed. Liver assessments, liver risk factors and liver signs and symptoms for all potential Hy's law cases will be listed separately.

4.2.3.4 Vital signs

Vital sign results and change from baseline will be summarized over time, height is collected only at screening. Vital sign results outside reference limits will be presented along with key subject information for subjects who experience these results.

Vital signs values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the normal reference ranges below.

Table 7 Vital Signs Reference Ranges

Parameter	Low /Normal / High
Temperature	<36.0 C / 36.0-37.5 C / >37.5 C
Pulse	<60 / 60-100 / >100
Systolic blood pressure	<90mmHg / 90 -140mmHg / >140mmHg
Diastolic blood pressure	<60mmHg / 60 -90mmHg / >90mmHg
Respiratory rate	<12/min/ 12-20/min/ >20/min
Saturation of peripheral oxygen (SpO2)	<94%/ 94-100%/ NA

All individual vital signs data will be listed. Baseline weight, height and BMI data will be listed along with baseline characteristics. Additionally, weight and BMI will be listed by time point separately.

Physical examination results will be listed only.

4.2.3.5 ECG

Triplicate ECGs will be performed and the average of the 3 measurements, or 2 measurements if 3 were not collected, will be used for analysis; 1 measurement will be used, if only one measurement is available. ECG will be summarized over time, presenting results and change from baseline for each continuous ECG variable.

Additionally, ECG parameters will be classified as Low (L), Normal, and High (H) according to the reference ranges provided in Table 8.

Table 8 ECG Reference Ranges

Parameter	Low - High
PR interval (ms)	120 - 200
P Wave Duration (ms)	≤ 120
QRS interval (ms)	60 - 109
QT interval (ms)	320 - 450
QTcF interval (ms)	320 - 450
QTcB interval (ms)	320 - 450
RR (ms)	600-1200
ECG HR (bpm)	40-100

A shift table presenting overall evaluation of ECG at baseline versus last observation on treatment will be provided. The worst results (normal, abnormal - not clinically significant, abnormal - clinically significant, not done) of the 3 measurements, or 2 measurements if 3 were not collected, will be used for analysis.

Number and percentage of subjects with QTcF and QTcF intervals meeting below listed criteria, at any observation on treatment, will be summarized by phase:

- QTcF value above 450 ms
- QTcF value above 480 ms
- QTcF increase by more than 30 ms
- QTcF increase by more than 60 ms
- QTcF value above 450 and increase by more than 30 ms
- QTcF value above 500 and increase by more than 60 ms

Same summaries will be repeated for QTcB values.

All ECG data will be listed. Details on ECG abnormalities will be included in this listing.

4.2.4 CCI

CCI

4.2.4.1 Pharmacokinetics

Whole blood concentrations of AZD2811 for each scheduled time point will be summarized by cycle using standard summary statistics for PK concentrations:

- n
- n < LLOQ
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- The geometric mean (geomean calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale)
- Geomean ± standard deviation (calculated as exp[μ±s])
- Median
- Minimum
- Maximum

The analysis population is Pharmacokinetics.
Individual whole blood concentrations of AZD2811 and metabolite will be graphically presented over time using log scale. Concentrations data will also be summarized using geometric mean.

Besides, whole blood concentrations of AZD2811 and serum durvalumab concentrations will be listed. Other exploratory analyses planned as per study objectives will be handled outside this SAP.

5 INTERIM ANALYSES

Due to the early termination of enrolment, only the final analyses will be performed.

6 CHANGES OF ANALYSES FROM PROTOCOL

1. Laboratory: The frequency of changes with respect to normal ranges between baseline and each post-treatment time point won't be tabulated. Instead the frequency will be presented for changes between baseline and maximum on treatment only.
2. The number and percentages of subjects with at least one dose interruption and at least one dose reduction will not be presented separately for the planned length of cycles but overall only.
3. Clarification: Given the decision on 14 December 2021 to terminate enrolment, the abbreviated CSR will focus on reporting of safety endpoints as there were a limited number of patients with evaluable data to give meaningful efficacy and CCI [redacted]. This was noted in the CSP v9.0 but has been further clarified with additional details of planned analyses in this SAP.

7 REFERENCES

D6132C0001 (AZD2811) Clinical Study Protocol Version 9.0

8 APPENDICES

Appendix A Oncology early phase study outputs

Appendix B Example of subject who permanently discontinued during a dose interruption

Appendix C Visit windows

AstraZeneca

Appendix A Oncology early phase study outputs

TFL number	Title	Template	Abbreviated CSR
Table 14.1.1	Subject disposition (Enrolled)	TDEM010	X
Table 14.1.2	Important protocol deviations (Safety)	SP2	X
Table 14.1.3	Analysis sets	TDEM030	X
Table 14.1.5	Demographic characteristics (Safety)	SP4	X
Table 14.1.6	Subject characteristics (Safety)	SP8	X
Table 14.1.7	Subject recruitment by region, country and center (Safety)	ASP1	X
Table 14.1.8	Nicotine use and consumption (Safety)	ASP2	X
Table 14.1.9	Medical history (Safety)	SP7(i)	X
Table 14.1.10	Disease characteristics at baseline (Safety)	TDEM110	X
Table 14.1.11	All allowed concomitant medications during study (Safety)	SP10	X
Table 14.2.2.1	Summary of whole blood total AZD2811 and metabolite (AZ12102238) concentrations (ng/mL) (Pharmacokinetics)	PK3(i)	X
Table 14.3.1.1	Duration of exposure (Safety)	TEXP010	X
Table 14.3.1.2	Dose interruptions reductions and cycle delays by study interventions (Safety)	TEXP040	X
Table 14.3.1.3	Treatment cycles received (Safety)	TEXP080	X

TFL number	Title	Template	Abbreviated CSR
Table 14.3.1.4	Dose intensity of investigational product (Safety)	TEXP100	X
Table 14.3.2.1	Number of subjects with adverse events in any category (Safety)	TAE010	X
Table 14.3.2.2	Number of subjects with adverse events by system organ class and preferred term, all causality (Safety)	S9(i)	X
Table 14.3.2.3	Number of adverse events, by system organ class and preferred term (Safety)	S16(i)	X
Table 14.3.2.5	Number of subjects with adverse events, most common (frequency of >10%), by preferred term (Safety)	S8	X
Table 14.3.2.6	Number of subjects with adverse events by system organ class, preferred term and maximum reported CTCAE grade (Safety)	TAE050	X
Table 14.3.2.7	Number of subjects with adverse events of CTCAE Grade 3 or higher by system organ class and preferred term (Safety)	TAE060	X
Table 14.3.2.9	Number of subjects with adverse events, assessed by investigator as possibly related to study interventions by system organ class, preferred term and maximum reported CTCAE grade (Safety)	TAE050	X
Table 14.3.2.10	Number of subjects with adverse events of CTCAE grade 3 or higher assessed by investigator as possibly related to study interventions, by system organ class and preferred term (Safety)	S9(ii)	X

TFL number	Title	Template	Abbreviated CSR
Table 14.3.2.11	Number of subjects with adverse events leading to dose reduction of study interventions by system organ class and preferred term (Safety)	S22	X
Table 14.3.2.12	Number of subjects with adverse events leading to dose interruption of study interventions by system organ class and preferred term (Safety)	S22	X
Table 14.3.2.13	Number of subjects with adverse events leading to dose modification of study interventions by system organ class and preferred term (Safety)	S22	X
Table 14.3.3.1.1	All Deaths (Safety)	TDTH010	X
Table 14.3.3.1.2	Number of subjects with adverse events with outcome of death, by system organ class and preferred term (Safety)	S13(i)	X
Table 14.3.3.2	Listing of deaths (Enrolled)	TDTH040	X
Table 14.3.3.3	Adverse events with outcomes of death – key subject information (Safety)	S14	X
Table 14.3.4.1.1	Number of subjects with serious adverse events, by system organ class and preferred term (Safety)	S17(i)	X
Table 14.3.4.1.2	Number of serious adverse events, by system organ class and preferred term (Safety)	S16(ii)	X
Table 14.3.4.1.3	Number of subjects with serious adverse events, judged by investigator as possibly related to study interventions (Safety)	S17(ii)	X

TFL number	Title	Template	Abbreviated CSR
Table 14.3.4.2	Serious adverse events - Listing of key information for SAEs (Safety)	TAE180	X
Table 14.3.5.1	Number of subjects with adverse events leading to discontinuation of study intervention, by system organ class and preferred term (Safety)	S19(i)	X
Table 14.3.5.2	Adverse events leading to discontinuation of study interventions – key subject information (Safety)	TAE210	X
Table 14.3.6.1	Adverse events of special or potential interest of durvalumab - list of preferred terms	AS9	X
Table 14.3.6.2	Number of subjects with adverse events of special or potential interest of durvalumab by system organ class and preferred term (Safety)		X
Table 14.3.6.9	Adverse events of special or potential interest of durvalumab - Listing of key information (Safety)	TAE250	X
Table FDAAA1	Non-serious adverse events occurring in greater than 5% of subjects (Safety)	FDAAA1	(FDA)
Table 14.3.7.1.1	Clinical chemistry, coagulation and hematology laboratory variables over time (Safety)	S25(lab)	X
Table 14.3.7.1.2	Clinical chemistry, coagulation and hematology laboratory variables, CTCAE grade change from baseline to maximum on treatment (Safety)	TLAB020	X

TFL number	Title	Template	Abbreviated CSR
Table 14.3.7.1.3	Clinically important changes in clinical chemistry, coagulation and hematology laboratory variables parameters (Safety)	TLAB060	X
Table 14.3.7.1.4	Proportion of subjects with elevated liver test based on measured laboratory values (Safety)	AS15	X
Table 14.3.7.1.5	Subjects with potential Hy's Law – individual subject data (Safety)	S32	X
Table 14.3.7.2	Clinical chemistry, coagulation and hematology laboratory variables, treatment-emergent changes outside local reference range – key subject information (Safety)	S28	X
Table 14.3.8.1	Vital signs variables, over time (Safety)	S25(vital)	X
Table 14.3.8.2	Vital signs variables, treatment-emergent changes outside predefined criteria – key subject information (Safety)	S28	X
Table 14.3.8.3	ECG variables over time (Safety)	S25(ecg)	X
Table 14.3.8.4	ECG, baseline versus last observation on treatment (Safety)	S41(ecg)	X
Table 14.3.8.5	QTcF, QTcF intervals and QTcB, at any observation on treatment (Safety)	S35	X
Figure 14.2.2.1	Individual total AZD2811 blood concentration-time plots - Log scale (Pharmacokinetics)	PK1	X
Figure 14.2.2.2	Individual metabolite (AZ12102238) blood concentration-time plots – Log scale (Pharmacokinetics)	PK1	X

TFL number	Title	Template	Abbreviated CSR
Figure 14.2.2.3	Geomean +/- gSD total AZD2811 blood concentration-time plots – Log scale (Pharmacokinetics)	PK1	X
Figure 14.2.2.4	Geomean +/- gSD metabolite (AZ12102238) blood concentration-time plots – Log scale (Pharmacokinetics)	PK1	X
Figure 14.3.7.1	ALT versus total bilirubin, expressed as multiples of ULN (Safety)	S9	X
Figure 14.3.7.2	AST versus total bilirubin, expressed as multiples of ULN (Safety)	S9	X
Figure 14.3.7.3	Liver biochemistry test results over time – subjects with elevated ALT or AST, and elevated total bilirubin, at any time (Safety)	S10	X
Appendix 16.2.1	Discontinued subjects	APL01	X
Appendix 16.2.1	Subjects with important protocol deviations	APL03	X
Appendix 16.2.2	Subjects affected by the global/country situation	APL24	X
Appendix 16.2.3	Subjects affected by the global/country situation - details	APL25	X
Appendix 16.2.3.1	Subjects excluded from analysis set	APL04	X
Appendix 16.2.4.1	Demographic and baseline characteristics, Assigned to study intervention	APL06	X
Appendix 16.2.4.2.1	Radiotherapy prior to treatment and post treatment, Assigned to study intervention		X

TFL number	Title	Template	Abbreviated CSR
Appendix 16.2.4.2.2	Cancer therapy prior to treatment (other than protocol specified disease) and post treatment, Assigned to study intervention		X
Appendix 16.2.4.2.3	Relevant medical history and current medical conditions at study entry, Assigned to study intervention		X
Appendix 16.2.4.2.4	Prior and concomitant procedures, Assigned to study intervention		X
Appendix 16.2.4.2.5	Subject characteristics – ECOG performance status, Assigned to study intervention		X
Appendix 16.2.4.2.6	Substance Use – Tobacco, Assigned to study interventions		X
Appendix 16.2.4.2.7	Subject characteristics – metastatic disease, Assigned to study intervention		X
Appendix 16.2.4.2.8	Physical examination, Assigned to study intervention		X
Appendix 16.2.4.2.9	Pathology, Assigned to study intervention		X
Appendix 16.2.4.2.10	Concomitant medication on entry and during the study, Assigned to study intervention	APL08	X
Appendix 16.2.5.1	Administration of study interventions, Safety	APL09	X
Appendix 16.2.5.2	Duration of exposure and relative dose intensity, Safety analysis set		X

TFL number	Title	Template	Abbreviated CSR
Appendix 16.2.6.1.1.x	Tumor assessment details for subject Exxxxxxx (RECIST v1.1), Assigned to study intervention	EFF011(A)-(F)	X
Appendix 16.2.6.1.2	Progression details, Assigned to study intervention		X
Appendix 16.2.6.1.3	Survival details, Assigned to study intervention		X
Appendix 16.2.6.1.4	Best objective response, Assigned to study intervention		X
Appendix 16.2.6.1.5	Percentage change from baseline in sum of lesion diameters, Assigned to study intervention		X
Appendix 16.2.6.2.1	Individual whole blood total AZD2811 and metabolite concentrations (ng/mL), Pharmacokinetics	APL13	X
Appendix 16.2.6.2.2	Individual serum durvalumab concentrations (ng/mL), Pharmacokinetics	APL13	X
Appendix 16.2.7.1	Adverse events, Safety	APL14	X
Appendix 16.2.7.2	Adverse events in subjects with subsequent therapy within 90 days after end of study treatment, Safety	APL14	X
Appendix 16.2.7.3	Adverse events, Enrolled, subjects who were not exposed to treatment	APL15	X
Appendix 16.2.8.1	Laboratory reference ranges glossary		X
Appendix 16.2.8.2	Individual laboratory measurements, Safety	APL16	X

TFL number	Title	Template	Abbreviated CSR
Appendix 16.2.9	Individual vital signs data, Safety	APL18	X
Appendix 16.2.10.1	Electrocardiogram data, Safety	APL19	X
Appendix 16.2.10.2	Abnormalities in electrocardiogram, Safety	APL19	X
Appendix 16.2.10.3	Pregnancy test, Safety		X
Appendix 16.2.10.4	Pregnancy report, Safety		X
Appendix 16.2.10.5	Liver assessment for all potential Hy's Law cases, Safety		X
Appendix 16.2.10.6	Liver risk factors for all potential Hy's Law cases, Safety		X
Appendix 16.2.10.7	Liver signs and symptoms for all potential Hy's Law cases, Safety		X
Appendix 16.2.10.8	Weight and BMI, Safety	APL21	X

Appendix B Example of subject who permanently discontinued during a dose interruption

Example of the dosing pattern for a subject:

Dose	Start date	Stop date	Reason for change
CCI	23/01/11	14/02/11	NA
0mg	15/02/11	28/02/11	AE (dose interrupted)
CCI	01/03/11	13/03/11	AE (dose restarted and reduced)
0mg	14/03/11	15/03/11	AE (dose interrupted)
0mg	16/03/11		RECIST progression (permanent discontinued)

The data will be recorded as above on the EXL module. The date of last dose for this subject used in the programming and recorded on the EXL module is 13/03/11 and the reason for permanent discontinuation recorded on EXL should be AE. This subject will have one dose interruption according to the summary tables as the second dose interruption will not be included as an interruption.

Appendix C Visit windows

Parameter for target lesion RECIST assessments

Week	Scheduled Day	Visit Window		Analysis Visit
		Lower Limit	Upper Limit	
Screening	-21 to -1	-	≤1	Baseline
CCI	[redacted]			

Where X=44 + 8k; k=1,2,3…

Parameter for laboratory and vital signs

Cycle	Day	Scheduled Day	Visit Window		Analysis Visit
			Lower Limit	Upper Limit	
	1	1, pre-dose, or last non-missing assessment prior to first dose of study treatment	-	≤1	Baseline
C1	CCI				
C1					
C2					
C2					
C3					
C3					
C4					
C4					
C5 [a]					
C5					
C5					

Cycle	Day	Scheduled Day	Visit Window	Analysis Visit
	CCI			
C5				
CX				
CX				

Where X=5+k*1; k=1,2,3…

[a] Assessments performed pre-dose on CCI will be considered part of the induction phase.

[b] CCI

Parameter for urinalysis

Cycle	Day	Scheduled Day	Visit Window		Analysis Visit
			Lower Limit	Upper Limit	
	1	1, pre-dose, or last non-missing assessment prior to first dose of study treatment	-	≤1	Baseline
C1	[redacted]				
C2					
C3					
CX					

Where X=3+k*1; k=1,2,3…Parameter for ECG parameters

Cycle	Day	Scheduled Day	Visit Window		Analysis Visit
			Lower Limit	Upper Limit	
	CCI				
C5 [a]					
End of treatment	Last dose day	Last dose day	NA	NA	End of treatment

[a] Assessments at CCI only applicable for subjects who continued into maintenance phase.

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