Statistical Analysis Plan

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A Phase III, Randomized, Multicenter, Double-blind, Placebo-controlled Study to Determine the Efficacy of Adjuvant Durvalumab in Combination with Platinum-based Chemotherapy in Completely Resected Stage II-III NSCLC (MERMAID-1)

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Study Statistician

PPD _____ Date _____

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Global Product Statistician

PPD _____ Date

TABLE OF CONTENTS

TABLE OF CONTENTS 4
LIST OF ABBREVIATONS 7
AMENDMENT HISTORY 10
1 STUDY DETAILS 13
1.1 Study Objectives 13
1.1.1 Primary Objective 13
1.1.2 Secondary Objectives 14
1.1.3 Safety Objective 14
1.1.4 CCI [redacted] [a] 14
1.2 Study Design 16
1.3 Number of Patients 17
2 ANALYSIS SETS 18
2.1 Definition of Analysis Sets 18
2.1.1 Full Analysis Set (Intention to Treat) 19
2.1.2 MRD+ Analysis Set 19
2.1.3 Safety Analysis Set 19
2.2 Protocol Deviations 19
3 PRIMARY AND SECONDARY VARIABLES 21
3.1 Derivation of RECIST Visit Responses 21
3.1.1 New Lesions – Site Investigator Data 21
3.1.2 Overall Visit Response – Site Investigator Data 22
3.2 Efficacy Variables 22
3.2.1 Disease-free Survival (DFS) 22
3.2.2 Overall Survival (OS) 24
3.3 Safety Variables 24
3.3.1 Study Treatments 25
3.3.1.1 Exposure and Dose Interruptions 25
3.3.2 Dose Intensity 26
3.3.3 Adverse Events 27
3.3.4 Laboratory Data 28
3.3.5 Electrocardiograms 29
3.3.6 Vital Signs 30
3.4 CCI [redacted] 30
3.4.1 CCI [redacted] 30
3.4.1.1 CCI [redacted] 30
3.4.1.2 CCI [redacted] 30
3.4.2 CCI [redacted] 31

3.4.2.1 CCI [redacted] 31
3.4.2.2 CCI [redacted] 31
3.4.2.3 CCI [redacted] 32
3.4.2.4 CCI [redacted] 32
4 ANALYSIS METHODS 33
4.1 General Principles 33
4.1.1 Baseline 34
4.1.2 General Considerations for Safety and PRO Assessments 34
4.2 Analysis Methods 36
4.2.1 Multiplicity 36
4.2.2 Disease-free Survival (DFS) 37
4.2.2.1 Primary Analysis of DFS 37
4.2.2.2 Subgroup Analyses 39
4.2.2.3 Secondary Analysis of DFS 40
4.2.3 Overall Survival (OS) 40
4.2.4 CCI [redacted] 40
4.2.5 CCI [redacted] 40
4.2.6 CCI [redacted] 41
4.2.7 CCI [redacted] 41
4.2.8 Safety 42
4.2.8.1 Adverse Events (AEs) 42
4.2.8.2 AEs of Special Interest and Possible Interest 45
4.2.8.3 Laboratory Assessments 46
4.2.8.4 Electrocardiograms 48
4.2.8.5 Vital Signs 48
4.2.8.6 Other safety 48
4.2.9 Demographics and Baseline Characteristics 48
4.2.10 Concomitant and Other Treatments 49
4.2.11 Exposure 50
4.2.12 Coronavirus Disease 2019 (COVID-19) 50
5 INTERIM ANALYSES 51
5.1 Interim Efficacy Analysis 51
5.2 Independent Data Monitoring Committee 51
6 CHANGES OF ANALYSIS FROM PROTOCOL 51
7 REFERENCES 53
8 APPENDICES 54

LIST OF TABLES

Table 1 Summary of Outcome Variables and Analysis Populations 18
Table 2 RECIST 1.1 Overall Visit Responses 22
Table 3 Study Treatments 25
Table 4 Statistical Analyses to be Conducted 36

LIST OF FIGURES

Figure 1 Overall Study Design According to CSP v4.0 17

LIST OF APPENDICES

APPENDIX A Visit Windows 54
APPENDIX B Missing/Partial Dates Imputation..... 55

LIST OF ABBREVIATONS

Abbreviation or special term	Explanation
AE	Adverse event
AEPI	Adverse event of possible interest
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the serum drug concentration-time curve
BICR	Blinded independent central review
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumor DNA
CV	Coefficient of variation
DBL	Database lock
DBP	Diastolic blood pressure
DCO	Data cut-off
DFS	Disease-free survival
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
CCI	CCI
CCI	CCI

Abbreviation or special term	Explanation
CCI	CCI
FAS	Full analysis set
GHS	Global health status
HLT	Higher level term
HR	Hazard ratio
HRQoL	Health related quality of life
ICF1	Informed consent form 1
ICF2	Informed consent form 2
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
IP	Investigational product (in this study, durvalumab/placebo)
IPD	Important protocol deviations
ITT	Intent-to-treat
IV	Intravenous
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MRD+	MRD-positive
MRD-	MRD-negative
NA	Not applicable
NE	Not evaluable
NED	No evidence of disease
NL	New lesion
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD	Progression of disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
CCI	CCI
PORT	Post-operative radiotherapy
PRO	Patient reported outcome

Abbreviation or special term	Explanation
CCI	[redacted]
PT	Preferred term
q3w	Every 3 weeks
q4w	Every 4 weeks
CCI	[redacted]
CCI	[redacted]
QoL	Quality of Life
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	A commercially available integrated system of software products, commonly used for reporting and analysis of Clinical Studies
SBP	Systolic blood pressure
SoC	Standard of care
SOC	System organ class
SI	International system of units
TC	Tumor cell
TEAE	Treatment-emergent adverse event
CCI	[redacted]
TMB	Tumor mutational burden
TSH	Thyroid stimulating hormone
CCI	[redacted]
ULN	Upper limit of normal
VAF	Variant allele frequencies
VAS	Visual analogue scale
WES	Whole exome sequencing
WHODD	World Health Organization drug dictionary

AMENDMENT HISTORY

Date	Brief description of change
V1.0 (29Jan2021)	NA – first version
V2.0 (15Dec2022)	Updated to reflect CSP v4, including changes to primary, secondary and exploratory objectives. Updated the planned analyses throughout the document (there will be one analysis (ie, primary analysis) which will occur after DCO) Removed any references to PK and ADA analysis sets, endpoints and analyses throughout the document to reflect CSP v4. Removed any references to MRD- analysis set as it is no longer needed to support the primary endpoint due to CSP v4. Removed any references to health care resource use endpoints, variables and analyses to reflect CSP v4. Removed any references to BICR endpoints and analyses throughout the document. CCI [redacted] Throughout the document, when both the MRD+ analysis set and the FAS are mentioned, changed the order so that FAS is mentioned first and thereafter the MRD+ analysis set, to align with revised primary endpoint as per CSP v4. Section 2.1.3 – updated the treatment assignment for summaries for patients who only received SoC and did not receive any doses of either durvalumab or placebo (from "as randomized" to "in the placebo plus SoC chemotherapy treatment group"). Section 2.2 – removed exclusion criteria 10 as per latest Protocol Deviations Plan. Section 3.2.1 and 4.2.2.1 – removed 3- and 9-month DFS rates to align with CSP v4. Section 3.3.4 – added Hemoglobin, Lymphocytes and Leukocytes to the list of parameters that have CTCAE grades defined for both high and low values to align with CTCAE v5.0. Section 3.3.5 – removed reference to calculation of means for triplicates and summaries of ECG data and derivation of QTcF. Section 3.3.6 – removed any references relating to summaries, on-treatment and change from baseline. CCI [redacted]

Date	Brief description of change
	Section 3.4.2.4 – removed weighted health state utility derivation and evaluable population definition. CCI [redacted] Section 4 and section 4.2.1 – in alignment with CSP v4 clarified that no formal statistical analyses will be performed, and all analyses will be exploratory. Section 4.1.1 – Updated baseline definition for efficacy and PROs to last observed measurement prior to randomization (not on or prior to randomization). Section 4.1.2 – Imputation rules, added clarification that imputation of partial dates will only be applied for patients exposed to treatment. Section 4.2 and Table 4 – revised in line with changes to objectives. Sections 4.2.2 – 4.2.6 – revised in line with changes to objectives, endpoints, and analyses as per CSP v4. CCI [redacted] CCI [redacted] Section 4.2.8.1 – Removed summaries for time to first onset of AE, duration of AE, and event rate, and longer-term toxicity profile (will only be flagged in listings). Section 4.2.8.1 – Added imAEs (per Investigator) and infusion reaction AEs (per Investigator) to bulleted list. Section 4.2.8.2 – Removed AESI/AEPI summaries leading to steroid use, discontinuation of study treatment, and dose delay of study treatment. Section 4.2.8.2 – Removed summaries for time to onset and resolution of imAEs. Section 4.2.8.3 – Removed all graphical presentations of laboratory data (including liver enzymes), as well as summaries of absolute value and change from baseline in hematology and chemistry, and urinalysis shift table. Section 4.2.8.3 – Thyroid functions tests: removed summaries for subjects for on-treatment elevated TSH. Added shift tables to maximum and minimum on-treatment. Section 4.2.8.3– Renal function tests: removed summaries of CrCl reversibility, and added clarification that worst CrCl rate on-treatment will be presented in summaries. Section 4.2.8.5 – Removed all graphical presentations and summaries of vital signs data. Section 5.1 – Aligned with CSP v4: no interim analysis planned.

Date	Brief description of change
	Section 7 – Removed references no longer used in this document due to updates as listed above. Minor formatting changes throughout Section 4.1.2 – Removed cut-off rule for summaries. Table 1 and related paragraphs in Section 4.2 – updated based on requirements due to small number of patients expected in MRD+ analysis set. Table 4 – removed analyses for MRD+ analysis set (only simple summaries will be provided, as further noted in Section 4.2)

1 STUDY DETAILS

This SAP contains a more detailed description of the analyses in the CSP and is based on version 4 of the CSP, dated 02 August 2022, and on version 3 of the Protocol Deviations Plan, dated 25 May 2021. Any changes to any specifications in the CSP will be described in Section 6 of this document.

Prior to CSP V4.0, the primary objective of this study was to compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the MRD+ analysis set. A secondary objective was to compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the FAS. The study was sized for the primary endpoint of DFS in the MRD+ analysis set and for the secondary endpoint of DFS in the FAS.

Following approvals of neoadjuvant and adjuvant immunotherapy options for patients with resectable NSCLC, AstraZeneca has decided to close enrolment to MERMAID-1. These approvals were based on the two Phase III clinical studies (IMpower010 and PEARLS/KEYNOTE-091) that reported positive results for PD-(L)1 inhibitors (used as monotherapy) in the adjuvant setting. One Phase III clinical study (Checkmate816) has reported positive results for nivolumab (anti-PD-1 immunotherapy) in the neoadjuvant setting.

Under CSP V4.0 as a result of the decision to close study enrollment, the intended patient numbers will not be reached. The primary objective of this study is now to compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the FAS rather than in the MRD+ analysis set. A secondary objective is now to compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the MRD+ analysis set. No multiple testing procedure for controlling the type I error rate will be implemented (see Section 4.2.1).

1.1 Study Objectives

1.1.1 Primary Objective

Primary objective:	Endpoint/variables:
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by DFS in all patients	DFS in FAS (using Investigator assessments according to RECIST 1.1)

DFS Disease-free survival; RECIST Response Evaluation Criteria in Solid Tumours; SoC Standard of care.

1.1.2 Secondary Objectives

Secondary objectives:	Endpoint/variables:
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by DFS in MRD+ patients	DFS in MRD+ analysis set (using Investigator assessments according to RECIST 1.1)
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by OS in MRD+ patients and in all patients	OS in MRD+ analysis set and in FAS

DFS Disease-free survival; FAS Full analysis set; MRD+ Minimal residual disease-positive; OS Overall survival; RECIST Response Evaluation Criteria in Solid Tumours; SoC Standard of care.

1.1.3 Safety Objective

Safety objective:	Endpoint/variables:
To assess the safety and tolerability profile of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy in MRD+ patients and in all patients	AEs, physical examinations, vital signs, and laboratory findings

AE Adverse event; MRD+ Minimal residual disease-positive; SoC Standard of care.

1.1.4 CCI [a]

CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

CCI

[redacted]

1.2 Study Design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-arm study to evaluate the efficacy and safety of durvalumab plus SoC chemotherapy compared to placebo plus SoC chemotherapy in patients with completely resected stage II-III NSCLC who are MRD+ post-surgery.

Prior to CSP V4.0, the study was designed to screen approximately CCI patients and randomize approximately CCI patients with stage II-III NSCLC, whose tumors are *EGFR* and *ALK* wild type, and who have undergone complete resection. Randomized patients were to include approximately CCI MRD+ and CCI MRD- patients. The number of MRD- patients was to be capped at 100. Within the randomized MRD- population, it was expected to have approximately 30%/70% Asian/non-Asian patients.

Following a decision to close recruitment on 25 May 2022, a total of 691 patients were enrolled, and up to approximately 100 patients were expected to be randomized within the study. The randomized population is expected to include up to approximately 25 MRD+ and 75 MRD- patients.

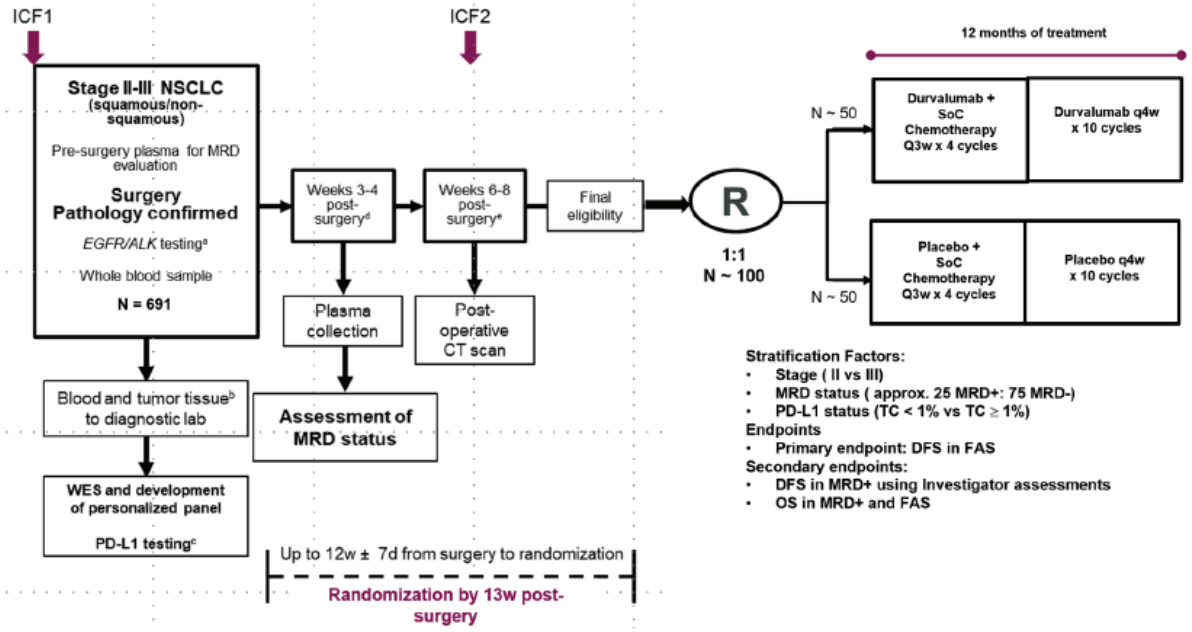
The study has opened in 188 centers globally. Note that enrollment has closed for this study.

Patients will be randomized 1:1 to durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy. Randomization will be stratified by disease stage (stage II vs stage III), MRD status (MRD+ vs MRD-), and PD-L1 TC expression (< 1% vs ≥ 1%). Patients will receive one of the following SoC regimens, depending on histology and per Investigator's decision: paclitaxel/carboplatin (squamous), pemetrexed/cisplatin (non-squamous), or pemetrexed/carboplatin (non-squamous).

Patients will receive SoC chemotherapy q3w for up to 4 cycles plus durvalumab or placebo via IV infusion q3w for up to 4 cycles. Patients will then receive up to 10 additional cycles of durvalumab or placebo q4w (for a total of 12 months of treatment), until disease recurrence, or until other specific treatment discontinuation criteria are met (whichever occurs first). Prior to CSP V4.0, all patients were to be followed for disease recurrence until the primary analysis, and were to be followed for survival until the completion of the study. For an overview of the original study design, see Figure 1 in the CSP.

On 25 May 2022, AstraZeneca closed study recruitment. This was based on changes in the treatment landscape as outlined in Section 2.1 of the CSP. All randomized patients will be followed until the primary DCO (defined as the date of the last visit of the last patient in the study, which is approximately 12 months after last patient was randomized) when no further visits will occur. For an overview of the revised study design, see Figure 1.

Figure 1 Overall Study Design According to CSP v4.0



[a] While it is ***preferred*** that patients are identified and sign ICF1 prior to surgery, patients will be permitted to sign ICF1 after surgery. In this case, whole blood and resected tumor tissue must be collected as soon as possible for creation of the personalized panel. A plasma sample must still be collected at Week 3-5 (Day 21-35) post-surgery, even if creation of the personalized panel is delayed. **Note that enrollment has closed for this study**.
[b] *EGFR/ALK* status should be assessed on pre-surgical biopsy. If pre-surgical biopsy is not available or evaluable, testing will be conducted on resected tumor tissue while the personalized MRD panel is in development. Patients will still be allowed to continue with first screening procedures while testing is ongoing but will not be eligible for randomization if their tumor tissue tests positive for EGFR mutations or ALK translocations.
[c] PD-L1 status is required for randomization.
[d] The plasma sample used to determine MRD status must be collected at Week 3-5 (Day 21-35) post-surgery. Investigators will not be notified of the patient's MRD status and eligibility to continue into second screening will be managed through the IWRS.
[e] A CT scan performed once a patient signs ICF2 can be used as the baseline scan provided this scan was performed 28 days + 7 days **prior to randomization**.
ALK Anaplastic lymphoma kinase; CT Computed tomography; d Day; DFS Disease-free survival; EGFR Epidermal growth factor receptor; FAS Full analysis set; ICF1 Informed consent form 1; ICF2 Informed consent form 2; MRD Minimal residual disease; MRD+ MRD-positive; MRD- MRD-negative; NSCLC Non-small cell lung cancer; OS Overall survival; PD-L1 Programmed cell death-ligand 1; PD-L1 TC<1%/≥1% Expression of PD-L1 on tumor membrane, at any intensity, in<1% or ≥1% of tumor cells; PRO Patient-reported outcomes; q3w Every 3 weeks; q4w Every 4 weeks; R Randomization; SoC Standard of care; w Week; WES Whole exome sequencing.

1.3 Number of Patients

Prior to CSP V4.0, approximately CCI eligible patients were planned to be randomized 1:1 to durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy. Of the patients randomized into the study, approximately CCI patients were required to be MRD+, as determined by the result from their post-surgical plasma sample. The study was sized for the

primary endpoint of DFS in the MRD+ analysis set and for the secondary endpoint of DFS in the FAS.

Under CSP V4.0, the originally planned number of randomized patients will not be met. There will be one analysis (ie, primary DFS analysis) which will occur after DCO (see Section 4.2.6) and OS will be analyzed at this time.

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

The populations for analyses are summarized in Table 1 per outcome variable.

Table 1 Summary of Outcome Variables and Analysis Populations

Outcome variable	Population
Primary efficacy data	
DFS (using Investigator assessments)	FAS
Secondary efficacy data	
DFS (using Investigator assessments)	MRD+
OS	FAS, MRD+
CCI	
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
Study population/Demography data	
Demography	FAS, MRD+
Baseline and disease characteristics	FAS, MRD+
Important deviations	FAS, MRD+
Medical/surgical history	FAS
Previous anti-cancer therapy	FAS
Concomitant medications/procedures	FAS
Subsequent anti-cancer therapy (including radiotherapy)	FAS, MRD+
Safety data	
Exposure	Safety
AEs	Safety

Outcome variable	Population
Laboratory measurements	Safety
Vital signs	Safety
ECGs	Safety

AE Adverse event; DFS Disease-free survival; CCI , CCI ; FAS Full analysis set; MRD+ Minimal residual disease-positive; OS Overall survival; PFS Progression-free survival; CCI CCI ; CCI ;CCI

2.1.1 Full Analysis Set (Intention to Treat)

The FAS will include all randomized patients. The FAS will be used for all efficacy analyses, including CCI Treatment groups will be assigned based on the randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently receive study treatment are included in the analysis in the treatment group to which they were randomized. The analysis of data using the FAS therefore follows the principles of ITT.

2.1.2 MRD+ Analysis Set

The MRD+ analysis set will include all patients in the FAS who are MRD+, as determined by results from the post-surgical plasma sample based on the assay that was used at the time of randomization. Treatment groups will be assigned based on the randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently receive study treatment are included in the analysis in the treatment group to which they were randomized.

2.1.3 Safety Analysis Set

The safety analysis set will consist of all randomized patients who received at least 1 dose (any amount) of study treatment (durvalumab/placebo and/or SoC). Safety data will not be formally analyzed but summarized using the safety analysis set according to the treatment received. If a patient receives any amount of durvalumab, with or without SoC, they will be summarized in the durvalumab plus SoC chemotherapy treatment group. If a patient only receives placebo, with or without SoC, they will be summarized in the placebo plus SoC chemotherapy treatment group. Patients who only received SoC and did not receive any doses of either durvalumab or placebo will be summarized in the placebo plus SoC chemotherapy treatment group.

2.2 Protocol Deviations

The following general categories will be considered IPDs and will be listed and discussed in the CSR as appropriate:

- Inclusion criteria deviations: Patients who deviate from inclusion criteria 1, 4, 5, 6, and/or 12 per Section 5.1 of the CSP.
- Exclusion criteria deviations: Patients who deviate from exclusion criteria 1 and/or 2 per Section 5.2 of the CSP.
- Discontinuation criteria for study product met but patient not withdrawn from study treatment.
- IP deviation:
  (a) Patient received incorrect IP to that to which they were randomized.
  (b) Patients who were randomized but did not receive IP or chemotherapy.
- Excluded medications taken: Received prohibited concomitant systemic anti-cancer therapy.
- Deviations related to study procedure: Baseline RECIST scan > 49 days before randomization.

Patients who receive the wrong treatment at any time will be included in the safety analysis set as described in Section 2.1. During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the study team leader and/or statistician.

The IPDs will be listed and summarized by randomized treatment group. IP deviation of patients who were randomized but did not receive IP or chemotherapy will lead to exclusion from the safety analysis set. None of the other deviations will lead to patients being excluded from the analysis sets described in Section 2.1. A per-protocol analysis excluding patients with specific IPDs is not planned.

The programmatic determination of the IPDs above will be a separate process outlined in the study Protocol Deviations Plan, which will also include full details regarding IPDs as well as the activities and responsibilities related to the IPD process.

In addition, other study deviations captured from the eCRF module for inclusion/exclusion criteria will be tabulated and listed. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

A ‘deviation bias’ sensitivity analysis may be performed, excluding patients with deviations that may affect the efficacy of the trial therapy if > 10% of patients in either treatment group:

- Did not have the intended disease or indication or
- Did not receive any randomized therapy.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of DBL and will be documented prior to the primary analysis being conducted.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST Visit Responses

For this adjuvant study, where patients with no evidence of disease at baseline (as assessed by CT/MRI) will be entered in the study, the definition of NLs in RECIST 1.1 is used to for the assessment of disease recurrence.

For all patients, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1. It will also be used to determine if and when a patient has disease recurrence in accordance with RECIST.

Baseline radiological tumor assessments are to be performed no more than 28 days + 7 days before randomization and ideally as close as possible to the date of randomization. Tumor assessments are then performed every 12 weeks ± 1 week following randomization until unequivocal disease recurrence or primary DFS analysis. Upon detection of disease recurrence, an additional follow-up scan should be performed 4 to 8 weeks later and evaluated using post progression radiological criteria.

If an unscheduled assessment is performed, and the patient has not had disease recurrence, every attempt should be made to perform the subsequent assessments according to the original imaging visit schedule (relative to the date of randomization). If a dose delay of study treatment (ie, durvalumab/placebo and/or SoC) occurs, RECIST scans should continue according to the original imaging visit schedule. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

3.1.1 New Lesions – Site Investigator Data

At each post-baseline visit the Investigator should record an overall assessment based on the presence or absence of unequivocal NLs. This section provides the definitions of the criteria used to determine and record overall response at the investigational site at each visit.

Details of any NLs will be recorded with the date of assessment. The presence of one or more unequivocal NLs is assessed as progression and will indicate disease recurrence.

A lesion identified at a follow-up assessment as local/regional, distant, or second primary NSCLC is considered a NL and will indicate disease recurrence. The development of a new cancer other than NSCLC should be regarded as an SAE.

The finding of a NL should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. If a NL is equivocal, for example, because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit. If repeat scans (at least 4 weeks later, but preferably at the next scheduled visit) definitively confirm there is a NL, then recurrence should be declared using the date of the initial post-baseline scan where the equivocal NL was first identified, without an intervening period of lesion absence.

Both equivocal and unequivocal NLs will be recorded in the eCRF. Unequivocal NLs will be identified via a Yes/No tick box on the unequivocal new lesions eCRF form. If the question 'Any unequivocal new lesions since baseline' has not been answered with Yes or No and the NL details are blank this is not evidence that no unequivocal NLs are present, but should not overtly affect the derivation. This scenario (ie, whereby NL response is NE), should only occur in exceptional cases, as missing data for the NL field should always be queried.

3.1.2 Overall Visit Response – Site Investigator Data

Table 2 defines how NL information will be used to determine an overall visit response.

Table 2 RECIST 1.1 Overall Visit Responses

Target lesions	Non-target lesions	New lesions	Overall visit response
NA	NA	NE	**NE**
NA	NA	No	**NED**
NA	NA	Equivocal	**NED***
NA	NA	Yes	**PD**

* Disease recurrence (ie, PD) may be backdated to a timepoint where an equivocal new lesion was identified, under specific conditions outlined in Section 3.1.
NA Not applicable, NE Not evaluable; NED No Evidence of Diseases; PD Progressive disease.

3.2 Efficacy Variables

3.2.1 Disease-free Survival (DFS)

Disease-free survival as assessed by the Investigator is the primary endpoint in this study and is defined as the time from the date of randomization until any one of the following events below, whichever occurs first, regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to disease recurrence (ie, date of DFS event or censoring – date of randomization + 1 day):

- Date of disease recurrence using Investigator RECIST 1.1 assessments
  - Local, regional, or distant disease recurrence
  - Diagnosis of a second primary NSCLC
- Date of death from any cause

Disease-free survival rate at 6 and 12 months is defined as the proportion of patients alive and disease free at 6 and 12 months respectively, estimated from Kaplan-Meier plots of the primary endpoint of DFS.

Disease recurrence should be based on the finding of an unequivocal NL. However, if a NL is initially equivocal (ie, where an equivocal lesion converts to unequivocal), then the progression date should be backdated to the post-baseline follow-up scan when the NL first appeared without an intervening period of lesion absence. If equivocal lesions are present at baseline, they will not be documented on the baseline eCRF.

Patients who have not experienced disease recurrence and are alive at the time of analysis, will be censored at the latest date of assessment from their last evaluable RECIST 1.1 assessment.

However, if the patient experiences disease recurrence or dies after 2 or more missed visits, the patient will be censored at the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits (note: an NE visit is not considered a missed visit). Given the scheduled visit assessment scheme (ie, every 12 weeks ± 1 week after randomization until appearance of disease recurrence or until primary DFS analysis) the definition of 2 missed visits will be 26 weeks (2 × 12 weeks + 1 week for an early assessment and + 1 week for a late assessment).

If the patient has no evaluable assessments or does not have baseline data, they will be censored at day 1 unless they die within 2 visits of baseline (ie, 25 weeks [2 × 12 weeks + 1 week for a late assessment]), then they will be treated as an event with the date of death as the event date. Additionally, patients with unequivocal evidence of disease at baseline (as assessed by the Investigator) will be censored at randomization (day 1).

The primary endpoint analysis of DFS will be based on Investigator RECIST 1.1 assessments. The DFS time will always be derived based on scan/assessment dates and not visit dates.

RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For Investigator assessments, the date of disease recurrence will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates disease recurrence.

- When censoring a patient for DFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

3.2.2 Overall Survival (OS)

Overall survival is defined as the time from the date of randomization until death due to any cause regardless of whether the patient discontinues from randomized therapy or receives another anti-cancer therapy (ie, date of death or censoring – date of randomization + 1 day). Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (SUR_DAT, recorded within the SURVIVE module of the eCRF).

Survival calls will be made in the week following the date of DCO for the primary analysis, and if patients are confirmed to be alive or if the death date is after the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner, and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws. In instances where the SURVIVE module is not completed then all relevant eCRF fields will be used to determine the last recorded date on which the patients were known to be alive.

If a patient is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive + 1 day from the database and the death date using the available information provided. Refer to Appendix B for imputation rules for missing or partial death dates.

3.3 Safety Variables

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. These will be collected for all patients. For physical examination, only information on whether the assessment was performed or not is recorded, and any abnormal findings are reported as either medical history or AEs.

Safety data will be summarized from the 'On-treatment' period, unless otherwise specified. 'On-treatment' is defined as assessments between the date/time of start of study treatment (ie, durvalumab/placebo and/or SoC) and 90 days following discontinuation of study treatment (ie, the last dose of durvalumab/placebo and/or SoC), or up to and including the date of initiation of the first subsequent anti-cancer therapy (including radiotherapy, except for palliative radiotherapy), whichever occurs first.

3.3.1 Study Treatments

Study treatment in this study refers to durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy. Study treatments are described in Table 3. Exposure will be defined for durvalumab, placebo and SoC chemotherapy regimens.

Table 3 Study Treatments

Study treatment name		Route of administration	Dosing instructions
Durvalumab		IV	1500 mg infusion over 60 min q3w × 4 cycles followed by 1500 mg over 60 min q4w × 10 cycles up to a total of 12 months of treatment
Placebo		IV	Infusion over 60 min q3w × 4 cycles followed by infusion over 60 min q4w × 10 cycles up to a total of 12 months of treatment
Standard of care[a]	Carboplatin/ Paclitaxel	IV	Paclitaxel (200 mg/m^2) and carboplatin (AUC 6) Day 1 of each 3-week cycle for 4 cycles
	Cisplatin[b]/ Pemetrexed	IV	Pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) Day 1 of each 3-week cycle for 4 cycles
	Carboplatin/ Pemetrexed	IV	Pemetrexed (500 mg/m^2) with carboplatin (AUC 5) Day 1 of each 3-week cycle for 4 cycles

[a] Patients will receive one of the specified SoC regimens, depending on histology and per Investigator's decision.
[b] In the event of unfavorable tolerability, patients can switch from cisplatin to carboplatin therapy at any point during the study. However, it is preferred that all patients receive at least 1 cycle of cisplatin.
AUC Area under the serum drug concentration-time curve; IV Intravenous; min Minutes; q3w Every 3 weeks; q4w Every 4 weeks; SoC Standard of care.

3.3.1.1 Exposure and Dose Interruptions

Exposure (ie, duration of treatment) will be defined as follows:

- Total (or intended) exposure of durvalumab/placebo
  - Total (or intended) exposure = min (last dose date where dose > 0 mg + *xx* days, date of death, date of DCO) – first dose date + 1 day

    where *xx* = 20 if the last dose occurs during the durvalumab/placebo plus SoC portion of the study (cycles 1 to 4), and 27 if the last dose occurs during the durvalumab/placebo monotherapy portion of the study (cycles 5 to 14)

- Actual exposure of study treatment (defined for durvalumab and placebo only)
  - Actual exposure = intended exposure – total duration of dose interruptions and cycle delays

- Calculation of duration of dose delays/interruptions (for actual exposure, defined for durvalumab and placebo only)
  - Duration of dose delays/interruptions = sum of positive values of [date of the dose – date of previous dose – (*xx* + 3) days]
    where *xx* is 21 for the durvalumab/placebo plus SoC portion of the study (cycles 1 to 4), and 28 for the durvalumab/placebo monotherapy portion of the study (cycles 5 to 14)

Dose reductions of durvalumab/placebo are not permitted, and the actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

The total (or intended) exposure for each SoC regimen (ie, combination of SoC agents) will also be summarized by combining the SoC agents together (ie, the maximum total exposure among all SoC agents will be considered).

- The total (or intended) exposure for each SoC agent is defined as follows:
  - Total (or intended) exposure = min (last dose date where dose > 0 mg + 20 days, date of death, date of DCO) – first dose date + 1 day

Number of Treatment Cycles Received

Exposure will also be measured by the number of cycles received. For SoC, a cycle corresponds to a period of 21 days, and for durvalumab/placebo a cycle corresponds to one dose of treatment. If a cycle is delayed or 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.

Patients who Permanently Discontinue During a Dose Delay

If a decision is made to permanently discontinue study treatment (ie, durvalumab/placebo and/or SoC) in-between cycles or during a dose delay then the date of last administration of study medication recorded will be used in the calculation of exposure.

3.3.2 Dose Intensity

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. Relative dose intensity will be derived for durvalumab or placebo and is 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. When accounting for the calculation of intended cumulative dose 3 days should be added to the date of last dose to reflect the protocol allowed window for dosing.

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

3.3.3 Adverse Events

Adverse events and SAEs will be collected throughout the study, from date of informed consent (SAEs will be collected following signature of the first informed consent [ICF1]; all SAEs and AEs will be collected following signature of the second informed consent [ICF2]) until 90 days after the last dose of study treatment (durvalumab/placebo and/or SoC). A TEAE is defined as an AE with an onset date, or a pre-existing AE worsening (by Investigator report of a change in intensity), during the 'on-treatment' period as defined in Section 3.3. The Medical Dictionary for Regulatory Activities (using the latest or current MedDRA version) will be used to code the AEs. Adverse events will be graded according to the NCI CTCAE version 5.0.

In the unlikely event that durvalumab/placebo and SoC chemotherapy are delivered on separate dates, AEs with date of onset on or after the earliest first dose of any of the components of the combination should be considered to be treatment emergent.

Adverse Events of Special Interest and Possible Interest

Some clinical concepts (including some selected individual PTs and HLTs) have been considered 'AEs of special interest' (AESI) and 'AEs of possible interest' (AEPI) to the durvalumab program.

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

The AEPIs reported in the AstraZeneca-sponsored durvalumab studies are defined as AEs that could have a potential inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab but are more likely to have occurred due to other pathophysiological mechanisms, thus, the likelihood of the event being inflammatory or immune-mediated in nature is not high and/or is most often or usually explained by the other causes.

These AESIs and AEPIs are identified as a list of categories provided by the clinical team. Other categories may be added as necessary or existing terms may be merged. An AstraZeneca medically qualified expert, after consultation with the Global Patient Safety Physician, has reviewed the AEs of interest and identified which PTs contribute to each AESI/AEPI. A further review will take place prior to DBL to ensure any further terms not already included are captured within the categories.

Immune-mediated Adverse Events (imAE)

Durvalumab belongs to a class of drugs called immune checkpoint inhibitors. Because the mechanism of action of this class of drugs is to block the inhibitory signals that prevent T-cell activation, this drug may potentially cause imAEs.

Immune-mediated adverse drug reactions will be identified from both AESIs and AEPIs based on programmatic rules that consider interventions involving systemic steroid therapy, immunosuppressant use, and/or endocrine therapy (which, in the case of AEPIs, occurs after first considering an Investigator's causality assessment and/or an Investigator's designation of an event as immune-mediated). Infusion-related reactions and hypersensitivity/anaphylactic reactions are not considered imAE because they are common to monoclonal antibody drugs in general and occur due to a mechanism of action different than that for imAEs as defined in the imAE charter. Further details are provided in the imAE charter.

In addition, medical review of those AESI/AEPI may be performed to classify them as imAEs or not imAEs via an independent manual adjudication process. This process is in addition to the Investigator assessment of imAEs as recorded in the eCRF.

3.3.4 Laboratory Data

Laboratory data will be collected throughout the study, from second screening to the second follow-up visit (12 weeks ± 1 week after completion or discontinuation of study treatment ie, durvalumab/placebo and/or SoC). Blood and urine samples for determination of hematology, clinical chemistry, and urinalysis will be collected as described in Section 8.2.1 of the CSP. For the definition of baseline and the derivation of post-baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 4.1.2 will be used.

Change from baseline in hematology and clinical chemistry variables will be calculated for each postdose visit on-treatment. Common Terminology Criteria for Adverse Event (CTCAE) grades will be defined at each visit according to the CTCAE grade criteria using local or project ranges as required, after conversion of lab result to corresponding SI units. The following parameters have CTCAE grades defined for both high and low values: Hemoglobin, Leukocytes, Lymphocytes, Potassium, Sodium, Magnesium, and Corrected calcium.

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

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

Creatinine clearance (CL) will be derived according to the Cockroft-Gault formula (Cockcroft and Gault 1976).

Males:

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

Females:

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

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or on limits of range) and high (above range).

The maximum or minimum on-treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-baseline value at any time.

Local reference ranges will be used for the primary interpretation of laboratory data at the local laboratory. Project reference ranges will be used throughout for reporting purposes. The denominator used in laboratory summaries of CTCAE grades will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a baseline and at least 1 post-baseline (scheduled or unscheduled) value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have at least 1 post-baseline (scheduled or unscheduled) value recorded.

3.3.5 Electrocardiograms

Resting 12-lead ECGs will be recorded at second screening and as clinically indicated throughout the study. Overall evaluation of ECG is collected in terms of normal or abnormal,

and the relevance of the abnormality is termed as 'clinically significant' or 'not clinically significant'. Triplicate ECGs will be obtained in case of clinically significant ECG abnormalities.

At each time point the Investigator's assessment of the ECG will be collected locally. Heart rate, duration of QRS complex, RR, PR and QT intervals will be collected.

3.3.6 Vital Signs

Vital signs data will be collected throughout the study, from second screening to the first follow-up visit (4 weeks ± 3 days after completion or discontinuation of study treatment, ie, durvalumab/placebo and/or SoC).

3.4 Exploratory Variables

No analyses will be performed on exploratory variables as part of this SAP. All data will be either summarized or listed only.

3.4.1 CCI

3.4.1.1 CCI

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3.4.1.2 CCI

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3.4.2 CCI

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3.4.2.1 CCI

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3.4.2.2 CCI

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3.4.2.3 CCI

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3.4.2.4 CCI

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[redacted]

[redacted]

CCI [redacted]

4 ANALYSIS METHODS

Prior to CSP V4.0, a formal statistical analysis was to be performed to test the main hypotheses:

- H0: No difference between durvalumab plus SoC chemotherapy and placebo plus SoC chemotherapy
- H1: Difference between durvalumab plus SoC chemotherapy and placebo plus SoC chemotherapy

Under CSP V4.0 no formal statistical analyses will be performed, and all analyses will be exploratory.

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, and will be presented by treatment group. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. For log transformed data it is more appropriate to present geometric mean, CV, median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group. Overall totals will be calculated for baseline summaries only.
- For continuous data, the mean, median and quartiles 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.
- For efficacy analysis summaries, hazard ratios will be rounded to 2 decimal places. CIs will be rounded to 3 decimal places. P-values will be rounded to 3 decimal places, except p-values less than 0.0005 (eg, 0.0002) which will be displayed as <0.001. P-values output as <0.0001 by statistical software will not be rounded and displayed in the same way (‘<0.0001’).

- SAS® version 9.4 or later will be used for all analyses.

4.1.1 Baseline

In general, for efficacy and PRO endpoints the last observed measurement prior to randomization will be considered the baseline measurement. However, for PRO endpoints, if an evaluable assessment is only available after randomization but before the first dose of study treatment (ie, durvalumab/placebo and/or SoC) then this assessment will be used as baseline.

For safety endpoints the last observation before the first dose of study treatment will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal predose 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 predose 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.

If two visits are equally eligible to assess patient status at baseline (eg, screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average can be taken as a baseline value. For non-numeric laboratory tests (ie, some of the urinalysis parameters) where taking an average is not possible 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 treatment.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value – baseline value) / baseline value × 100.

4.1.2 General Considerations for Safety and PRO Assessments

Time windows will be defined for any safety and PRO presentations that summarize values by visit. The following conventions will apply:

- The time windows will be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window will be based on the actual date and not the intended date of the visit.
- All unscheduled visit data 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 2 visits (the lower limit of the first post-baseline visit will be day 2). If an even number of days exists between 2 consecutive

visits then the upper limit will be taken as the midpoint value minus 1 day. An example is provided in Appendix A.

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on-treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- For visit-based summaries
  - If there is more than one value per patient within a time window then the closest value to the scheduled visit date will be summarized, or the earlier, in the event the values are equidistant from the nominal visit date. If there are two values recorded on the same day and CTCAE grades are available then the record with the highest toxicity grade should be used. Alternatively, if there are two records recorded on the same day and the toxicity grade is the same (or is not calculated for the parameter) then the average of the two records should be used. The listings will highlight the value for the patient that contributed to the summary table, wherever feasible. Note: in summaries of extreme values 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.
- For summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a patient level statistic such as a maximum.

Imputation Rules

Missing safety data will generally not be imputed. However, safety assessment values of the form of '< x' (ie, below the lower limit of quantification) or '> x' (ie, above the upper limit of quantification) will be imputed as 'x' in the calculation of summary statistics but displayed as '< x' or '> x' in the listings. Additionally, AEs that have missing causality (after data querying) will be assumed to be related to durvalumab/placebo, or SoC (whichever is missing).

Partial dates will be imputed for prior cancer therapy, previous radiotherapy, and prior and concomitant medications and AEs, as well as for other modules, where required, and only for patients exposed to treatment.

The original incomplete or missing dates will be presented in the listings.

All AEs will be considered as treatment-emergent unless the opposite can be clearly stated. Imputation will be done only in the context of identifying TEAEs.

All medications/therapies will be considered as concomitant unless the opposite can be clearly stated.

For the handling of partial date of birth and missing/partial start and/or stop dates of AEs, medications/therapies, deaths and subsequent anti-cancer therapies (including radiotherapy), refer to Appendix B.

4.2 Analysis Methods

The following table (Table 4) details the statistical analysis planned for each endpoint, making it clear which analysis is regarded as primary for that endpoint, where applicable. All endpoints compare durvalumab plus SoC chemotherapy vs placebo plus SoC chemotherapy in all randomized patients (FAS), unless stated otherwise.

Table 4 Statistical Analyses to be Conducted

Endpoints Analyzed	Notes
Disease-free survival (DFS)	Primary analysis using stratified log-rank test using Investigator assessments (RECIST 1.1) for the FAS
	Subgroup analysis using Cox proportional hazards model using Investigator assessments (RECIST 1.1) for the FAS
	Kaplan-Meier estimates of DFS rates at 6 and 12 months using Investigator assessments (RECIST 1.1) for the FAS and MRD+ analysis set
Overall survival (OS)	Secondary analysis using stratified log-rank test for the FAS
	Subgroup analysis using Cox proportional hazards model for the FAS
	Kaplan-Meier estimates of OS rates at 6 and 12 months for the FAS and MRD+ analysis set

DFS Disease-free survival; FAS Full analysis set; RECIST Response Evaluation Criteria in Solid Tumors

4.2.1 Multiplicity

Prior to CSP V4.0, in order to provide strong control of the type I error rate, α=5% (2-sided), a multiple testing procedure with gatekeeping strategy was to be used across the primary endpoint of DFS in the MRD+ analysis set, the secondary endpoint of DFS in the FAS, the secondary endpoint of OS in the MRD+ analysis set and the secondary endpoint of OS in the FAS.

Under CSP V4.0, no methods for multiplicity control will be performed and the analyses of all endpoints will be considered exploratory.

4.2.2 Disease-free Survival (DFS)

4.2.2.1 Primary Analysis of DFS

Disease-free survival, using Investigator assessment according to RECIST 1.1, will be analyzed using the log-rank test stratified by disease stage (stage II vs III), PD-L1 TC expression (< 1% vs ≥ 1%) and MRD status (MRD+ vs MRD-) on the FAS.

The treatment effect will be estimated in terms of the HR and its associated 95% CI from a Cox proportional hazards model (Cox 1972) (with ties = Efron) stratified by disease stage, PD-L1 TC expression and MRD status and the CI calculated using a profile likelihood approach.

The stratification factor covariates in the statistical modelling will be based on the values entered into IWRS at randomization, even if it is subsequently discovered that these values were incorrect. A sensitivity analysis may be performed based on the values entered in the eCRF if more than 10% of randomized patients have discrepancies in stratification factors between IWRS and eCRF data.

For the purpose of statistical analysis of the primary and relevant secondary endpoints, a plan for collapsing levels of stratum will be agreed upon, in case there are insufficient events in one level of any strata.

Supportive Summaries/Graphs

Kaplan-Meier plots of DFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a DFS event will be provided along with median time to DFS with 95% CI for each treatment group estimated based on the Kaplan-Meier curves. The CIs for median DFS will be derived based on Brookmeyer-Crowley method with a log-log transformation.

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of complementary log-log (event times) vs log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect can be described by presenting piecewise HR calculated over distinct time periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of treatment-by-covariate interactions, which will be investigated. In addition, the Kaplan-Meier curve along with landmark analyses (eg, 1-year DFS rate) will also help in understanding the treatment benefit. In the presence of non-proportional hazards, a rank-based Max-Combo test will be performed. The Max-Combo test is robust to different scenarios of non-proportional hazards.

The location of the disease recurrence (local/regional, distant or second primary NSCLC) will be summarized by treatment group.

The DFS rates at month 6 (DFS-6) and month 12 (DFS-12) will be estimated based on the Kaplan-Meier curves along with their 95% CIs and presented by treatment group.

The treatment status of patients at disease recurrence will be summarized. This will include the number (%) of patients who were on treatment at the time of disease recurrence, the number (%) of patients who have completed study treatment prior to disease recurrence, the number (%) of patients who discontinued study treatment prior to disease recurrence, the number (%) of patients who have not had disease recurrence and were on treatment, have completed treatment, or discontinued treatment. A distribution of the number of days prior to disease recurrence will also be provided for the patients who have discontinued treatment.

The number of patients prematurely censored will be summarized by treatment group. A patient would be defined as prematurely censored if they have not had disease recurrence or died and the latest scan prior to DCO was more than one scheduled tumor assessment interval plus 2 weeks (14 weeks) prior to the DCO date.

Additionally, summary statistics will be presented for the number of days from censoring to DCO for all censored patients. A summary of the duration of follow-up will be summarized using median time from randomization to date of censoring (date last known to have not had disease recurrence or died) in censored patients only (patients who have not had disease recurrence or died), presented by treatment group.

Additionally, summary statistics for the number of weeks between the time of disease recurrence and the last RECIST assessment prior to disease recurrence will be presented for each treatment group.

Summaries of the number and percentage of patients who miss two or more consecutive RECIST assessments will be presented for each treatment group.

All the collected RECIST 1.1 data will be listed for all randomized patients. In addition, a summary of disease recurrence (ie, sites of recurrence) will be produced.

A summary table of first subsequent cancer therapies relative to recurrence by treatment group will be provided.

4.2.2.2 Subgroup Analyses

4.2.2.2.1 Graphical Approaches

Subgroup analyses may be conducted on the FAS comparing DFS, using Investigator assessments according to RECIST 1.1, between durvalumab plus SoC chemotherapy vs placebo plus SoC chemotherapy in the following subgroups (but not limited to):

- PD-L1 status (TC < 1% vs ≥ 1%)
- PD-L1 status (TC < 25% vs ≥ 25%)
- TMB (high vs low)
- Histology (squamous vs non-squamous)
- Sex (male vs female)
- Age at randomization (< 65 vs ≥ 65)
- Smoking status (smoker [current or former smoker] vs non-smoker [never smoked])
- Race (Asian vs non-Asian)

The subgroup analyses for the stratification factors will be based on the values recorded in the eCRF. Should the value not have been captured in the eCRF the value entered into the IWRS will be used.

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment groups. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors. If a baseline imbalance is observed between treatment groups, an ad-hoc subgroup analysis may be used to investigate any potential for impact on the main results.

No adjustment to the significance level for subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of DFS.

Additionally, for each subgroup level of a factor, the HR (durvalumab plus SoC chemotherapy : placebo plus SoC chemotherapy) and 95% CI will be calculated from a Cox proportional hazards model that only contains a term for treatment. The Cox models will be fitted using SAS® PROC PHREG with the Efron method to control for ties, and using a BY statement for the subgroup factor. These HRs and associated two-sided 95% profile likelihood CIs will be summarized and presented on a forest plot, along with the results of the overall primary analysis.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and DFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

4.2.2.3 Secondary Analysis of DFS

Disease-free survival, using Investigator assessment according to RECIST 1.1, will be presented for the MRD+ analysis set as described below.

Kaplan-Meier plots of DFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a DFS event will be provided along with median time to DFS with 95% CI for each treatment group estimated based on the Kaplan-Meier curves. Additionally, the DFS rates at month 6 (DFS-6) and month 12 (DFS-12) will be estimated based on the Kaplan Meier curves along with their 95% CIs and presented by treatment group.

4.2.3 Overall Survival (OS)

Overall survival will be analyzed for the FAS using a stratified log-rank test, using the same methodology as described for the primary DFS endpoint. The effect of treatment will be estimated by the HR together with its corresponding 95% CI from a Cox proportional hazards model.

For both the FAS and MRD+ analysis set, Kaplan-Meier plots of OS will be presented by treatment group. The OS rates at month 6 (OS-6) and month 12 (OS-12) will be estimated based on the Kaplan-Meier curves along with their 95% CIs and presented by treatment group. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median time to OS and corresponding 95% CI for each treatment.

4.2.4 CCI [redacted]

4.2.5 CCI [redacted]

4.2.6 Data Cut-offs

All randomized patients will be followed until the primary DCO when no further visits will occur. This will be followed by DBL and then the primary DFS analysis. The study will then be concluded.

Details regarding the approach used for removing post-DCO data from SAS datasets can be found in the AstraZeneca Oncology Guidance on Data Cut-off Processing and Clean file/ DBL Considerations document as well as the DCO Specifications for this study.

4.2.7 CCI

CCI

CCI

CCI

CCI

CCI

[redacted]

4.2.8 Safety

Safety and tolerability data from all cycles of treatment will be combined. The safety analysis set will be used for reporting of safety according to actual treatment group as defined in Section 2.1.3. Safety summaries will be descriptive only. No formal statistical analyses will be performed on the safety variables.

4.2.8.1 Adverse Events (AEs)

All AEs, both in terms of current MedDRA PT and CTCAE grade, will be summarized descriptively by count (n) and percentage (%) for each treatment group. Any AE occurring before study treatment (ie, before the administration of the first dose of durvalumab/placebo and/or SoC) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'. However, any AE occurring before the administration of the first dose of study treatment on study day 1 that increases in severity after the first dose will be regarded as treatment emergent and thus will be included in the majority of summary tables.

Adverse events observed up until 90 days following discontinuation of study treatment (ie, the last dose of durvalumab/placebo and/or SoC) or until the initiation of the first subsequent anti-cancer therapy (including radiotherapy, except for palliative radiotherapy) following discontinuation of study treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only, as a number of AEs up to 90 days following discontinuation of study treatment are likely to be attributable to subsequent therapy.

Any AEs that occur between the start of subsequent anti-cancer therapy and up until 90 days following discontinuation of study treatment will be flagged in the data listings.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved) and Investigator's assessment of severity and relationship to durvalumab/placebo or SoC. Frequencies and percentages of patients reporting each PT will be presented (ie, multiple events per patient will not be accounted for apart from on the episode level summaries).

Summary information (the number and percentage of patients by SOC and PT separated by treatment group) will be tabulated for:

- All AEs
- All AEs possibly related to durvalumab/placebo only (as determined by the reporting Investigator)

- All AEs possibly related to SoC only (as determined by the reporting Investigator)
- All AEs possibly related to durvalumab/placebo or SoC (as determined by the reporting Investigator)
- AEs with maximum CTCAE grade 3 or 4
- AEs with maximum CTCAE grade 3 or 4, possibly related to durvalumab/placebo only (as determined by the reporting Investigator)
- AEs with maximum CTCAE grade 3 or 4, possibly related to SoC only (as determined by the reporting Investigator)
- AEs with maximum CTCAE grade 3 or 4, possibly related to durvalumab/placebo or SoC (as determined by the reporting Investigator)
- AEs with outcome of death
- AEs with outcome of death possibly related to durvalumab/placebo only (as determined by the reporting Investigator)
- AEs with outcome of death possibly related to SoC only (as determined by the reporting Investigator)
- AEs with outcome of death possibly related to durvalumab/placebo or SoC (as determined by the reporting Investigator)
- All SAEs
- All SAEs possibly related to durvalumab/placebo only (as determined by the reporting Investigator)
- All SAEs possibly related to SoC only (as determined by the reporting Investigator)
- All SAEs possibly related to durvalumab/placebo or SoC (as determined by the reporting Investigator)
- AEs leading to discontinuation of durvalumab/placebo only
- AEs leading to discontinuation of SoC only
- AEs leading to discontinuation of durvalumab/placebo or SoC
- AEs leading to discontinuation of durvalumab/placebo only, possibly related to durvalumab/placebo only (as determined by the reporting Investigator)
- AEs leading to discontinuation of SoC only, possibly related to SoC only (as determined by the reporting Investigator)
- AEs leading to discontinuation of durvalumab/placebo or SoC, possibly related to durvalumab/placebo or SoC (as determined by the reporting Investigator)
- AEs leading to dose interruption of durvalumab/placebo only
- AEs leading to dose interruption of SoC only
- AEs leading to dose interruption of durvalumab/placebo or SoC

- Immune mediated AEs (as determined by the reporting Investigator)
- Infusion reaction AEs (as determined by the reporting Investigator)

An overall summary of the number and percentage of patients in each category will be presented, as well as an overall summary of the number of episodes in each category. Summaries of the number and percentage of patients with AEs will be provided by maximum reported CTCAE grade, SOC, PT and treatment group. In addition, a truncated AE table of most common AEs and another table showing most common AEs with CTCAE grade 3 or 4, showing all events that occur in at least 5% (ie, ≥ 5%) of patients overall will be summarized by PT, by decreasing frequency in the total column (the total column will not be displayed in the AE tables). This cut-off may be modified after review of the data. When applying a cut-off (ie, *x*%), the raw percentage should be compared to the cut-off, no rounding should be applied first (ie, an AE with frequency of 4.9% will not appear if a cut-off is 5%).

Fluctuations observed in CTCAE grades during study will be listed for those AEs which have CTCAE grade ≥ 3.

In addition, all AEs will be listed (including listings for AEs that required treatment with steroids, immunosuppressants, or endocrine treatment, grade changes for AEs of CTCAE grade ≥ 3, and grade changes for AEs of CTCAE grade ≥ 3 that required treatment with steroids, immunosuppressants, or endocrine treatment). Listings of key patient information for SAEs, and AEs leading to discontinuation of durvalumab/placebo or SoC will also be provided.

4.2.8.1.1 Deaths

Two summaries of all deaths will be provided with number and percentage of patients in the safety analysis set and FAS by treatment group, categorized as:

- Total number of deaths (regardless of date of death)
- Death related to disease under investigation only as determined by the Investigator
- Death related to disease under investigation and an AE with outcome of death
  (a) AE onset prior to subsequent anti-cancer therapy, defined as an AE with onset date (or pre-treatment AEs that increase in severity) on or after the date of first dose of study treatment and up to and including the earlier of 90 days following the date of last dose of study treatment or the date of initiation of the first subsequent anti-cancer therapy
  (b) AE onset after start of subsequent anti-cancer therapy, defined as an AE with onset date more than 90 days following the date of last dose of study treatment or after the date of initiation of the first subsequent anti-cancer therapy (whichever occurs first)

- AE with outcome of death only
  (a) AE onset prior to subsequent anti-cancer therapy, defined as an AE with onset date (or pre-treatment AEs that increase in severity) on or after the date of first dose of study treatment and up to and including the earlier of 90 days following the date of last dose of study treatment or the date of initiation of the first subsequent anti-cancer therapy
  (b) AE onset after start of subsequent anti-cancer therapy, defined as an AE with onset date more than 90 days following the date of last dose of study treatment or after the date of initiation of the first subsequent anti-cancer therapy (whichever occurs first)
- Death after end of safety follow-up period (last dose of study treatment [durvalumab/placebo and/or SoC] + 90 days) and not due to disease under investigation
- Unknown reason for death
- Other deaths

This summary will be repeated for all deaths on-treatment or within 90 days of last dose of study treatment. All deaths will be listed along with time from first and last dose, primary and secondary causes, and relationship to disease using the FAS.

4.2.8.2 AEs of Special Interest and Possible Interest

Preferred terms used to identify AESI/AEPI will be listed before DBL and documented in the Trial Master File. Grouped summary tables of certain MedDRA PTs will be produced and may also show the individual PTs which constitute each AESI grouping. Groupings will be based on PTs provided by the medical team prior to DBL, and a listing of the PTs in each grouping will be provided.

Summaries of the above-mentioned grouped AE categories will include number (%) of patients who have:

- Any AESI/AEPI
- Any AESI/AEPI by SOC, PT and maximum CTCAE grade
- Any AESI/AEPI of maximum CTCAE grade 3 or 4
- Any serious AESI/AEPI
- Any AESI/AEPI with outcome of death
- Any AESI/AEPI possibly related to study treatment (durvalumab/placebo or SoC)
- Any AESI/AEPI leading to concomitant medication use (high dose steroids)
- Any AESI/AEPI leading to concomitant medication use (endocrine therapy)
- Any AESI/AEPI leading to concomitant medication use (other immunosuppressants)

An overall AESI/AEPI summary will be presented, including number and percentage of patients in each of these categories. Any AESI/AEPI presented by outcome will also be provided.

In addition, a listing of key patient information for AESI/AEPI will be provided.

Immune-mediated Adverse events (imAEs)

The imAEs (as classified by the Sponsor) will be summarized in the similar manner as for the summaries for AESI/AEPI described above. Time to onset and resolution of imAE will also be summarized. Further details are covered in the latest version of the imAE charter.

4.2.8.3 Laboratory Assessments

Data obtained up until the 90 days following discontinuation of study treatment (ie, durvalumab/placebo and/or SoC) or until the initiation of subsequent anti-cancer therapy (including radiotherapy, except for palliative radiotherapy) following discontinuation of study treatment (whichever occurs first) will be used for reporting. This will more accurately depict laboratory toxicities attributable to study treatment only as some toxicities up to 90 days following discontinuation of the study treatment are likely to be attributable to subsequent therapy. Any data post 90 days after the last dose of the study treatment will not be summarized.

Data summaries will be provided in SI units.

Shift tables for laboratory values by worst CTCAE grade will be produced, and for specific parameters separate shift tables indicating hyper- and hypo- directionality of change will be produced. The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- Hematology: Hemoglobin (low and high); Leukocytes (low and high); Lymphocytes (low and high - count, absolute); Neutrophils (low - count, absolute); Platelets (low)
- Clinical chemistry: ALT (high), AST (high), ALP (high), Total Bilirubin (high), Albumin (low), Magnesium (hypo and hyper), Sodium (hypo and hyper), Potassium (hypo and hyper), Corrected Calcium (hypo and hyper), Glucose (low), Creatinine (high), GGT (high), Amylase (high), Lipase (high).

In addition, all laboratory data will be listed.

4.2.8.3.1 Liver Enzyme Elevations and Hy's Law

The following summaries will include the number (%) of patients who have:

- Elevated ALT, AST, and Total bilirubin on-treatment
  - ALT ≥ 3× – ≤ 5×, > 5× – ≤ 8×, > 8× – ≤ 10×, > 10× – ≤ 20×, and > 20× ULN on-treatment
  - AST ≥ 3× – ≤ 5×, > 5× – ≤ 8×, > 8× – ≤ 10×, > 10× – ≤ 20×, and > 20× ULN on-treatment
  - Total bilirubin ≥ 2× – ≤ 3×, > 3× – ≤ 5×, > 5× ULN on-treatment
  - ALT or AST ≥ 3× – ≤ 5×, > 5× – ≤ 8×, > 8× – ≤ 10×, > 10× – ≤ 20×, > 20× ULN on-treatment
  - ALT or AST ≥ 3× ULN and Total bilirubin ≥ 2× ULN on-treatment (Potential Hy's law): The onset date of ALT or AST elevation should be prior to or on the date of Total Bilirubin elevation

Individual patient data where ALT or AST (ie, ≥ 3× ULN) plus Total Bilirubin (ie, ≥ 2× ULN) are elevated at any time will be listed also.

4.2.8.3.2 Assessment of Thyroid Function Test Results

The following summaries will include the number and percentage of patients who have elevated or low thyroid stimulating hormone (TSH).

- TSH > ULN
- TSH > ULN with TSH ≤ ULN at baseline
- TSH > 3 × ULN
- TSH > 3 × ULN with TSH ≤ ULN at baseline
- TSH > 10 × ULN
- TSH > 10 × ULN with TSH ≤ ULN at baseline
- TSH < LLN
- TSH < LLN with TSH ≥ LLN at baseline

In addition, summaries will include shift tables comparing baseline value to maximum on-treatment value and baseline value to minimum on-treatment value. Thyroid function test data will be listed also.

4.2.8.3.3 Assessment of Renal Function Test Abnormalities

In addition to the analysis for serum creatinine, the number and percentage of patients with worst CrCl rate on-treatment (derived per Section 3.3.4) meeting the following categories will be presented:

- Normal: CrCl ≥ 90 mL/min
- Mild Impairment: CrCl ≥ 60 - < 90 mL/min
- Moderate Impairment: CrCl ≥ 30 - < 60 mL/min
- Severe Impairment: CrCl ≥ 15 - < 30 mL/min
- Kidney Failure: CrCl < 15 mL/min

4.2.8.4 Electrocardiograms

Since ECGs are only collected as clinically indicated, abnormalities in ECG data obtained at any time during the study will be listed only. No summaries will be produced.

4.2.8.5 Vital Signs

All vital signs data (SBP, DBP, pulse rate, temperature, respiratory rate and weight) will be listed only. No summaries will be produced.

4.2.8.6 Other safety

Listings will be provided for pregnancy reports and medication error reports occurring throughout the study.

4.2.9 Demographics and Baseline Characteristics

The following will be summarized for all patients in the FAS and MRD+ analysis set (unless otherwise specified) by treatment group:

- Patient disposition (all patients, including screening failures [split by whether or not ICF2 was signed] and reason for screening failure)
- Important protocol deviations
- Inclusion in analysis sets (all patients only)
- Demographics (age, age group [< 50, ≥ 50 - < 65, ≥ 65 - < 75 and ≥ 75 years], sex, race and ethnicity)
- Patient characteristics at baseline (height, weight, weight group [< 70, 70-90, > 90 kg], BMI, BMI group [< 18.5, ≥ 18.5 - < 25, ≥ 25 - < 30, ≥ 30 kg/m^2])
- Patient recruitment by region, country and center
- Previous disease-related treatment modalities (chemotherapy and radiation therapy)
- Disease characteristics at baseline (ECOG performance status, primary tumor location, histology type [squamous, non-squamous, other], tumor grade, extent of resection, pleural invasion status, surgical methods, and overall disease classification)
- Extent of disease at baseline
- Pathological TNM classification post-surgery

- Disease related medical history (past and current) (FAS only)
- Relevant surgical history (FAS only)
- Nicotine use, categorized (non-smoker [never], smoker [current, former])
- Stratification factors as per IWRS and eCRF

The data mentioned above will also be presented in listings. Additionally, a listing of EGFR/ALK results will also be provided.

4.2.10 Concomitant and Other Treatments

Information on any medications or therapies from first screening to 90 days after the last dose of study treatment (ie, durvalumab/placebo and/or SoC) will be recorded in the eCRF. Thereafter, only subsequent regimens of anti-cancer therapy will be recorded in the eCRF.

Other anti-cancer therapies, investigational agents, and radiotherapy should not be given once the patient has had their surgical resection and while they are randomized and on study drug. The only exception is for PORT.

Medications received prior to, concomitantly, or post-study treatment will be coded using the WHODD ATC classification codes. Concomitant medications/therapies will be summarized for the FAS by ATC classification codes.

For the purpose of inclusion in prior and/or concomitant medication or therapy summaries, incomplete medication or radiotherapy start and stop dates will be imputed as detailed in Section 4.1.2.

Prior, concomitant and post-study treatment medications and therapies are defined based on imputed start and stop dates as follows:

- Prior medications/therapies are those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant medications/therapies are those that started prior to study treatment and are ongoing at the first dose date of study treatment, or that started on or after the first dose date of study treatment but on or before the last dose date of study treatment.
- Post-study treatment medications/therapies are those with a start date after the last dose date of study treatment.

In addition, all post-treatment anti-cancer medications and surgical procedures will be summarized for the FAS and MRD+ analysis set.

The following summaries will be produced for the FAS (unless otherwise specified):

- Summary of allowed concomitant medications
- Summary of disallowed concomitant medications
- Summary of post-study treatment anti-cancer therapies (including radiotherapy) (FAS and MRD+ analysis set)
- Summary of PORT

All concomitant and other treatment data will be listed.

Missing coding terms should be listed and summarized as 'Not coded'.

4.2.11 Exposure

Exposure will be summarized for the safety analysis set. The following summaries will be produced by treatment group:

- Total exposure
- Actual exposure (durvalumab/placebo only)
- Number of, and reasons for, interruptions and delays of durvalumab/placebo
- Number of, and reasons for, delays and dose reductions/increases of chemotherapy
- Cumulative exposure over time for durvalumab/placebo
- Number of treatment cycles received
- RDI (durvalumab/placebo only)

Exposure of durvalumab/placebo over time will be plotted in a line graph. The plot will show percentage of patients still on treatment against time since first dose.

Details of study drug administration and dose intensity will also be provided in listings.

4.2.12 Coronavirus Disease 2019 (COVID-19)

Summaries of data relating to patients diagnosed with COVID-19 and the impact of COVID-19 on study conduct (eg, missed visits, delayed or discontinued study treatment [ie, durvalumab/placebo and/or SoC], and other protocol deviations) may be generated. In addition, DFS and OS sensitivity analyses may be performed by repeating the summaries and analyses except that any patient who had a death with primary/secondary cause as being COVID-19 related (including infection) will be censored at their COVID related death date. For AE and Deaths summaries of COVID-19 related events including infections and deaths maybe produced.

5 INTERIM ANALYSES

5.1 Interim Efficacy Analysis

Prior to CSP v4.0, one interim and one final analysis of OS was to be performed. Under CSP V4.0, there will be one analysis of OS at the time of the DFS (ie, primary DFS analysis) which will be the final analysis.

5.2 Independent Data Monitoring Committee

This study will use an external IDMC to assess ongoing safety analyses in an unblinded manner. The committee will first meet to review the safety data from the study from a DCO approximately 12 months after the first patient has been dosed with IP or after the first 50 patients have received at least 1 dose of IP (whichever occurs first). The frequency of subsequent reviews will be determined by the IDMC, but will be no more frequent than every 6 months.

This committee will be composed of therapeutic area experts and biostatisticians, who are not employed by AstraZeneca and are free from conflict of interest.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way based on the safety data that has been reviewed. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will include the recommendation and any potential protocol amendments, and will not contain any unblinding information.

The final decision to modify or stop the study will sit with the sponsor. The sponsor or IDMC may call additional meetings if at any time there is concern about the safety of the study.

Full details of the IDMC procedures and processes can be found in the IDMC Charter. The safety of all AstraZeneca/MedImmune clinical studies is closely monitored on an ongoing basis by AstraZeneca/MedImmune representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the CSP and letters to Investigators.

6 CHANGES OF ANALYSIS FROM PROTOCOL

The following are changes, additions or clarifications from the planned analyses described in version 4 of the CSP.

The secondary efficacy endpoints of DFS in MRD+ analysis set (using Investigator assessments according to RECIST 1.1) and OS in MRD+ analysis set will not be analyzed, only descriptive summaries will be provided.

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7 REFERENCES

CCI
CCI

Cockcroft and Gault 1976

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41.

Cox 1972

Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34(2):187-220.

CCI
CCI user guide: basic information on how to use the CCI
CCI version 3.0, September 2019. Available from: CCI

CCI

Litwin et al 1998

Litwin MS, Lubeck DP, Henning JM, Carroll PR. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: results of the CaPSURE database. J Urol 1998;159:1988-92.

Sprangers and Aaronson 1992

Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. J Clin Epidemiol 1992;45:743-60.

8 APPENDICES

APPENDIX A Visit Windows

For example, the visit windows for vital signs data (with 3 weeks between scheduled assessments during the first 4 cycles and 4 weeks between scheduled assessments during subsequent cycles) are:

- Day 22, visit window 2 – 32
- Day 43, visit window 33 – 53
- Day 64, visit window 54 – 74
- Day 85, visit window 75 – 98
- Day 113, visit window 99 – 126
- Day 141, visit window 127 – 154
- Day 169, visit window 155 – 182
- Day 197, visit window 183 – 210
- Day 225, visit window 211 – 238
- Day 253, visit window 239 – 266
- Day 281, visit window 267 – 294
- Day 309, visit window 295 – 322
- Day 337, visit window 323 – 350

Note: The same rules should be followed if a patient has more than 14 cycles due to delayed durvalumab/placebo. Also, due to the differing assessment schedules the visit windows will be different for the different endpoints.

APPENDIX B Missing/Partial Dates Imputation

Imputation of partial date of birth

Patients with a partial date of birth will have an assumed date of birth of 1st January [given year]) for calculation of age at randomization.

Imputation of partial start/end dates for AEs and medications/therapies

In practice, for AEs and medications/therapies, original incomplete or missing start dates will be imputed as below:

- Missing day: impute the 1st of the month unless month is same as month of first dose of study treatment (ie, durvalumab/placebo and/or SoC) then impute first dose date;
- Missing day and month: impute 1st January unless year is the same as year of first dose of study treatment (ie, durvalumab/placebo and/or SoC) then impute first dose date;
- Completely missing: impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

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

Original incomplete or missing stop dates for AEs and medications/therapies will be imputed as below:

- Missing day: impute the last day of the month unless month is same as month of last dose of study treatment (ie, durvalumab/placebo and/or SoC) then impute last dose date;
- Missing day and month: impute 31st December unless year is the same as year of last dose of study treatment (ie, durvalumab/placebo and/or SoC) then impute last dose date;
- Completely missing:
  - AE: since there is no ongoing flag recorded in eCRF, then assume that AE is still present (ie, do not impute a date);
  - Medication/therapy: if the ongoing flag is missing then assume that medication is still being taken (ie, do not impute a date). If the medication has stopped and start date of medication is prior to first dose of study treatment (ie, durvalumab/placebo and/or SoC) then impute the first dose date, if the medication started on or after first dose of study treatment (ie, durvalumab/placebo and/or SoC) then impute a date that is after the last dose date.

When imputing a stop date, ensure that the new imputed date is sensible ie, is after the start date of the AE or medication/therapy.

Duration of AEs or medications/therapies will not be derived using imputed dates.

Imputation of partial death dates

If a patient is known to have died where only a partial death date is available then the date of death will be imputed as the latest of the last date known to be alive + 1 day 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 ie, censored at the last known alive date.

Imputation of partial start dates of subsequent anti-cancer therapy (including radiotherapy)

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

If the imputed start date for a subsequent anti-cancer therapy (including radiotherapy) results in a start date that is not after the date of last dose of study treatment (ie, durvalumab/placebo and/or SoC), this will be flagged and discussed with the clinical team.

Other parameters

- No other imputation will be made.

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