AstraZeneca

Statistical Analysis Plan

Study Code	D910MC00001
Version Number	2.0
Date	14 March 2023

A Phase III, Randomized, Multicenter, Double-blind, Placebo-controlled Study of Durvalumab for the Treatment of Stage II-III NSCLC Patients with Minimal Residual Disease Following Surgery and Curative Intent Therapy (MERMAID-2)

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Study Statistician

PPD _____ _____
Date

A Phase III, Randomized, Multicenter, Double blind, Placebo controlled Study of Durvalumab for the Treatment of Stage II III NSCLC Patients with Minimal Residual Disease Following Surgery and Curative Intent Therapy (MERMAID 2)

Global Product Statistician

PPD _____ Date

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LIST OF ABBREVIATIONS

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
AZ SOL	AstraZeneca standard output library
BMI	Body mass index
CL	Clearance
COVID-19	Coronavirus Disease 2019
CrCl	Creatinine clearance
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumor DNA
DBL	Database lock
DBP	Diastolic blood pressure
DCO	Data cut-off
DFS	Disease-free survival
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor

Abbreviation or special term	Explanation
CCI	CCI
CCI	CCI
CCI	CCI
FAS	Full analysis set
GGT	Gamma-glutamyl transferase
HLT	Higher-level term
HRQoL	Health related quality of life
ICF1	Informed consent form 1
ICF2	Informed consent form 2
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
imAE	Immume-mediated adverse events
IP	Investigational product
IPD	Important protocol deviation
IV	Intravenous
IWRS	Interactive Web Response System
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRD	Minimal residual disease
MRD+	MRD-positive
MRD-	MRD-negative
MTP	Multiple testing procedure
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable

Abbreviation or special term	Explanation
NED	No evidence of diseases
NL	New lesion
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD	Progression of disease
PD-L1	Programmed cell death ligand 1
PFS	Progression free survival
CCI	CCI
CCI	CCI
PORT	Post-operative radiotherapy
CCI	CCI
CCI	CCI
PT	Preferred term
q4w	Every 4 weeks
q6w	Every 6 weeks
q12w	Every 12 weeks
CCI	CCI
CCI	CCI
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
SI	International System of Units

Abbreviation or special term	Explanation
SoC	Standard of Care
SOC	System organ class
TC	Tumour cell
TEAE	Treatment-emergent adverse event
CCI	CCI
TMB	Tumour mutational burden
TSH	Thyroid stimulating hormone
CCI	CCI
ULN	Upper limit of normal
VAF	Variant allele frequencies
VAS	Visual analogue scale
WHODD	World Health Organization drug dictionary

AMENDMENT HISTORY

Date	Brief description of change
V1.0 (25Feb2021)	NA – first version
V2.0 (14Mar2023)	Updated to reflect CSP V2.0, including changes to primary, secondary and exploratory objectives. Updated the planned analyses throughout the document (All analyses of the objectives and endpoints are now descriptive only and considered exploratory.) Removed any references to blinded independent central review endpoints and analyses throughout the document. Throughout the document, when both PD-L1 TC≥1% analysis set and FAS are mentioned, the order has been changed such that the FAS is mentioned first and thereafter the PD-L1 TC≥1% analysis set, to align with the revised primary endpoint as per CSP V2.0. Section 2.1 – Table 1 updated as per CSP V2.0. Section 2.2 – removed 'deviation bias' sensitivity analysis. CCI Section 4 – in alignment with CSP V2.0, clarified that no formal statistical analyses will be performed. Section 4.1 – revised decimal places for continuous data as per AZSOL general principles. Section 4.2 – general wording and Table 5 revised in line with changes to objectives. Section 4.2.1 – removed methods for multiplicity. Section 4.2.2 – removed some supportive summaries/graphs, sensitivity and secondary analyses of Disease-free survival. Section 4.2.2.1 • removed summary of treatment status of patients at disease recurrence. • removed summary of patients prematurely censored. • removed summary of number of weeks between the time of disease recurrence and the last RECIST assessment. • removed summary of patients who miss two or more consecutive RECIST assessments. Section 4.2.2.2 – removed subgroup analyses. Section 4.2.3 – revised Overall survival description to be listed only.

Date	Brief description of change
	Section 4.2.4 – revised Progression-free survival description to be listed only. Section 4.2.5 – revised time to first and second subsequent therapy or death description to be listed only. Section 4.2.6 – Data Cut-Offs revised as per CSP V2.0. CCI [redacted] • CCI [redacted] • CCI [redacted] CCI [redacted] Section 4.2.9 • removed section on summary of long term tolerability. • revised wording for AE with outcome of death, as per AZSOL. Section 4.2.9.1 • removed summaries for time to onset and duration of the first AE, event rate, and longer-term toxicity profile. • replaced summary table on "most common AEs with CTCAE grade 3 or 4" with summary table on "most common AEs with maximum CTCAE grade 3 or 4". • summary for death limited to all deaths on the FAS. Section 4.2.9.2 – removed AESI/AEPI summaries leading to steroid use, discontinuation of study treatment and dose delay of study treatment. Section 4.2.9.3 • removed all graphical presentations of laboratory data, as well as summaries of absolute value and change from baseline in hematology and chemistry, and urinalysis shift table. • Thyroid function tests: removed summaries on elevated on-treatment TSH. Added shift tables to maximum and minimum on-treatment. • Renal function tests: removed summaries of CrCl reversibility. Section 4.2.9.4 – revised electrocardiograms description to be listed only. Section 4.2.9.5 – revised vital signs description to be listed only. Section 4.2.11 – added a summary of subsequent anti-cancer therapy. Section 4.2.13 – removed sensitivity analyses. Section 4.4 – Observation period removed as per CSP V2.0. Section 5.1 – aligned with CSP V2.0, no interim analyses are planned. Section 5.2 – added provision of a final safety report post-DBL. Section 6 – updated to include reference to the CSP amendment.

Date	Brief description of change
	Section 7 – removed references no longer used in this document due to updates as listed above. Appendix B – revised imputation for completely missing medication/therapy end dates, partial death dates. Minor formatting changes throughout. AZ Global Product Statistician signatory updated.

1. STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the clinical study protocol (CSP) version 2.0, dated 02 August 2022, and on version 2.0 of the Protocol Deviations Plan, dated 12 May 2021. Any changes to any specifications in the CSP will be described in Section 6 of this document.

Prior to CSP V2.0, the primary objective of this study was to compare the efficacy of durvalumab to placebo in terms of DFS in the PD-L1 TC≥1% analysis set. A secondary objective was to compare the efficacy of durvalumab to placebo in terms of DFS in the FAS. The study was sized for the primary endpoint of DFS in the PD-L1 TC≥1% analysis set and for the secondary endpoint of DFS in the FAS.

Following changes in the treatment landscape and the approvals of neoadjuvant and adjuvant immunotherapy options for patients with resectable NSCLC, AstraZeneca decided to close recruitment to MERMAID-2 on May 25, 2022. 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. In addition, one Phase III clinical study (Checkmate816) has reported positive results for nivolumab (anti-PD-1 immunotherapy) in the neoadjuvant setting.

Under CSP V2.0 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 assess DFS in both treatment arms in the FAS rather than in the PD-L1 TC≥1% analysis set. The secondary objective is now to report the safety in both treatment arms. All analyses of the objectives and endpoints are descriptive only and considered exploratory, therefore there will be no requirement to include a multiple testing procedure to control the type I error rate.

1.1 Study Objectives

1.1.1 Primary Objective

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

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

1.1.2 Secondary Objectives

Secondary/Safety objective:	Endpoint/variables:
To assess the safety and tolerability profile of durvalumab monotherapy compared to placebo	AEs, physical examinations, vital signs, and laboratory findings

AE Adverse event.

1.1.3 CCI

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[redacted]

1.2 Study Design

This is a Phase III, randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and safety of durvalumab adjuvant therapy compared to placebo in patients with stage II-III non-small cell lung cancer (NSCLC) who have undergone curative intent therapy (complete resection ± neoadjuvant and/or adjuvant therapy), who have no evidence of RECIST 1.1- defined disease recurrence, and who become minimal residual disease-positive (MRD+) during a 96-week surveillance period.

Prior to CSP V2.0, the study was designed to screen approximately [redacted] patients and randomize approximately [redacted] MRD+ patients with stage II-III NSCLC whose tumors are epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild type,

and who have completed curative intent therapy. Randomized patients were to include approximately CCI PD-L1 TC≥1% and CCI PD-L1 TC<1% patients.

Following the decision to close recruitment early, a total of 416 patients have signed informed consent for the study and approximately 30 are expected to be randomized within the study.

Eligible patients will be enrolled in a 96-week surveillance period during which they will be monitored for the emergence of MRD. During surveillance, the patient will be evaluated for MRD by plasma sampling every 6 weeks (q6w±3d) and will receive computed tomography (CT) scans every 12 weeks (q12w±1w) for up to 96 weeks.

Patients who become MRD+ during surveillance (including cases where analysis of the first plasma sample collected [marking the start of surveillance] returns an MRD+ status) will undergo a second screening period. Note: Patients who received prior neoadjuvant immunotherapy must be MRD- based on analysis of the first plasma sample collected (which marks the start of surveillance).

MRD+ patients will be randomized 1:1 to treatment with durvalumab monotherapy 1500 mg or placebo every 4 weeks (q4w) intravenously (IV). Randomization will be stratified by PD-L1 status (TC<1% vs TC≥1%), time from start of surveillance to emergence of MRD (≤6 months vs >6 months), and prior neoadjuvant immunotherapy (Yes vs No).

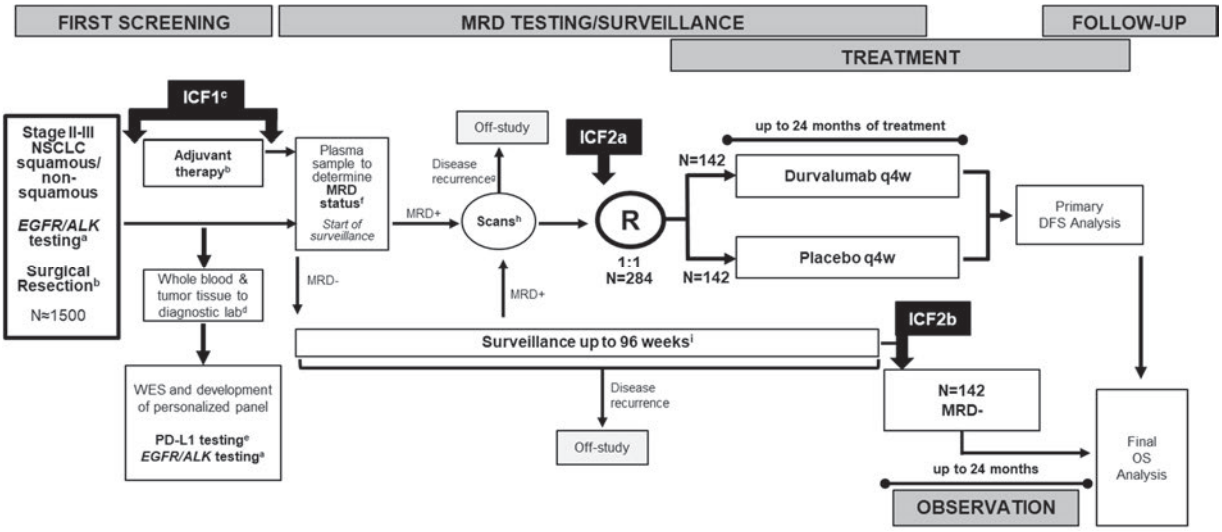
Patients will be treated for up to a total of 24 months (26 cycles), until disease recurrence, or until other specific treatment discontinuation criteria are met (whichever comes first).

Up to 142 of the patients who complete their 96-week surveillance period, remain MRD-, and have no evidence of RECIST 1.1-defined disease recurrence may be eligible for entry into an observation period. These patients will be followed for serious adverse events (SAEs), disease-free survival (DFS), overall survival (OS), subsequent anti-cancer therapy, and MRD assessments for 24 months or until primary DFS analysis (whichever occurs first) after which patients will be followed for OS until the end of the study. For an overview of the original study design described above, see Figure 1, in the CSP. [Note: following implementation of CSP V2.0 no patients will enter the observation period.]

On 25 May 2022, AstraZeneca closed study recruitment. This was based on changes in the treatment landscape as outlined in Section 10.1 of the CSP. At the time of CSP V2.0 implementation at site, patients in first screening for surveillance and randomized patients in study specific follow-up (i.e. who are not actively receiving study treatment) will be discontinued from the study. Patients in second screening (signed ICF2a but not yet randomized) and patients currently receiving study treatment will have the option to receive open-label durvalumab. Given the current disposition of patients within the study, it is

expected that the majority of patients will be discontinued from the study. For an overview of the original study design, see Figure 1.

Figure 1 Original Study Design



[a] Results from local *EGFR/ALK* testing of either a pre-surgery biopsy or the resected tumor tissue performed as part of standard care may be used for this study, provided testing was performed using a well-validated, local regulatory-approved kit. *EGFR/ALK* status can also be assessed by the central laboratory using either a pre-surgical biopsy or on resected tumor tissue from surgery if local testing is not available. Patients whose tumors are positive for *EGFR* mutations and/or *ALK* translocations will be excluded from the study. Only patients with wild-type status should provide a plasma sample for MRD assessment at the start of surveillance (see footnote f).

[b] Patients will receive curative intent therapy (complete resection ± neoadjuvant and/or adjuvant therapy) as SoC within the clinics. Details of surgery and prior therapy will be captured in the appropriate section of the eCRF and will be included as a subgroup analysis. Please note that PORT can be included as part of adjuvant therapy and must be completed before starting surveillance. See CSP Figure 2 for potential scenarios for permissible curative therapy in this study.

[c] ICF1 can be signed during or immediately following the completion of curative intent therapy and should be signed as soon as possible to allow the Sponsor access to the biosamples required for creation of the personalized panel for MRD detection (see footnote d) and for central testing of *EGFR/ALK* and/or PD-L1 (if required, see footnotes a and e).

[d] The whole blood and resected tumor tissue samples must be sent as soon as possible after ICF1 is signed but no later than 1-2 weeks after completion of adjuvant therapy or 3-5 weeks after surgery (if no adjuvant therapy is given) to enable creation of the personalized panel for MRD detection.

[e] PD-L1 status must be known prior to and is required for randomization.

[f] Surveillance is initiated once the first plasma sample used to determine MRD status is **collected** (approximately 8±1 weeks after completion of adjuvant therapy or up to 12±1 weeks post-surgery [if no adjuvant therapy is given; See CSP Figure 2).

[g] If scans conducted during the first screening or during surveillance demonstrates evidence of RECIST 1.1-defined disease recurrence and/or metastatic disease, the patient is considered a screen failure and is no longer eligible to participate in the study

[h] Before an MRD+ patient can be randomized, a CT scan of the chest and abdomen (including liver and adrenal glands) and a brain MRI (preferred) or brain CT with IV contrast must be performed to confirm no evidence of disease recurrence and/or metastatic disease.

[i] During surveillance, patient visits will occur q6w±3d for plasma collection and q12w±1w for CT scans.

ALK Anaplastic lymphoma kinase; DFS Disease-free survival; EGFR Epidermal growth factor receptor; ICF Informed consent form; MRD Minimal residual disease; N number; NSCLC Non-small cell lung cancer; OS Overall survival; PD-L1 Programmed cell death ligand-1; q4w Every 4 weeks; R Randomization; WES Whole exome sequencing.

1.3 Number of Patients

The study was originally sized for the primary endpoint of DFS in the PD-L1 TC≥1% analysis set and for the secondary endpoint of DFS in the FAS.

Prior to CSP V2.0, approximately 284 patients with stage II-III NSCLC who are MRD+ were planned be randomized 1:1 to durvalumab or placebo. Of the patients randomized into the study, at least 170 patients were required to be PD-L1 TC≥1% at study entry. The primary analysis was planned to be performed in the PD-L1 TC≥1% analysis set. An analysis on the full analysis set (FAS) (all MRD+ stage II-III NSCLC patients randomized) was planned to be performed as a secondary objective of the study.

Under CSP V2.0, the originally planned number of randomized patients will not be met. There will be one single analysis (i.e., primary DFS analysis) which will occur at end of study, i.e. after the last patient has either discontinued the study or has signed consent (ICF3) to receive open-label durvalumab, whichever occurs later. The study concludes the collection of data thereafter and clinical database will be locked approximately 4 weeks after the last patient last visit.

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/ Safety data	
Exposure	Safety

Outcome variable	Population
AEs	Safety
Laboratory measurements	Safety
Vital signs	Safety
ECGs	Safety
CCI	
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
Study population/Demography data	
Demography	FAS, PD-L1 TC≥1%
Baseline and disease characteristics	FAS, PD-L1 TC≥1%
Important deviations	FAS
Medical/surgical history	FAS
Previous anti-cancer therapy	FAS
Concomitant medications/procedures	FAS
Subsequent anti-cancer therapy (including radiotherapy)	FAS

AE Adverse event; DFS Disease-free survival; ECG Electrocardiogram; CCI ; CCI , 5 Level health state utility index; FAS Full analysis set; OS Overall survival; PD-L1 Programmed cell death ligand 1; PD-L1 TC≥1% Expression of PD-L1 on tumour cell membrane, at any intensity, in ≥1% of tumour cells; PFS Progression-free survival; CCI ; CCI ; CCI ; CCI ; CCI ; CCI ; TC Tumor cell; CCI ; CCI .

2.1.1 Full Analysis Set

The FAS will include all randomized patients. The FAS will be used for all efficacy analyses including patient-reported outcomes (PROs). Treatment groups will be compared on the basis of 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.

2.1.2 PD-L1 TC≥1% Analysis Set

The PD-L1 TC≥1% analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 TC≥1% as defined by the Ventana SP263 PD-L1 immunohistochemistry (IHC) assay (i.e. 1% PD-L1– membrane expression in tumoral tissue) at randomization. Treatment groups will be presented based on the basis of the randomized study treatment.

2.1.3 Safety Analysis Set

The safety analysis set will consist of all randomized patients who received any amount of study treatment. 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, they will be summarized in the durvalumab treatment group. If a patient only receives placebo, they will be summarized in the placebo treatment group.

2.2 Protocol Deviations

The following general categories will be considered important protocol deviations (IPDs) and will be listed and discussed in the CSR as appropriate:

- Inclusion criteria deviations: Patients who deviate from inclusion criteria 2, 6, 11 and/or 13 per Section 5.1 of the CSP.
- Exclusion criteria deviations: Patients who deviate from exclusion criteria 4 and/or 13 per Section 5.2 of the CSP.
- Discontinuation criteria for study product met but patient not withdrawn from study treatment.
- Investigational product (IP) deviation:
  (a) Patient received incorrect IP to that to which they were randomized.
  (b) Patients who were randomized but did not receive IP.
- 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 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 may be reported in an appendix to the CSR.

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/magnetic resonance imaging [MRI]) will be entered in the study, the definition of new lesions (NLs) in RECIST 1.1 is used for the assessment of disease recurrence.

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

Baseline radiological tumour assessments are to be performed no more than 28 days + 7 days prior to randomization and ideally as close as possible to the date of randomization. Tumour assessments are then performed every 8 weeks ± 1 week following randomization until week 48, and then every 12 weeks ± 1 week 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 (i.e. durvalumab/placebo) occurs, RECIST scans should continue according to the original imaging visit schedule. This schedule is to be followed in order to minimise 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: i.e. 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 (4 to 8 weeks later) 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 new unequivocal lesions (post-randomization) 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 (i.e. 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 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 (i.e. PD) may be backdated to a timepoint where an equivocal NL was identified, under specific conditions outlined in section 3.1 and 3.2.1.
NA Not applicable; NE Not evaluable; NED No Evidence of Diseases (only relevant if there were neither target lesions nor non-target lesions at baseline); PD Progressive disease.

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 (i.e., date of DFS event or censoring – date of randomization + 1 day):

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

Disease recurrence should be based on the finding of an unequivocal NL. However, if a NL is initially equivocal (i.e. 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 DCO 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 (i.e. every 8 weeks ± 1 week after randomization for the first 48 weeks, then every 12 weeks ± 1 week thereafter until appearance of disease recurrence or until

primary DFS analysis) the definition of 2 missed visits will change. The definitions are shown in Table 3.

Table 3 Definition of Two Missed Visits

Previous RECIST assessment	Two missed visits (duration)	Explanation
Study day < 274 (week 39)	18 weeks	2 × 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks.
Study day 274 to < 344 (>week 39 to < week 49)	22 weeks	Over this period, the scheduled frequency of RECIST assessments changes from q8w to q12w. Take the average of 8 and 12 weeks which gives 10 weeks. 2 × 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks.
Study day 344 onwards (week 49)	26 weeks	2 × 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks.

RECIST Response Evaluation Criteria in Solid Tumours; q8w Every 8 weeks; q12w Every 12 weeks.

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 (i.e. 17 weeks [2 × 8 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 on the FAS analysis set will be based on Investigator assessments according to RECIST 1.1. 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.

3.3 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 (i.e. durvalumab/placebo) and 90 days following discontinuation of study treatment (i.e. the last dose of durvalumab/placebo), 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 or placebo. Study treatments are described in Table 4. Exposure will be defined for durvalumab and placebo regimens.

Table 4 Study Treatments

Study treatment name	Route of administration	Dosing instructions
Durvalumab	IV	1500 mg infusion over 60 min q4w.
Placebo	IV	Infusion over 60 min q4w.

IV Intravenous; min Minutes; q4w Every 4 weeks.

3.3.2 Exposure and Dose Interruptions

Exposure (i.e. duration of treatment) will be defined as follows:

- Total (or intended) exposure of study treatment
  - Total (or intended) exposure = min (last dose date where dose > 0mg + 27 days, date of death, date of DCO) – first dose date +1 day
- Actual exposure of study treatment
  - Actual exposure = intended exposure – total duration of dose interruptions and cycle delays
- Calculation of duration of dose delays/interruptions (for actual exposure)

- Duration of dose delays/interruptions = sum of positive values of [date of the dose – date of previous dose – (28 + 3) days], where records corresponding to either a dose interruption or a dose delay are identified based on eCRF item “Action taken, study drug”=”Dose interruption” as collected in the Exposure eCRF form.

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

Number of treatment cycles received

Exposure will also be measured by the number of cycles received. A cycle corresponds to a period of one dose of treatment (28 days). If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

Patients who permanently discontinue during a dose delay

If a decision is made to permanently discontinue study treatment (i.e. durvalumab/placebo) 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.

3.3.3 Dose Intensity

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

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

3.3.4 Adverse Events

Adverse events and SAEs will be collected throughout the study. SAEs will be collected following signature of the first informed consent [ICF1] and following signature of the second informed consent for the observation period [ICF2b], and all SAEs and AEs will be collected following signature of the second informed consent for the treatment period [ICF2a]) until 90 days after the last dose of study treatment (durvalumab/placebo). A treatment-emergent

adverse event (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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 5.0.

Adverse Events of Special Interest and Adverse Events of Possible Interest

Some clinical concepts (including some selected individual preferred terms [PTs] and higher-level terms [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.

3.3.5 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 i.e. durvalumab/placebo). 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 standard international (SI) units. The following parameters have CTCAE grades defined for both high and low values: 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 Cockcroft-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.

3.3.6 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.

3.3.7 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, i.e. durvalumab/placebo).

3.4 CCI

3.4.1 CCI

CCI

[redacted]

[redacted]

[redacted]

3.4.2 CCI

CCI

[redacted]

3.4.3 CCI

CCI

[redacted]

CCI

CCI

3.4.4 CCI

3.4.4.1 CCI

CCI

CCI

CCI

CCI

3.4.4.2 CCI

CCI

CCI

CCI

3.4.4.3 CCI

CCI

CCI

4. ANALYSIS METHODS

Prior to CSP V2.0, a formal statistical analysis was to be performed to test the main hypotheses:

- H0: No difference between durvalumab and placebo
- H1: Difference between durvalumab and placebo

Under CSP V2.0 no formal statistical analyses will be performed, and all analyses will be exploratory. All data will either be summarized or listed only.

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, coefficient of variation (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, standard deviation, median and quartiles will be rounded to 1 additional decimal place 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, with the exception of 100% which will be presented as a whole number.
- 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 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 pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of the first dose, where neither time nor a nominal pre-dose indicator are captured, will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

If two visits are equally eligible to assess patient status at baseline (e.g. 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 (i.e. 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

The following conventions will apply for visit windows on safety and ePRO:

- 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 windows with more than one record
  - 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' (i.e. below the lower limit of quantification) or '> x' (i.e. above the upper limit of quantification) will be imputed as 'x' in the calculation of summary statistics but displayed as '< x' or '> x' in the listings. Additionally, AEs that have missing causality (after data querying) will be assumed to be related to durvalumab or placebo.

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.

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.

4.2 Analysis Methods

Only descriptive summaries or listings will be produced. The following table (Table 5) details the statistical analysis. Where listings are specified, these will be produced on the FAS only and will include the PD-L1 TC≥1% analysis set status.

Table 5 Statistical Analyses to be Conducted

Endpoints	Notes
Disease-free survival (DFS)	Primary analysis using descriptive summaries based on Investigator assessments (RECIST 1.1) for the FAS. Listing only for PD-L1 ≥1% analysis set.
Overall survival (OS)	Listing only.
Progression-free survival (PFS)	Listing only.
CCI [redacted]	CCI [redacted]

Endpoints	Notes
CCI	CCI
Change from baseline in PRO endpoints CCI	Listing only.
Time to deterioration CCI	Listing only.

DFS Disease-free survival; CCI ; CCI ; FAS Full analysis set; OS Overall survival; PFS Progression-free survival; CCI ; RECIST Response Evaluation Criteria in Solid Tumors.

4.2.1 Multiplicity

Under CSP V2.0, 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 summarized, for the FAS. This will include the number (%) of patients with event or censored, along with the reason for event/censoring. Kaplan-meier curves will also be produced.

DFS data on the PD-L1 ≥1% analysis set will be listed only.

Supportive Summaries

Additionally, a summary of time to MRD+ emergence during surveillance may be provided and this may also be included in the DFS supportive listing.

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

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 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.

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

All the collected RECIST 1.1 data will be listed.

4.2.2.2 Subgroup Analyses

No subgroup analyses will be performed.

4.2.3 Overall Survival (OS)

Overall survival will be listed only, for the FAS.

4.2.4 CCI

CCI

4.2.5 CCI

CCI

4.2.6 Data Cut-Offs

Following implementation of CSP V2.0, the DCO will occur after the last patient has either discontinued the study or has signed consent (ICF3) to receive open-label durvalumab, whichever occurs later. This will be followed by DBL and 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

4.2.8 CCI

CCI

4.2.9 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.

4.2.9.1 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 (i.e. before the administration of the first dose of durvalumab/placebo) 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 (i.e. the last dose of durvalumab/placebo) 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. Frequencies and percentages of patients reporting each PT will be presented (i.e. 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 system organ class (SOC) and PT separated by treatment group) will be tabulated for:

- All AEs

- All AEs possibly related to study treatment (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 study treatment (as determined by the reporting Investigator)
- SAEs with outcome of death
- SAEs with outcome of death possibly related to study treatment (as determined by the reporting Investigator)
- All SAEs
- All SAEs possibly related to study treatment (as determined by the reporting Investigator)
- AEs leading to discontinuation of study treatment
- AEs leading to discontinuation of study treatment, possibly related to study treatment (as determined by the reporting Investigator)
- AEs leading to dose interruption of study treatment

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 maximum CTCAE grade 3 or 4, showing all events that occur in at least 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 (i.e. *x*%), the raw percentage should be compared to the cut-off, no rounding should be applied first (i.e. an AE with frequency of 4.9% will not appear if a cut-off is 5%).

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.

Deaths

A summary of all deaths will be provided with number and percentage of patients in the 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 SAE 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)
- SAE 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] + 90 days) and not due to disease under investigation
- Unknown reason for death
- Other deaths

All deaths will be listed along with time from first and last dose, primary and secondary causes, and relationship to disease using the FAS.

4.2.9.2 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 serious AESI/AEPI with outcome of death
- Any AESI/AEPI possibly related to study treatment
- 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.

4.2.9.3 Laboratory Assessments

Data obtained up until the 90 days following discontinuation of study treatment (i.e. durvalumab/placebo) 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: Alanine aminotransferase (ALT) (high), Aspartate aminotransferase (AST) (high), Alkaline phosphatase (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.

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 (i.e. ≥ 3× ULN) plus Total Bilirubin (i.e. ≥ 2× ULN) are elevated at any time will be listed also.

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.

Assessment of Renal Function Test Abnormalities

In addition to the analysis for serum creatinine, the number and percentage of patients with creatinine clearance (CrCl) rate on-treatment (derived per Section 3.3.5) 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

4.2.9.4 Electrocardiograms

Since ECGs are only collected as clinically indicated, abnormalities in ECG data obtained at any time during the study will be listed only.

4.2.9.5 Vital Signs

All vital signs data (SBP, DBP, pulse rate, temperature, respiratory rate and weight) will be listed only.

4.2.10 Demographics and Baseline Characteristics

The following will be summarized for all patients in the FAS and PD-L1 TC ≥1% analysis set (unless otherwise specified) by treatment group:

- Patient disposition (all patients, including screening failures [split by whether or not ICF2a was signed] and reason for screening failure, and status in regards to the surveillance period)
- Important protocol deviations (FAS only)
- Inclusion in analysis sets (all patients)

- 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], body mass index [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, radiation therapy and immunotherapy) (FAS only)
- Disease characteristics at baseline (Easter Cooperative Oncology Group [ECOG] performance status, primary tumor location, histology type [squamous, non-squamous, other], tumor grade, and overall disease classification)
- Extent of disease at baseline
- TNM classification at baseline
- Disease related medical history (past and current) (FAS only)
- Relevant surgical history (FAS only)
- Nicotine use, categorized ([never, former, current])
- 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.

4.2.11 Concomitant and Other Treatments

Information on any medications or therapies from first screening to 90 days after the last dose of study treatment (i.e. durvalumab/placebo) 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 completed curative intent therapy and while they are randomized and on study drug.

Medications received prior to, concomitantly, or post-study treatment will be coded using the World Health Organization drug dictionary (WHODD) Anatomical Therapeutic Chemical (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.

The following summaries will be produced for the FAS:

- Summary of allowed concomitant medications
- Summary of disallowed concomitant medications
- Summary of subsequent anti-cancer therapies (including radiotherapy)

All concomitant and other treatment data will be listed.

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

4.2.12 Exposure

Exposure will be summarized for the safety analysis set.

The following summaries will be produced by treatment group:

- Total exposure
- Actual exposure
- Number of, and reasons for, interruptions and delays of study treatment
- Cumulative exposure over time for study treatment
- Number of treatment cycles received
- RDI

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.

For patients on study treatment at the time of the DFS analysis, the DCO date will be used to calculate exposure.

4.2.13 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 [i.e. durvalumab/placebo], and other protocol deviations) may be generated. For AE and deaths, summaries of COVID-19 related events including infections and deaths maybe produced.

Supportive listings may be produced.

4.3 Surveillance Period

For the purpose of the CSR, data collected during the surveillance period may be included in listings for patients in the FAS only, and will be flagged to distinguish between data collected in the surveillance period and the treatment period.

Additional exploratory summaries and analyses may be performed on top of the summary of time to MRD+ emergence mentioned in Section 4.2.2.1.

5. INTERIM ANALYSES

5.1 Interim Efficacy Analysis

Prior to CSP V2.0, an interim analysis of OS was to be performed at the time of the DFS primary analysis.

Under CSP V2.0, no interim analyses will be performed.

5.2 Independent Data Monitoring Committee (IDMC)

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 approximately 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, 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 (v17, 07 April 2022). 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 Clinical Study Protocol and letters to Investigators.

Following the decision to stop recruitment, a decision was made on 21 November 2022 (during IDMC#1) to have no further IDMCs. A final safety report following DBL will be provided to the IDMC members.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The following are changes from the planned analyses described in version 2 of the CSP.

Overall visit response table updated to more accurately reflect RECIST 1.1 evaluations and responses applicable to this study.

Except that change, this SAP has been produced in line with section 10.4 of CSP V2.0, which states:

“Under CSP v2.0, as a result of the decision by AstraZeneca to close enrollment to the study and end study assessments early, all analyses of the objectives and endpoints listed in Section 3 will be descriptive only and considered exploratory. Further details will be included in the SAP.”

7. REFERENCES

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

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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.

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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 4 weeks between scheduled assessments) are:

Day 29, visit window 2 - 42
Day 57, visit window 43 - 70
Day 85, visit window 71 - 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
Day 365, visit window 351 - 378
Day 393, visit window 379 - 406
Day 421, visit window 407 - 434
Day 449, visit window 435 - 462
Day 477, visit window 463 - 490
Day 505, visit window 491 - 518
Day 533, visit window 519 - 546
Day 561, visit window 547 - 574
Day 589, visit window 575 - 602
Day 617, visit window 603 - 630
Day 645, visit window 631 - 658
Day 673, visit window 659 - 686
Day 701, visit window 687 - 714
Day 729, visit window 715 - 742

Note: The same rules should be followed if a patient has more than 26 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 (i.e. durvalumab/placebo) 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 (i.e. durvalumab/placebo) then impute first dose date;
- Completely missing: impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

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

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

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

durvalumab/placebo) then impute the earlier of either the DCO or the day after the last dose date.

When imputing a stop date, ensure that the new imputed date is sensible i.e. 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 imputed death date using the following:

- For missing day only – using the 1st of the month
- For missing day and month – using the 1st of January
- If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e. censored at the last known alive date.

Imputation of 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 that date that is not after the date of last dose of study treatment (i.e. durvalumab/placebo), this will be flagged and discussed with the clinical team.

Other parameters

- No other imputation will be made.

SIGNATURE PAGE

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