Clinical Study Protocol	
Drug Substance	Durvalumab
Study Code	D933YC00001
Version	6.0
Date	28 Aug 2023

A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre Study of Durvalumab as Consolidation Therapy in Patients with Locally Advanced, Unresectable, Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed following Definitive, Platinum-Based, Chemoradiation Therapy (PACIFIC 5)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

EudraCT number 2018-002294-22

VERSION HISTORY

Version 6.0, 28 August 2023

All Sections

Updated "patient" to "participant" as per latest template.

Section 1.1 – SoA, Section 4.1 – Overall design, 7.1.1 – Procedures for discontinuation of study treatment and Section 8.1.2 – Survival assessments

- Revised visit frequency from every 6 months to every 2 months in the table header of SoA Table 2 "Schedule of activities for participants who have discontinued treatment with durvalumab /placebo" to be consistent with the survival follow-up frequency and updated the wording in Section 8.1.2 for clarification.
- Clarified participants who permanently discontinue drug for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 scans regardless of whether or not the participants started a subsequent anticancer therapy.

Section 1.2 – Synopsis and Section 9.6 –Interim analyses

Removed IDMC review of unblinded OS interim analysis.

Section 6.1.3 – Duration of treatment and Section

Added the clarification that participants in placebo arm will no longer receive any further placebo treatment after the study unblinded.

Section 6.2.4 – Methods for ensuring blinding

Specified the blinding of assigned study treatment will remain until final analysis of PFS.

Section 4.4 – End of study definition,6.1.3 – Duration of treatment and Section 6.6 – Treatment after the end of the study,

Moved the relevant information on participant/study data management post final DCO and study completion in Section 4.4 and Section 6.1.3 to Section 6.6 for consolidation.

Section 7.2 – Lost to follow-up

Specified how to perform patient follow-up when onsite visit is not applicable.

Section 7.3 – Withdrawal from the study

Updated the description of participant withdraw from the study per CSP template.

Section 8.3 – Collection of adverse events

- Clarified NCI CTCAE version 5.0 will be utilised for all events with an assigned CTCAE grading.
- Update the listing of Adverse events of special interest and to include rare/less AEs non-infectious encephalitis, non-infectious meningitis and vasculitis per latest template.

Section 8.4 – Safety reporting and medical management

Clarified all pregnancies including pregnancy in the partner of male participants.

Section 8.8.3 – Storage, reuse, and destruction of biomarker samples

Updated the storage duration for samples collected in China per local practice.

Section 1.2– Synopsis, Section 9.2 – Sample size determination and Section 9.5 – Statistical analyses The DCOs for PFS final, OS interim and final analysis are updated as follows:

- Updated that PFS final analysis will be performed when reaching approximately CCI BICR PFS events or approximately CCI months follow-up post last participant randomization, whichever occurs first.

- Updated that OS final analysis will be performed when reaching approximately CCI OS events or approximately CCI months follow-up post last participant randomization, whichever occurs first.
- Updated that OS second interim analysis will be performed at approximately 12 months after the OS first interim analysis. If the estimated DCO for OS final analysis is within 24 months after OS first interim analysis, the OS second interim analysis may be removed.

Appendix E- Guidelines for evaluation of objective tumour response using RECIST 1.1 Criteria

Added "Not Applicable" and corresponding definition for Guidelines of evaluation of objective tumour response using RECIST 1.1 Criteria.

Section 4.4 – End of study definition, Section 8.4.4 – Medication Error, Appendix A1 – Regulatory and ethical considerations, Appendix A6 – Dissemination of Clinical Study Data, Appendix A7 - Data Quality Assurance

Administrative updates as per EU Clinical Trial Regulation (CTR) requirement in case of study transition the study transits and falls under the new EU 536/2014 Regulation in future.

Version History- Version 4.0, 05 Nov 2020

Updated the typo in Section 1.2 - Synopsis

Version 5.0, 26 May 2021

Section 1.2 – Synopsis, and Section 3 – Objectives and endpoints

Updated the primary objective and key secondary objective to exclude patients with sensitizing EGFR mutations or ALK rearrangements (mITT population). Updated the PFS and OS in the ITT population as secondary objectives. Introduced other secondary efficacy objectives including PROs for the mITT population.

Section 1.2 – Synopsis, and Section 4.1 – Overall design

Increased the total sample size from approximately 360 to 400. Removed the cap for the patients with PD-L1<1% outside of China.

Section 1.2 – Synopsis, and Section 4.4 – End of study definition

Estimated date of last patient completed has been updated to Q4 2024 in line with latest calculations.

Section 2.1 – Study rationale

Added the rationale for removing the patients with sensitizing EGFR mutations and ALK rearrangements from primary analysis and key secondary analysis.

Section 4.2.2 – Predictive biomarkers and rationale for an unselected population in Study D933YC00001

Removed the rationale for the cap for the patients with PD-L1<1% outside of China.

Section 8.1 – Efficacy assessments

Re-wording for PFS2 assessment.

Section 9.2 – Sample size determination

Updated the primary efficacy endpoint and key secondary efficacy endpoint to exclude patients with sensitizing EGFR mutations or ALK rearrangements. Thus, the total sample size has been increased from approximately 360 to 400. Updated relevant statistical calculations for PFS and OS analysis.

Section 9.3 – Populations for analyses

Updated analysis populations to exclude patients with sensitizing EGFR mutations or ALK rearrangements from the primary and key secondary efficacy analyses. Specifically, full analysis set (FAS) was replaced by ITT, and mITT population was introduced; analysis population updated in Table 11 accordingly.

Section 9.5 – Statistical analyses

Updated efficacy analyses throughout to be performed in the mITT (primary population), and separately in the ITT population.

Section 9.5.7 – Methods for multiplicity control

Updated MTP to exclude patients with sensitizing EGFR mutations or ALK rearrangements from the primary endpoint PFS (mITT) and key secondary endpoint OS (mITT) analyses. Moved secondary endpoint PFS (ITT) and OS (ITT) to the 3rd layer and 4th layer of the MTP in Figure 3, respectively. Updated statistical calculations for PFS FA and OS analyses.

Section 9.6 – Interim analyses

Updated the statistical calculations for OS interim analyses.

Section 10 – References

Added the following references:

.Faivre-Finn et al 2021
Faivre-Finn C, Vincente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste J, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC – an update from the PACIFIC trial. J Thorac Oncol 2021;16(5) :860-67.

Version 4.0, 05 November 2020

Section 1.1 – Schedule of activities, Table 1 and Table 2

Table 1

Clarified that CCI [redacted] should be collected at Cycle 13.

Table 2

Corrected PRO assessment information to align with Table 1.

Section 1.2 – Synopsis

Statistical methods

Generally, following updates have been made in this section, and relevant subsections in section 9 (specifically, section 9.2, section 9.5.1, section 9.5.7, section 9.6),
1) PFS interim analysis removed, maturity of PFS final analysis increased from 68% to 70%, additional criteria to ensure minimum follow-up (9 months from last subject randomized). The change has been made to ensure sufficient events (maturity) in China cohort at PFS final analysis, considering a 1year delay in enrolment in China than outside of China.
2) Modify OS interim analyses and OS final analysis, to be in line with the changes to PFS.

Section 2.3.1 – Potential benefits of durvalumab

Added PACIFIC 4-year survival data.

Section 3 – Objectives and endpoints

Added foot note c 'Exploratory endpoints and analyses related to PFS/ORR analyses using irRECIST data may be presented outside of the main CSR'.

Section 4.1 – Overall design

Updated the number of patients who received prior cCRT to at least 60%, and cap the number of patients with PD-L1<1% at approximately 33% outside of China. Number of patients with EGFR mutation or ALK rearrangement will be capped at approximately 7% of the total randomisation.

Section 4.1.1

COVID-19 mitigation guidance is added.

Section 4.2.2 – Predictive biomarkers and rationale for an unselected population in Study D933YC00001

Rational for PD-L1 negative cap is added.

Section 5.1 – Inclusion criteria – Part I Screening

Updated inclusion criteria#7 by updating the cap of EGFR and ALK mutant patients to 7%.

Section 5.2 – Exclusion criteria

Updated exclusion criteria#7 by adding sarcomatoid variant.

Updated exclusion criteria#8 by adding 'Grade 2 AE of laboratory abnormality for inclusion criteria 12 related lab parameters may be included as long as within the specified range in inclusion criteria 12'.

Updated exclusion criteria#20 by adding 'Or the patient is not willing to/can not continue screening procedures during the screening period.'

Added exclusion criteria#21 Meet any of the study protocol specified capping criteria.

Updated other exclusions to clarify patient who is not willing to or not able to continue screening is considered as screen failure but not withdrawal.

Section 8.1.1 Central reading of scans

Updated 'an exploratory analysis of PFS may be presented outside of the main CSR'.

Section 8.1.3 Second progression

Deleted 'The follow up scan confirming an immediate prior RECIST 1.1 defined radiological progression is not to be considered as the second progression'.

Section 8.1.4.3 - Administration of patient-reported outcomes questionnaire.
Added back-up option of PRO data collection at the time of technical or other device-related issues prohibit completion on the device.

Section 8.4.5.1 – Specific toxicity management and dose modification information - durvalumab

Web portal of Toxicity Management Guidelines is removed.

Section 9.2 – Sample size determination

Update the relevant statistical calculations for PFS and OS analysis.

Section 9.4.1.1 – RECIST 1.1-based endpoint

Removed 'PFS and ORR by irRECIST 1.1 criteria using BICR assessments will also be performed for exploratory purpose.'

Section 9.4.1.2 – Primary endpoint

Removed 'For exploratory purpose, PFS will also be assessed using irRECIST 1.1 data obtained from BICR'.

Section 9.4.1.5 – Objective response rate

Removed 'For exploratory purpose, ORR by irRECIST 1.1 criteria using BICR assessments will also be reported'.

Section 9.4.1.8 - Time from randomisation to second progression

Update the definition of PFS2 and relevant analysis rules.

Section 9.5 - Statistical analyses
COVID-19 related data analysis is added.

Section 9.5.1 – Efficacy analyses

Removed 'The analysis will be performed when (approximately) 245 PFS events have occurred across the durvalumab and placebo treatment arms (68% maturity)'.

Section 9.5.1.1– Primary endpoint: Progression-free survival
1% PD-L1 cut-off is added.

Table 13

Remove the exploratory endpoints and analyses related to PFS/ORR analyses using irRECIST data, as they may be presented outside of the main CSR.

Change the analysis method for landmarks (OS24, PFS12, PFS18).

Section 9.5.1.1– Primary endpoint: Progression-free survival

Removed 'An exploratory analysis of PFS based on BICR assessments according to irRECIST 1.1 criteria will be performed. The stratified log rank test used for the primary analysis of PFS will be repeated'.

Updated PD-L1 status (tumour cells [TCs] ≥ 1% vs TCs < 1%).

Section 9.5.1.3 – Proportion of patients alive at 24 months

The analysis of comparison of OS24, PFS12 and PFS18 were removed to be consistent with other durvalumab studies. Kaplan Meier estimates of APF12, OS24, PFS12 and PFS18 will still be provided for each treatment arm.

Section 9.5.1.4 – Objective response rate

Removed 'ORR by irRECIST 1.1 criteria using BICR assessments will also be reported'.

Section 9.5.7 – Methods for multiplicity control

Remove PFS IA, update the statistical calculations for PFS FA and OS analyses (OS IA1, OS IA2, OS FA), and make relevant updates for wordings of MTP.

Section 9.6 – Interim analyses

Remove PFS IA, update the statistical calculations for OS interim analyses

Section 9.6.1 – Data monitoring committee
Updated the review period of IDMC to periodically in accordance with IDMC charter.

The details regarding whether IDMC to review the efficacy data for OS are removed.

Section 10 – References

Removed 'Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med 2007; 26(24): 4505-19'.

Added 'Paz-Ares L 2020
Paz-Ares L, Spira A, Raben D, et al. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, Stage III non-small-cell lung cancer in the PACIFIC trial[J]. Annals of Oncology, 2020.'

Appendix E

Removed 'and is the only lesion available' from 'A previously irradiated lesion may be selected as a Target Lesion provided that it fulfils the criteria for reproducible measurability and is the only lesion available.'

Appendix I
Appendix of COVID-19 mitigation is added.

Version 3.0, 07 May 2019

Section 1.1 - Schedule of activities, table 1 and table 2

Clarified that the tumour efficacy assessments (RECIST) should be conducted relative to date of randomization, and PRO assessments should be conducted relative to date of C1D1 (ie. CCI [redacted])

Table 1

Screening visit was divided into part I and part II.

Screening visit part I was created to allow more time for tumour sample analysis to be conducted. Mandatory tumour biopsy for PD-L1, CCI [redacted], EGFR, and ALK tests were moved to screening visit part I. It was clarified that a biopsy procedure during the screening period is not allowed, and an irradiated sample is not acceptable. Demography and some eligibility criteria would also be conducted in screening visit part I. Annotations a, c, f, l, and o were updated accordingly.

Other screening activities remain in screening visit part II.

To avoid duplication, baseline characteristics was deleted. Baseline characteristics would be checked accordingly in inclusion and exclusion criteria at both screening part I and part II.

CCI [redacted] for biomarker".

Tumour assessments (RECIST) was updated to indicate assessments would not be stopped at clinical progression/deterioration.

Updated annotation b to emphasize 3 days window from randomization to 1st dose.

Updated annotation m to indicate TSH doesn't need to be checked prior to dosing.

Table 2

Updated PRO assessment information, PRO would be collected until PFS2.

Tumour assessments (RECIST) was updated to indicate assessments would not be stopped at clinical progression/deterioration.

1.2 Synopsis

CCI test was downgraded from secondary objective to exploratory objective.

Two-part screening process related information was updated. Study period information was updated.

Specified sensitizing EGFR mutation types and only sensitizing mutation would be excluded.

Treatment through progression related wording was added. ePRO would be followed until PFS2.

Some statistical considerations were updated.

1.3 Schema

Study Design Figure was updated to include two-part screening visit information.

2.3.1 Potential benefits of durvalumab

Related wording was updated with recent available information.

3 Objectives and endpoints

CCI test was downgraded from secondary objective to exploratory objective.

4.1 Overall design

Specified sensitizing EGFR mutation types and only sensitizing mutation would be excluded.

5. Study Population

Updated the definition of enrolled patients.

5.1 Inclusion criteria and 5.2 Exclusion criteria

Inclusion criteria during screening visit part I were created.

The original inclusion criteria in CSP version 2.0 are under screening visit part II. Some of the criteria were moved to part I screening, but the criteria numbers would not be assigned again to other criteria.

Inclusion # 5 was updated to reflect correct radiation therapy requirements.

5.4 Screen Failures

Clarified patients who do not meet eligibility criteria after signing part I screening ICF, or both part I and part II screening ICFs are both screen failures.

6 Study Treatments

Blinding requirements related wording was updated.

6.1.3 Duration of treatment

Treatment through progression related wording was added.

Long term OS collection post Final Data Cutoff was added.

6.2.1 Patient enrolment and randomization

Patient screening and randomization process was updated to reflect two-part screening visit information.

Emphasized 3 days window from randomization to 1st dose.

6.2.4 Method for ensuring blinding

Wording about unblind after treatment discontinuation was updated.

8. Study assessment and procedure

Screening related wordings were updated to reflect two-part screening process.

8.1.4.3 Administration of patient-reported out comes questionnaires

Updated wording about ePRO completion requirements in patients who are unable to read.

8.3.2 Time period and frequency for collection adverse event and serious event information

Clarified AE and SAE would be collected after part II screening ICF is signed.

8.8 Biomarker

Clarified PD-L1 will be tested for all enrolled patients and CCI would be tested for all randomized patients.

8.8.1 Collection of patient selection biomarker date Updated tumour sample collection related wording to reflect two-part screening process, and updated tumour sample requirements. CCI [redacted] was changed to optional test in China. 8.8.2 Exploratory biomarker CCI [redacted] for biomarker research. 9 Statistical Consideration Section was updated to reflect current considerations about population analysis, outcome measurements, statistical analyses, and interim analysis.
Version 2.0, 22 Aug 2018
Section 1.1 – Schedule of activities Schedule about early patient review for safety was removed. PRO assessment schedules were changed from relative to randomization date to relative to Cycle 1 Day 1 Visit date. PRO assessment window time was added. Table 1, Table 2 and their footnotes were updated to reflect the most updated RECIST, ePRO and EGFR/ALK evaluations' requirements. Section 1.2 – Synopsis, Section 4.1 – Overall design, Section 6.2.3 – Methods of assigning treatment arms, Section 9 – Statistical analysis Stratification factors was updated to replace disease staging with PD-L1 status. Section 1.2 – Synopsis, Section 4.1 – Overall design and Section 9.2 – Sample size determination Total screening patients number and total sites number were removed to avoid confusion, as they are just estimated numbers. Wording also updated to reflect this is a randomized study. Specified the study will maintain an approximately 1:1 balance between cCRT and sCRT. Clarified the 15% randomization cap was applicable to EFGR mutation or ALK rearrangement patients.

Text corrected to state: 1) A recruitment period of approximately 22 months and a follow-up period of 7 months are expected for the PFS endpoint. 2) A recruitment period of approximately 22 months and a follow-up period of 43 months are expected for the OS endpoint.

Section 1.2 – Synopsis and Section 3 – Objectives and Endpoints

CCI testing was moved to exploratory objective.

Section 1.2 – Synopsis and Section 9 – Statistical Considerations

Statistical considerations were updated.

Section 2.1 – Study rationale

Statements about Chemoradiotherapy as SoC for unresectable stage III NSCLC patients was removed, and information about PACIFIC study PFS result was updated. Some redundant descriptions were removed.

Section 4.1 – Overall design

Text corrected to state: patients randomized should be received cCRT or sCRT; and number of patients with EGFR mutation or ALK rearrangement will be capped at approximately 15% of the total randomisation.

Section 4.2 – Scientific rationale for study design

Rationale about using placebo control was updated to reflect most updated information.

Section 4.4 – End of study definition

The wording "rest of world" in study duration paragraph was removed to avoid confusion.

Section 4.4 – End of study definition and Section 6.1.3 – Duration of treatment

Additional follow-up for long-term efficacy assessment was added.

Section 5 – Study Population

Inclusion criterion#7 added as one inclusion criterion of PD-L1 status: Tumor PD-L1 status, with the Ventana SP263 PD-L1 IHC assay determined by a reference laboratory, must be known prior to randomization. Patient with unknown PD-L1 status is not eligible for the

study. "Unknown" refers to (1) insufficient sample which is not able to be analyzed, or (2) sample could be analyzed but results not interpretable.

Inclusion criterion #8 text corrected to state: "After approximately 15% EGFR or ALK mutant patients have been randomised".

Exclusion criterion #15 was updated to clarify patients should not participate in another clinical study with an IP administered in the last 4 weeks prior to randomization.

Lifestyle restrictions' contraception requirements was updated for male patients and female patients' non-sterilised male partners, to require a male condom plus spermicide (or male condom in countries where spermicides are not approved).

Rescreen patients should sign a new ICF instead of re-sign on the original ICF, in order to avoid the risk of ICF update during re-screening period.

Section 1.2 – Synopsis and Section 6 – Study treatments

"Unblinded pharmacist" was updated to "unblinded pharmacist and/or other appropriate unblinded site staff" to reflect the local practice in some sites.

Section 6.4 – Concomitant Medication

Table 6 was updated to reflect palliative radiotherapy on non-target lesion is not applicable in this protocol as supportive care.

Section 6.4.3 – Rescue medication

The description about dispensing rescue medications through IVRS/IWRS system was updated, this is only applicable when rescue medications are centrally provided by AZ.

Section 8 – Study assessments and procedures

Paragraph about maximum amount of blood collected from each patient was removed. No OS data will be recorded after final DCO was removed as it is incorrect.

Section 8.1.4 – Clinical outcome assessments

This section was updated to reflect most updated electronic patient reported outcome requirements.

Section 8.2.1 – Clinical safety laboratory assessments

Table 7, Table 8 and Table 9 were updated to remove the requirements about DM to calculate the lab testing results.

Section 8.2.5 – Early patient review for safety

This section was removed to keep consistency with PACIFIC study.

Section 8.3.4 – Adverse event data collection and Section 8.4.5 – Management of IP-related toxicities

AE grading scale guidance has been updated from CTCAE 4.03 to CTCAE 5.0.

Section 8.4.5.1 – Specific toxicity management and dose modification information - durvalumab

Description about Toxicity Management Guidelines has been updated as Appendix G was removed.

Section 8.5 – Pharmacokinetics

Blood sample volume was removed. Description about sample storage duration was updated.

Section 8.8.1 – Collection of patient selection biomarker data

This section was updated to reflect mandatory tissue sample is not only used for CCI but also tissue CCI analysis.

Section 8.8.2 – Exploratory biomarkers

CCI and exploratory tumour markers were updated as not applicable to China.

CCI was moved to section 8.8.1 – Collection of patient selection biomarker data.

CCI section was added to provide more detail.

Section 8.8.3 – Storage, reuse, and destruction of biomarker samples

Sample storage and disposal requirements was updated to follow local laws and regulations, not just for samples collected in China.

Section 8.8.5 – Chain of custody of biological samples

This section was updated to reflect most updated AZ sample management requirements.

Section 9 – Statistical Considerations Section was updated to reflect the updated considerations about analysis modules, interim analysis, and IDMC. Analysis for the patient reported outcomes also updated. Appendix G: Dose modification and toxicity management guidelines for immune-mediated, infusion related, and non-immune-mediated reactions. This Appendix was deleted.
Version 1.0, 14 March 2018
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Schedule of activities (SoA)

The procedures for the Screening and Treatment Periods in this study are presented in Table 1, and the procedures for the Follow-up Period are presented in Table 2.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, pharmacokinetic (PK) blood sample) to occur at the timepoints indicated in the Schedule of Activities (SoAs). Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in the SoAs. Safety assessments must be done prior to dosing.

For durvalumab monotherapy / placebo treatment

- Participants may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related adverse event (AE).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumour efficacy (Response Evaluation Criteria in Solid Tumors [RECIST]) and patient-reported outcome (PRO) assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see current Investigator Brochure [IB] for durvalumab).
- If a participant has a delay to an infusion of study treatment, all tumour efficacy assessments should still be conducted relative to date of randomisation, and PRO assessments should be conducted relative to the date of Cycle 1 Day 1 visit date (i.e. date of randomization/first dose).

Table 1 Schedule of activities for durvalumab/placebo treatment

	Screening Visit Part I	Screening Visit Part II	C1	C2	C3	C4	C5 to PD	For details, see Section
Week	**-12 to -1**	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-84 to -1**	**-28 to -1**	**1[b]**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				
Informed consent								
Informed consent: tumour sample collection[c] (part I screening ICF)	X							5.1
Informed consent: study procedures[c] (part II screening ICF)		X						5.1
Study procedures								
Physical exam (full)		X						8.2.2
Targeted physical exam (based on symptoms)			X	X	X	X	X	8.2.2
Vital signs		X	X	X	X	X	X	8.2.3
Weight		X	X	X	X	X	X	8.2.3
ECG[d]		X	As clinically indicated					8.2.4
Concomitant medications		<----------					---------->	6.4
Demography	X							5.1
Tobacco use		X						5.1
Eligibility criteria	X	X	X					5.1, 5.2
Randomisation			X					6.2
Laboratory assessments								
Clinical chemistry[e]		X	X[f]	X	X	X	X	Table 7
Haematology[e]		X	X[f]	X	X	X	X	Table 8

	Screening Visit Part I	Screening Visit Part II	C1	C2	C3	C4	C5 to PD	For details, see Section
Week	**-12 to -1**	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-84 to -1**	**-28 to -1**	**1[b]**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				
Coagulation		X	As clinically indicated					Table 9
TSH (reflex free T3 or free T4[g])		X	X[h]	X	X	X	X	Table 7
Urinalysis		X	As clinically indicated					Table 10
Hepatitis B and C and HIV		X						8.2.6
Pregnancy test[i,j]		X	X	X	X	X	X	8.2.1
Pharmacokinetics								
CCI [redacted]			[redacted]	[redacted]		[redacted]		8.5
Monitoring								
WHO/ECOG performance status		X	X	X	X	X	X	8.2.5
AE/SAE assessment[l]		<----------					---------->	8.3
IP administration								
Durvalumab (monotherapy)/placebo[m]			X	X	X	X	X	6.1.1.1, 6.1.2.1
Other assessments and assays								
CCI [redacted]			[redacted]	[redacted]		[redacted][j]		8.5
CCI [redacted]			[redacted]	[redacted]	[redacted]	[redacted]		8.8.2
CCI [redacted]			[redacted]	[redacted]			[redacted]	8.8.2

	Screening Visit Part I	Screening Visit Part II	C1	C2	C3	C4	C5 to PD	For details, see Section
Week	**-12 to -1**	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-84 to -1**	**-28 to -1**	**1[b]**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				
EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L[n]			X	q4w (±1 week) for the first 8 weeks (relative to the date of Cycle 1 Day 1 visit date i.e. date of randomization/first dose), q8w(±1 week) thereafter until the 48th week (relative to the date of Cycle 1 Day 1 visit date i.e. date of randomization/first dose), and then q12w(±1 week) thereafter until confirmed PD by RECIST 1.1 by investigational site review				8.1.4
Health resource use (HOSPAD)			X	X		X	X	8.9
CCI [redacted]	[redacted]							8.8.1
CCI [redacted]	[redacted]							6.2.1
Efficacy evaluations								
Tumour assessments (CT or MRI) (RECIST 1.1)[p]		X	On-study tumour assessments occur q8w ±1 week for the first 48 weeks (relative to the date of randomisation) and then q12w ±1 week thereafter until RECIST 1.1-defined radiological progression plus 1 or more additional follow-up scans for confirmation of progression until confirmed radiological progression. The on-study schedule of q8w ±1 week (relative to the date of randomisation) for the first 48 weeks and then q12w ±1 week thereafter MUST be followed regardless of any delays in dosing.					8.1

[a] A newly acquired sample ≤ 3 months old is preferred, but an archived sample ≤6 months old is acceptable (refer to lab manual for detail about sample age requirements). A biopsy procedure during screening period is not allowed. Newly acquired or archived tumour sample must be obtained before CRT. Any irradiated sample is not acceptable.

[b] Every effort should be made to minimise the time between randomisation and starting treatment (i.e. within 3 days of randomisation).

[c] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. Part I Screening: all participants will be required to provide informed consent to supply their tumour samples (archived or newly acquired) for entry into this study. A biopsy procedure during screening period is not allowed, and an irradiated sample is not acceptable. Part II screening ICF must be signed after participants complete CRT. Part I screening ICF needs to be signed prior to (or at the same time as) signature of the Part II screening ICF. The collection of additional biopsies upon progression is strongly encouraged. If laboratory or imaging procedures were performed for alternate reasons prior to signing inform consent of study

procedures, these can be used for screening purposes with consent of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days of randomisation.

[d] Any clinically significant abnormalities detected require triplicate ECG results.

[e] Serum or plasma clinical chemistry (including LFT monitoring), haematology, and coagulation parameters may be performed more frequently if clinically indicated.

[f] If part II screening clinical chemistry, haematology, and coagulation parameter assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

[g] Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[h] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

[i] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study treatment and then q4w. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

[j] Pre-dose same day as infusion

[k] Within 10 minutes of the end of infusion.

[l] For AEs/SAEs reported during part II screening, additional information such as medical history and concomitant medications may be needed

[m] Results for haematology, LFTs, electrolytes, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[n] Will be administered using a site-based electronic device. It is preferred that PRO questionnaires are completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid biasing the participant's responses to the questions.

[o] Documented EGFR and ALK status obtained from local lab uses a well-validated, local regulatory-approved kit is acceptable. EGFR and ALK status may also be tested in central lab at screening part I visit, if there's no available documentation of EFGR and ALK status from local lab.

[p] Tumor assessment will be performed on images from CT (preferred) or MRI, each preferably with iv contrast, of the chest and abdomen (including the entire liver and both adrenal glands). Additional anatomy, e.g. pelvis, should be imaged based on signs and symptoms of individual participants at Baseline and follow-up. If a participant's scan is assessed as a RECIST 1.1-defined radiological progression, a follow-up scan for confirmation of the prior radiological progression is collected no earlier than 4 weeks after and no later than the next regularly scheduled imaging visit after the prior RECIST 1.1-defined PD, and this scan is evaluated using the confirmation of radiological progression criteria outlined in Appendix E. If the subsequent scan confirms the immediate prior radiological PD, no additional scans are required; however, if the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue on the original imaging visit schedule until the next clinical progression/deterioration or RECIST 1.1-defined PD, which in turn will require a subsequent scan evaluated using confirmation of radiological progression criteria outlined in Appendix E. If an unscheduled assessment was performed and the participant has not progressed, every attempt should be made to perform the subsequent assessments at their next regularly scheduled visit. See Section 6.1.3 and Section 8.1 for additional details relevant to tumour assessment.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

ADA Anti-drug antibody; AE Adverse event; ALK Anaplastic lymphoma kinase; C Cycle; CT Computed tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; HIV Human immunodeficiency virus; ICF Informed consent form; IP Investigational Product; iv Intravenous; LFT Liver function test; miRNA Micro ribonucleic acid; MRI Magnetic resonance imaging; mRNA Messenger ribonucleic acid; NSCLC Non-small cell lung cancer; PD Progression of disease; PD-L1 Programmed death ligand 1; PK Pharmacokinetic; q4w Every 4 weeks; q8w Every 8 weeks; q12w Every 12 weeks; q28d Every 28 days; QLQ-LC13 13-item self-administered questionnaire for lung cancer; RNA Ribonucleic acid; SAE Severe Adverse Event; RECIST Response Evaluation Criteria in Solid Tumors; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization; WT Body weight.

Table 2 Schedule of activities for participants who have discontinued treatment with durvalumab /placebo

	Time since last dose of IP								
	Day (±3)	Months (±1 week)						12 months then every 2 months (±2 weeks)[a]	For details, see Section
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**		
EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L as well as health resource use (HOSPAD)[b]	Participant questionnaires and information related to health resource use should be completed relative to the date of Cycle 1 Day 1 visit date(i.e. date of randomization/first dose) as follows: q4w (±1 week) for the first 8 weeks, every 8 weeks ±1 week thereafter for the first 48 weeks (per Table 1), then every 12 weeks ±1 week thereafter until PFS2.								
Physical examination (full)	X								8.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								8.2.3
Weight	X	X	X						8.2.3
Pregnancy test[c]	X	As clinically indicated							8.2.1
AE/SAE assessment	X	X	X						8.3
Concomitant medications	X	X	X						6.4
WHO/ECOG performance status	At timepoints consistent with tumour assessments; at 30, 60, and 90 days after treatment discontinuation; and then at initiation of subsequent anticancer therapy[d]								8.2.5
Subsequent anticancer therapy[e] and second progression assessment[f, g]	<----------								8.1
Survival status[h]		X	X	X	X	X	X	X	8.1.2
Haematology	X	X	X						Table 8
Clinical chemistry	X	X	X						Table 7
TSH (reflex free T3 or free T4[i])	X	X	X						Table 7
PK assessment			X						8.5

	Time since last dose of IP								
	Day (±3)	Months (±1 week)						12 months then every 2 months (±2 weeks)[a]	For details, see Section
Evaluation	30	2	3	4	6	8	10		
CCI [redacted]			[redacted]		[redacted]				8.5
Tumour assessment (CT or MRI) (RECIST 1.1)[j]	On-study tumour assessments occur q8w ±1 week for the first 48 weeks (relative to the date of randomisation) and then q12w ±1 week thereafter until RECIST 1.1-defined radiological progression plus 1 or more additional follow-up scans for confirmation of progression until confirmed radiological progression, the end of study, death, study discontinuation, or Sponsor decision (whichever comes first). The on-study schedule of q8w ±1 week (relative to the date of randomisation) for the first 48 weeks and then q12w ±1 week thereafter MUST be followed regardless of any delays in dosing. Additional scans to be completed per standard practice post-progression.								8.1

[a] Participants on Survival Follow-up at the time of final DCO for the study will be considered to have completed the study and will continue to receive treatment per local standard of care.

[b] Will be administered using a site-based electronic device. It is preferred that PRO questionnaires are completed prior to any other study procedures and before discussion of disease progression to avoid biasing the participant's responses to the questions.

[c] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[d] WHO/ECOG performance status should also be collected at other study site visits that the participant attends, if appropriate study site staff are available to collect such information. In addition, WHO/ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.

[e] Details of any treatment for NSCLC (including surgery) after the last dose of IP must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.

[f] Following the first progression event used for the primary variable, PFS (the first progression), the site will be asked on a regular basis (q8w ±1 week for the first 48 weeks [relative to the date of randomisation], and then q12w ±1 week) if the participant has had a second progression event. Actual timing of assessments for a second progression event will be according to local standard practice. PFS2 assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. (The follow-up scan confirming an immediate RECIST 1.1-defined radiological progression is not to be considered as the second progression.)

[g] For participants who discontinue their assigned IP following progression, available readings of CT/MRI from local practice will be collected from participants` medical charts whilst information on subsequent anticancer treatment and/or PFS2 is collected.

[h] Participants may be contacted in the week following DCOs to confirm survival status. Details of any treatment for NSCLC (including surgery) post the last dose of IP must be recorded in the eCRF. Participants who decline to return to the study site for evaluations should be contacted by telephone as indicated in the SoAs as an alternative.

[i] Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[j] See Section 6.1.3 and Section 8.1 for additional details relevant to tumour assessment.

ADA Anti-drug antibody; AE Adverse event; C Cycle; CT Computed tomography; DCO Data cutoff; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; IP Investigational Product; MRI Magnetic resonance imaging; NSCLC Non-small cell

lung cancer; PD Progression of disease; PFS2 Time from randomisation to second progression; PK Pharmacokinetic; q8w Every 8 weeks; q12w Every 12 weeks; QLQ-LC13 13-item self-administered questionnaire for lung cancer; SAE Severe Adverse Event; RECIST Response Evaluation Criteria in Solid Tumors; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization

1.2 Synopsis

International Co-ordinating Investigator

PPD
PPD 106 Zhongshan 2nd Rd, Yuexiu, Guangzhou, Guangdong 510080 China

Protocol Title:

A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Study of Durvalumab as Consolidation Therapy in Patients with Locally Advanced, Unresectable, Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed following Definitive, Platinum-Based, Chemoradiation Therapy (PACIFIC 5)

Rationale:

Lung cancer has been the most common cancer in the world for several decades, and the majority of all lung cancers are non-small cell lung cancer. Approximately one-third of those patients with non-small cell lung cancer present with Stage III disease. Chemoradiation has been the standard of care for these patients for a decade, but progression-free survival is only about 8 months; new options are needed. The PACIFIC study has recently demonstrated that immuno-oncology agent durvalumab as consolidation therapy with concurrent chemoradiation therapy can prolong progression-free survival to about CCI months. The PACIFIC study restricted the patient population to those who have received concurrent chemoradiation therapy, but due to the noteworthy toxicity of concurrent chemoradiation therapy, many patients may have to use another option, that is, sequential chemoradiation therapy. This study will evaluate if the success of concurrent chemoradiation therapy followed by durvalumab can be translated to a broader population including those who have received sequential chemoradiation therapy, where an unmet need remains.

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab treatment compared with placebo in terms of PFS in randomised participants without sensitizing EGFR mutations or ALK rearrangements (i.e. mITT population)	PFS using BICR assessments according to RECIST 1.1[a]
Key secondary objective:	**Endpoint/variable:**
To further assess the efficacy of durvalumab compared with placebo in terms of OS in the mITT	OS

Objectives and Endpoints

Secondary objective:	Endpoint/variable:
To further assess the efficacy of durvalumab treatment compared with placebo in terms of PFS in all randomised participants (i.e. ITT population)	PFS using BICR assessments according to RECIST 1.1[a]
To further assess the efficacy of durvalumab compared with placebo in terms of OS in the ITT	OS
To further assess the efficacy of durvalumab compared with placebo in terms of OS24, ORR, DoR, PFS12, PFS18, PFS2, and TTDM in the mITT, and separately in ITT	OS24 ORR using BICR assessments according to RECIST 1.1[b] DoR using BICR assessments according to RECIST 1.1[b] PFS12 and PFS18 using BICR assessments according to RECIST 1.1 PFS2 as defined by local standard clinical practice TTDM using BICR assessments according to RECIST 1.1[b]
To assess the PK of durvalumab	Concentration of durvalumab in blood and non-compartmental PK parameters (such as peak concentration and trough, as data allow) (sparse sampling)
To investigate the immunogenicity of durvalumab	ADA (confirmatory results: positive or negative; titres [ADA neutralising antibodies will also be assessed])
To assess symptoms and health-related quality of life in participants treated with durvalumab compared with placebo using EORTC QLQ-C30 v3 and QLQ-LC13 in the mITT, and separately in the ITT	Change in patient-reported symptoms, functioning and global health status/QoL
To investigate the relationship between a participant's baseline tumour PD-L1 expression and efficacy outcomes with durvalumab compared with placebo in the mITT, and separately in the ITT	IHC analysis of tumoural PD-L1 expression and spatial distribution within the tumour microenvironment relative to efficacy outcomes (OS, PFS, and ORR)
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability profile of durvalumab compared with placebo	AEs, physical examinations, vital signs, electrocardiograms, and laboratory findings
Exploratory objective:	**Endpoint/variable:**

Objectives and Endpoints

To investigate the relationship between a participant's CCI and efficacy outcomes with durvalumab	CCI relative to efficacy outcomes (OS, PFS, and ORR)
To explore irRECIST criteria as an assessment methodology for clinical benefit of durvalumab compared with placebo by BICR	PFS and ORR using BICR assessments according to irRECIST
To investigate the relationship between durvalumab PK exposure and clinical outcomes, efficacy, AEs and/or safety parameters, if deemed appropriate	A graphical and/or a data-modelling approach will be used to analyse durvalumab PK exposure and the relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate
To describe and evaluate resource use associated with durvalumab treatment and underlying disease	Health resource utilisation measures including hospitalisation, outpatient visits, or emergency department visits
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on participant reported data
CCI [redacted]	[redacted]
To explore the relationship(s) between a participant's biomarker status and durvalumab PK exposure and clinical outcomes before and after treatment	Biomarker status before and after treatment and durvalumab PK exposure and relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate
To explore potential biomarkers in residual biological samples (eg, CCI [redacted], which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify participants likely to respond to durvalumab treatment	Correlation of biomarkers with response to durvalumab treatment and/or the progression of cancer

[a] The primary analysis of PFS will be based on programmatically derived PFS BICR assessment according to RECIST 1.1. See the statistical methods section for further details.

[b] Analysis of ORR and DoR will be based on BICR assessment according to RECIST 1.1. See the statistical methods section for further details.

Note: Prior irradiated lesions may be considered measurable and selected as target lesions, provided they fulfil the other criteria for measurability.

ADA Anti-drug antibody; AE Adverse event; BICR Blinded Independent Central Review; DoR Duration of response; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; IHC Immunohistochemical; irRECIST Immune-related Response Evaluation Criteria In Solid Tumors; ORR Objective response rate; OS Overall survival; OS24 Proportion of participants alive at 24 months from randomisation; PD-L1 Programmed death ligand 1; PFS Progression-free survival; PFS2 Time from randomisation to second progression; PFS12 Proportion of participants alive and

progression free at 12 months from randomisation; PFS18 Proportion of participants alive and progression free at 18 months from randomisation; PK Pharmacokinetic(s); QLQ-LC13 13-item self-administered questionnaire for lung cancer; QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumors; [redacted]; TTDM Time to death or distant metastasis.

Overall design:

This is a Phase III, randomised, double-blind, placebo-controlled, multicentre study assessing the efficacy and safety of durvalumab compared with placebo, as consolidation therapy in participants with locally advanced, unresectable, non-small cell lung cancer (Stage III), who have not progressed following definitive, platinum-based, chemoradiation therapy.

Participants will be required to undergo a two-part screening process. In screening visit part I, participants will be asked to consent for providing archived or newly acquired tumour samples to perform prospective tumour biomarker assessment (for PD-L1; EGFR mutation and ALK mutation will be tested, if there's no available result from local laboratories). Consent for prospective testing of the archived or newly acquired tumour samples could be given before, during or after chemoradiation. However, any irradiated sample is not acceptable and a biopsy procedure during screening period is not allowed. The purpose of screening visit part I is to allow more time for the tumour sample analysis to be conducted. Screening visit part II consent must be provided after participants complete CRT. Approximately 400 participants (who are in complete response, partial response, or have stable disease following definitive, platinum-based, concurrent or sequential chemoradiation therapy) will be randomised globally.

The study will be conducted in a double-blind manner. The participant, the Investigator, and the study site staff will be blinded to study treatment allocation. The study site pharmacist and/or other appropriate site staff will be unblinded to study treatment.

Randomisation will be stratified by the level of PD-L1 expression (PD-L1<1% versus PD-L1≥1%) and prior therapy (concurrent versus sequential chemoradiation therapy).

Study Period:

Estimated date of first participant enrolled: Quarter 4 2018 rest of world, Quarter 4 2019 China

Estimated date of last participant completed: approximately Quarter 1 2027

Number of participants:

Approximately 400 participants who received concurrent chemoradiation therapy or sequential chemoradiation therapy will be randomised 2:1 to durvalumab or placebo. The number of participants with sensitizing EGFR mutation (e.g., exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) or ALK rearrangement

randomised will be capped at approximately 7%. In order to reflect global clinical practice, study will recruit at least 60% of participants who received prior cCRT. The majority of participants will be recruited in China.

Screen failures are participants who do not fulfil the eligibility criteria for the study and therefore must not be randomised. Withdrawn participants will not be replaced.

Treatments and treatment duration:

The study includes the two-part screening process (part I up to 84 days; part II up to 28 days), Treatment Period (until treatment discontinuation criterion is met), and Follow-up Period.

Durvalumab monotherapy

- Durvalumab 1500 mg via intravenous infusion every 4 weeks, starting on Week 0, until confirmed radiological progression or other discontinuation criterion (Section 7.1) is met. (Please note, if a participant's weight falls to 30 kg or below (≤30 kg), then the participant should receive weight-based dosing equivalent to 20 mg/kg of durvalumab every 4 weeks after consultation between the Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the participant should start receiving the fixed dosing of durvalumab 1500 mg every 4 weeks).

Placebo

- Intravenous infusion bags of normal saline (0.9% [w/v] sodium chloride) injection via intravenous infusion every 4 weeks, starting on Week 0, until confirmed radiological progression or other discontinuation criterion (Section 7.1) is met

Duration of treatment

Unless specific treatment discontinuation criteria (Section 7.1) are met, participants in the durvalumab and placebo treatment arms will continue therapy until confirmed radiological progression (defined in Appendix E).

Progression during treatment

During the Treatment Period, participants who are clinically stable at an initial Response Evaluation Criteria in Solid Tumors 1.1-defined radiological progression of disease may continue to receive study treatment at the discretion of the Investigator and participants. A follow-up scan is to be collected after the initial Response Evaluation Criteria in Solid Tumors 1.1-defined radiological progression of disease, no less than 4 weeks after the prior assessment of progression of disease and no later than the next regularly scheduled imaging visit, and this scan is evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix E. Participants with confirmed PD who continue to receive study treatment at the discretion of the Investigator and participant (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit, and tumor

assessments should continue on their regular imaging schedule for the duration of treatment. If the subsequent scan does not confirm the immediate prior radiological progressive disease, scanning should continue until the next Response Evaluation Criteria in Solid Tumors 1.1-defined radiological progression of disease, which in turn will require a subsequent scan evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix E.

Follow-up of participants post discontinuation of study treatment

Participants who have discontinued study treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy will be followed up with tumour assessments until Response Evaluation Criteria in Solid Tumors 1.1-defined radiological progression of disease plus an additional follow-up scan or until death (whichever comes first) and followed for survival. PRO questionnaires will be followed up until PFS2.

Survival

All participants randomised in the study should be followed up for survival.

Independent Data Monitoring Committee:

The Independent Data Monitoring Committee will meet periodically in accordance with the IDMC charter to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings.

Full details of the Independent Data Monitoring Committee procedures and processes can be found in the Independent Data Monitoring Committee Charter.

Statistical methods

The primary aim of the study is to compare the efficacy of durvalumab with placebo in terms of progression-free survival per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) as assessed by Blinded Independent Central Review (BICR) in the modified intent-to-treat (mITT) population. Progression-free survival will be defined as the time from the date of randomisation until the date of objective disease progression or death by any cause, regardless of whether the participant withdraws from randomised therapy or receives another anticancer therapy prior to progression.

Secondary efficacy objectives include evaluation of overall survival in the mITT (key secondary), PFS and OS in the intent-to-treat (ITT), the proportion of participants alive at 24 months from randomisation, objective response rate, duration of response, the proportion of participants alive and progression free at 12 months from randomisation, the proportion of participants alive and progression free at 18 months from randomisation, the time from randomisation to second progression, and time to death or distant metastasis. Other secondary objectives include an assessment of safety and tolerability, durvalumab pharmacokinetic

exposure, immunogenicity, and patient-reported outcomes. Exploratory objectives are also included.

Efficacy data will be summarised and analysed based on the mITT (primary population), and separately based on the ITT population, and the treatment arms will be compared on the basis of randomised treatment, regardless of the treatment actually received. Participants who were randomised but did not subsequently go on to receive investigational product are included in the mITT/ITT population. Other populations include pharmacokinetics and safety.

Approximately 400 participants who received concurrent chemoradiation therapy or sequential chemoradiation therapy will be randomised 2:1 to durvalumab or placebo. Of the 400 randomised participants, approximately 375 participants without sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements will be included in the mITT population.

The final (primary) PFS analysis for superiority will be performed in the mITT when whichever of the following conditions have been met first:

- Reaching approximately CCI BICR progression-free survival events in the CCI across the durvalumab and placebo treatment arms (approximately CCI maturity)

OR

- Approximately CCI months follow-up from last participant randomized to the study.

The final OS analysis will be performed when reaching approximately CCI death events CCI maturity) or approximately CCI months follow-up from the last participant randomization in the mITT across the durvalumab and placebo treatment arms, whichever occurs first.

The study will randomise approximately 400 participants who received concurrent chemoradiation therapy or sequential chemoradiation therapy. Of the 400 randomised participants, approximately 375 participants without sensitizing EGFR mutations or ALK rearrangements will be included in the mITT population. If the true progression-free survival hazard ratio is CCI with an estimated CCI BICR PFS events in the mITT, the study will provide at least CCI power to demonstrate a statistically significant difference for progression-free survival with a CCI this translates to an approximately CCI month benefit in median progression-free survival over CCI months on placebo. The smallest treatment difference that would be statistically significant is a hazard ratio of CCI

The overall alpha level for comparison of the secondary key endpoint of overall survival CCI will be CCI . The final overall analysis for superiority will be performed when reaching approximately CCI death events

[redacted] maturity) or approximately [redacted] months follow-up from the last participant randomization, whichever occurs first. If the true overall survival hazard ratio is [redacted], with an estimated [redacted] OS events, this study will provide [redacted] power to demonstrate a statistically significant difference for overall survival, assuming a [redacted] 2-sided significance level (with overall 2-sided alpha for OS as [redacted]. This translates to a [redacted]-month benefit in median overall survival over [redacted] months on placebo. The smallest treatment difference that would be statistically significant is a hazard ratio of [redacted] Up to two interim analyses for OS will be conducted: 1) at the same time as primary PFS analysis and 2) at approximately [redacted] months after the OS first interim analysis, with approximately [redacted] of the target events respectively. If the expected DCO for OS final analysis is within [redacted] months after the OS first interim analysis, the OS second interim analysis may be removed.

If the interim results do not meet the criterion of stopping for superiority for a given hypothesis, then follow-up will continue until the final analysis, following which the hypothesis will be re-tested.

Progression-free survival will be analysed using a stratified log-rank test (stratified for the level of PD-L1 expression [PD-L1 <1% or PD-L1≥1%] and prior therapy [concurrent or sequential chemoradiation therapy]). The effect of treatment will be estimated by the hazard ratio together with corresponding 95% confidence interval and p-value.

Safety and tolerability data will be presented by treatment arm using the safety population.

1.3 Schema

The general study design is summarised in [redacted]


CCI

2 INTRODUCTION

Investigators should be familiar with the durvalumab IB.

2.1 Study rationale

By 2012 there were an estimated 1.8 million new cases of lung cancer, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total) (GLOBOCAN 2012). NSCLC represents approximately 80% to 85% of all lung cancers, and 30% of patients present with Stage III disease. Standard treatment for patients with a good performance status and unresectable Stage III NSCLC is platinum-based doublet chemotherapy and radiotherapy administered cCRT). However, the median PFS among patients who have received chemoradiotherapy is poor (approximately 8 months), and only 15% of patients are alive at 5 years. The PACIFIC study has recently demonstrated that immuno-oncology agent durvalumab as consolidation therapy with concurrent chemoradiation therapy (cCRT) can prolong PFS to about 17 months (Antonia et al 2017).

Chemoradiotherapy often induces initial tumour shrinkage and systemic control followed by eventual relapse. The initial tumour shrinkage observed in some patients following chemoradiotherapy is the result of cell death and tumour damage. Chemoradiotherapy-induced cell death can enhance the ability of the immune system to recognise and respond to the tumour through enhanced antigen release and presentation. Triggering or augmenting an antigenic antitumour response with chemoradiotherapy, followed by an anti-programmed death ligand 1 (PD-L1) therapy, could enhance antitumour activity by improving local control and decreasing systemic spread.

Both chemotherapy and radiotherapy can up-regulate the expression of PD-L1 (Zhang et al 2008b, Butts et al 2014, Deng et al 2014) due to the release of cytokines and other inflammatory molecules, which could therefore make such tumours sensitive to a PD-L1 directed therapy. The study by Deng et al showed that therapeutic blockade of PD-L1 could enhance thymus gland lymphocyte (T cell) effector function when PD-L1 is expressed in chronically inflamed tissues and tumours (Deng et al 2014). The study demonstrated that PD-L1 was upregulated in the tumour microenvironment after ionizing radiation and that administration of anti–PD-L1 enhanced the efficacy of radiation through a cytotoxic T lymphocyte (T cell)-dependent mechanism. Concomitant with radiation-mediated tumour regression, it was also observed that radiation and anti–PD-L1 synergistically reduced the local accumulation of tumour-infiltrating myeloid-derived suppressor cells that suppress T cells and alter the tumour immune microenvironment (Butts et al 2014, Deng et al 2014).

Durvalumab is a human monoclonal antibody that binds to PD-L1 and blocks its interaction with programmed death 1 (PD-1) and cluster of differentiation (CD)80 (B7.1). Durvalumab

following cCRT has shown promise in the PACIFIC study, an ongoing, randomised, double-blind, placebo-controlled, Phase III study to evaluate the efficacy and safety of durvalumab consolidation therapy in patients with locally advanced, unresectable Stage III NSCLC, who have not progressed following definitive, platinum-based, cCRT. The durvalumab treatment demonstrated a median PFS improvement of 11.2 months when compared with placebo, and durvalumab reduced risk of death and progression by 48% compared to placebo. Consistent OS and PFS benefit with durvalumab was observed across all prespecified subgroups with the exception of the EGFR-positive subgroup, for which survival benefit was uncertain (Faivre-Finn et al 2021). Therefore, in this study, participants harbouring EGFR mutations and ALK alterations will be removed from the primary objective and key secondary objective.

Other endpoints such as proportion of participants alive and progression free at 12 months from randomisation (PFS12), proportion of participants alive and progression free at 18 months from randomisation (PFS18), objective response rate (ORR), time to death or distant metastasis (TTDM), and duration of response (DoR) also provided support of the clinical benefit seen from durvalumab in this population (see Section 2.3.1 for details).

These combined data led to the hypothesis underlying this study: that durvalumab added after definitive chemoradiation therapy would provide clinical benefit by potentiating the pro-inflammatory effects of the definitive therapy.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the IB.

2.2.1 Immunotherapies

It is increasingly understood that cancers are recognised by the immune system, and under some circumstances, the immune system may control or even eliminate tumours (Dunn et al 2004).

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The programmed death 1 (PD-1) receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and programmed death ligand 2 (PD-L2; B7-DC; CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to a family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumour cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly over-expressed on tumour cells or on non-transformed cells in the tumour microenvironment (Pardoll 2012). PD-L1 expressed on the tumour cells binds to PD-1 receptors on the activated T cells, leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumour microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumour cells in response to endogenous anti-tumour activity.

The inhibitory mechanism described above is co-opted by tumours that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1-mediated inhibition of anti-tumour immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumour immune responses in patients with cancer. Results of pre-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance anti-tumour immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008a) with responses that tend to be more pronounced in patients with tumours that express PD-L1 (Powles et al 2014, Rizvi et al 2015a, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

Pre-clinical data has now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as CTLA-4 and PD-L1 has promising clinical activity. Ipilimumab was first granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell NSCLC, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumour types.

2.2.2 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with

PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumour elimination. In vitro studies demonstrate that durvalumab antagonises the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon (IFN)-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's anti-tumour immune response by binding to PD-L1 and shifting the balance towards an anti-tumour response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than CCI patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarised in Section 4.3.1 and Section 8.3.13. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of durvalumab may be found in the IB.

See Section 9.6.1 and Appendix A for information regarding the Data Monitoring Committee.

2.3.1 Potential benefits of durvalumab

Durvalumab, a human monoclonal antibody directed against human PD-L1, may offer benefit to this patient population. In the PACIFIC study, durvalumab treatment demonstrated a statistically significant (hazard ratio [HR]: 0.52; 98.9% confidence interval [CI]: 0.39, 0.70; p-value less than 0.0001) and clinically meaningful prolongation of PFS (according to Blinded Independent Central Review [BICR] assessment of RECIST 1.1) compared with placebo in patients with locally advanced, unresectable NSCLC whose disease had not progressed after platinum-based cCRT. The risk of progression or death was reduced by 48% on the durvalumab treatment compared with placebo. The durvalumab treatment demonstrated a median PFS improvement of 11.2 months when compared with placebo (the median PFS was 16.8 months in the durvalumab group and 5.6 months in the placebo group). The PFS benefit in favour of durvalumab was observed irrespective of PD-L1 expression (HR: 0.59; 95% CI: 0.43, 0.82 for less than 25% and HR: 0.41; 95% CI: 0.26, 0.65 for at least 25%).

The improvement of PFS is supported by the clinically meaningful incremental ORR of 12% over placebo (28.4% in the durvalumab group vs 16.0% in the placebo group; nominal p-value less than 0.001). The responses were durable with the median DoR not reached in the durvalumab group, compared to 13.8 months in the placebo group. TTDM was longer for the durvalumab group compared to the placebo group (HR: 0.52; 95% CI: 0.39, 0.69; nominal p-value <0.0001). The median TTDM was 23.2 months in the durvalumab group, compared to 14.6 months in the placebo group.

In addition, durvalumab treatment demonstrated a statistically significant OS benefit with clinically meaningful improvement compared to placebo (stratified HR for death, 0.68; 99.73% CI, 0.469 to 0.997; p=0.0025). The 4-year survival update demonstrated a long-term clinical benefit with durvalumab after chemoradiotherapy. Median OS were 47.5 months in durvalumab arm, compared to 29.1 months in placebo arm, with 18.4 months prolongation. The OS rate remains higher for durvalumab compared to placebo at 36 month (56.7% vs 43.6%, respectively) and 48 month (49.6% vs 36.3%, respectively) landmarks.

Please refer to the current IB for clinical experience with durvalumab.

2.3.2 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against tumour cells. By stimulating the immune system, however, there is the potential for adverse effects on normal tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and that may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypo- and hyper-thyroidism.

2.3.2.1 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis, adrenal insufficiency, hyper- and hypo-thyroidism, and type I diabetes mellitus), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including

neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

For information on all identified and potential risks with durvalumab, please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies, AEs reported very commonly include events such as fatigue, diarrhoea, nausea and vomiting, decreased appetite, and muscle and joint pain. A total of 5% to 10% of participants discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, severe adverse events (SAEs), and Common Toxicity Criteria (CTC) Grade 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.5).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

2.3.3 Overall benefit/risk

In summary, the potential for clinical benefit associated with inhibition of the PD-1/PD-L1 pathway, as supported by objective responses observed in earlier studies in participants with NSCLC and demonstrated in terms of PFS by a Phase III study in participants with locally advanced unresectable Stage III NSCLC after cCRT, outweighs the known and potential risks based on the AEs reported in participants treated with durvalumab and other PD-1/PD-L1 inhibitors. Thus, the benefit/risk assessment favours the conduct of this proposed study.

The safety of participants in this study will be assessed by an Independent Data Monitoring Committee (IDMC) via ongoing safety assessments periodically in accordance with the IDMC charter.

3 OBJECTIVES AND ENDPOINTS

Objectives and Endpoints

Primary objective:	Endpoint/variable:
To assess the efficacy of durvalumab treatment compared with placebo in terms of PFS in randomised participants without sensitizing EGFR mutations or ALK rearrangements (i.e. mITT)	PFS using BICR assessments according to RECIST 1.1[a]

Objectives and Endpoints

Key secondary objective:	Endpoint/variable:
To further assess the efficacy of durvalumab compared with placebo in terms of OS in the mITT	OS
Secondary objective:	**Endpoint/variable:**
To further assess the efficacy of durvalumab treatment compared with placebo in terms of PFS in all randomised participants (i.e. ITT)	PFS using BICR assessments according to RECIST 1.1[a]
To further assess the efficacy of durvalumab compared with placebo in terms of OS in the ITT	OS
To further assess the efficacy of durvalumab compared with placebo in terms of: OS24, ORR, DoR, PFS12, PFS18, PFS2, and TTDM in the mITT, and separately in the ITT	OS24 ORR using BICR assessments according to RECIST 1.1[b] DoR using BICR assessments according to RECIST 1.1[b] PFS12 and PFS18 using BICR assessments according to RECIST 1.1 PFS2 as defined by local standard clinical practice TTDM using BICR assessments according to RECIST 1.1[b]
To assess the PK of durvalumab	Concentration of durvalumab in blood and non-compartmental PK parameters (such as peak concentration and trough, as data allow) (sparse sampling)
To investigate the immunogenicity of durvalumab	ADA (confirmatory results: positive or negative; titres [ADA neutralising antibodies will also be assessed])
To assess symptoms and health-related quality of life in participants treated with durvalumab compared with placebo using EORTC QLQ-C30 v3 and QLQ-LC13 in the mITT, and separately in the ITT	Change in patient-reported symptoms, functioning and global health status/QoL
To investigate the relationship between a participant's baseline tumour PD-L1 expression and efficacy outcomes with durvalumab compared with placebo in the mITT, and separately in the ITT	IHC analysis of tumoural PD-L1 expression and spatial distribution within the tumour microenvironment relative to efficacy outcomes (OS, PFS, and ORR)
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability profile of durvalumab compared with placebo	AEs, physical examinations, vital signs, electrocardiograms, and laboratory findings

Objectives and Endpoints

Exploratory objective:	Endpoint/variable:
To investigate the relationship between a participant's CCI and efficacy outcomes with durvalumab	CCI relative to efficacy outcomes (OS, PFS, and ORR)
To explore irRECIST criteria as an assessment methodology for clinical benefit of durvalumab compared with placebo by BICR	PFS and ORR using BICR assessments according to irRECIST [c]
To investigate the relationship between durvalumab PK exposure and clinical outcomes, efficacy, AEs and/or safety parameters, if deemed appropriate	A graphical and/or a data modelling approach will be used to analyse durvalumab PK exposure and the relationship with clinical outcomes, efficacy, AEs and/or safety parameters, as deemed appropriate
To describe and evaluate resource use associated with durvalumab treatment and underlying disease	Health resource utilisation measures including hospitalisation, outpatient visits, or emergency department visits
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on participant reported data
CCI	[redacted]
To explore the relationship(s) between a participant's biomarker status and durvalumab PK exposure and clinical outcomes before and after treatment	Biomarker status before and after treatment and durvalumab PK exposure and relationship with clinical outcomes, efficacy, AEs and/or safety parameters, as deemed appropriate
To explore potential biomarkers in residual biological samples (eg, CCI), which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify participants likely to respond to durvalumab treatment	Correlation of biomarkers with response to durvalumab treatment and/or the progression of cancer

[a] The primary analysis of PFS will be based on programmatically derived PFS BICR assessment according to RECIST 1.1. See the statistical methods section for further details.

[b] Analysis of ORR, DoR, and TTDM will be based on BICR assessment according to RECIST 1.1. See the statistical methods section for further details.

[c] Exploratory endpoints and analyses related to PFS/ORR analyses using irRECIST data may be presented outside of the main CSR.

Note: Prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

ADA Anti-drug antibody; AE Adverse event; BICR Blinded Independent Central Review; DoR Duration of response; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life

questionnaire; IHC Immunohistochemical; irRECIST Immune-related Response Evaluation Criteria In Solid Tumors; ORR Objective response rate; OS Overall survival; OS24 Proportion of participants alive at 24 months from randomisation; PD-L1 Programmed death ligand 1; PFS Progression free survival; PFS2 Time from randomisation to second progression; PFS12 Proportion of participants alive and progression free at 12 months from randomisation; PFS18 Proportion of participants alive and progression free at 18 months from randomisation; PK Pharmacokinetic(s); QLQ-LC13 13-item self-administered questionnaire for lung cancer; QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumors; TTDM Time to death or distant metastasis; [redacted]; T cell T lymphocyte.

4 STUDY DESIGN

4.1 Overall design

This study is a Phase III, randomised, double-blind, placebo-controlled, multicentre study assessing the efficacy and safety of durvalumab compared with placebo as consolidation therapy in participants with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based, chemoradiation therapy.

Approximately 400 participants with locally advanced, unresectable NSCLC (Stage III) who received cCRT or sCRT will be randomised globally. These participants will be in complete response (CR), partial response (PR), or have stable disease (SD) following definitive, platinum-based, concurrent or sequential chemoradiation therapy.

Participants must have histologically or cytologically documented NSCLC and present with locally advanced, unresectable (Stage III) disease (according to Version 8 of the International Association for the Study of Lung Cancer [IASLC] Staging Manual in Thoracic Oncology. The number of participants with a sensitizing EGFR mutation (e.g., exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) or ALK rearrangement will be capped at approximately 7% of the total number of participants randomised. In order to reflect global clinical practice, study will recruit at least 60% of participants who received prior cCRT. The majority of participants will be recruited in China.

Participants will be randomised in a 2:1 ratio (durvalumab to placebo) to 1 of 2 arms:

- Durvalumab (1500 mg every 4 weeks [q4w] intravenously [iv] until confirmed radiological progression, or other discontinuation criterion is met)
- Placebo (matching placebo for infusion q4w iv until confirmed radiological progression, or other discontinuation criterion is met)

Randomisation will be stratified by the level of PD-L1 expression (PD-L1 <1% or PD-L1≥1%] and prior therapy (cCRT or sCRT). Participants must not have progressed following definitive, platinum-based, concurrent or sequential CRT (see Section 5.1 for details). For those participants randomised to the placebo arm, no crossover to the durvalumab arm is permitted; similarly, those participants randomised to the durvalumab arm cannot crossover to the placebo arm.

Administration of study treatment (ie, investigational product [IP] durvalumab or placebo) will commence on Day 1 following randomisation to durvalumab or placebo after confirmation of eligibility and will continue on a q4w schedule until confirmed radiological progression, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons which reaching the discontinuation criteria (Section 7.1).

Tumour assessments using computed tomography (CT)/magnetic resonance imaging (MRI) will be performed at the times specified in Table 1 and Table 2. RECIST 1.1 measurements (using BICR assessments) will be used to derive the primary variable of PFS and secondary variables of ORR, DoR, PFS12, and PFS18.

Once a participant has had objective radiological progression recorded and has discontinued study treatment, the participant will be followed up for survival status monthly at the first 4 months, and then every 2 months until death, withdrawal of consent, or the end of the study.

Once the planned statistical analyses have been performed, the analysis portion of the clinical study will have been completed. See Section 4.4 for more information on study completion.

In the event that a roll-over or safety extension study is available at the time of the final data cutoff (DCO) and database closure, participants currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any participant who would be proposed to move to such a study would be given a new informed consent.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered. Guidelines for the management of toxicities are described in Section 8.4.5.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.1.1 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS- CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

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

- Obtaining reconsent for the mitigation procedures (note, in the case of verbal reconsent, the Informed Consent Form (ICF) should be signed at the participant's next contact with the study site).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix I.

4.2 Scientific rationale for study design

The current SoC for unresectable Stage III disease is cCRT. The rationale for combining chemotherapy and radiotherapy is to combine the benefits of radiotherapy in terms of local regional control with the benefits of chemotherapy in terms of reducing the risks of metastatic disease. With CRT, there is the potential for chemotherapy, given during a course of radiotherapy, to enhance the effectiveness of radiotherapy (i.e. radiosensitisation) (O'Rourke et al 2010).

For patients with unresectable Stage III disease, combined modality therapy (chemoradiation) is superior to radiation alone, and cCRT is superior to sequential therapy (National Comprehensive Cancer Network [NCCN Guidelines 2014). cCRT regimens that may be used for all histologies for initial treatment include cisplatin/etoposide, cisplatin/vinblastine, or carboplatin/paclitaxel (TAXOL®). For non-squamous NSCLC, other cCRT regimens include cisplatin/pemetrexed (ALIMTA®) (NCCN Guidelines 2014). The guidelines for the treatment of patients with unresectable Stage III NSCLC in Europe (Vansteenkiste et al 2013) and Japan (Saijo et al 2010) are in line with those used in the US. The best survival outcomes can be achieved in patients with Stage III NSCLC with concurrent chemoradiation instead of sequential; however, cCRT also has a higher rate of Grade 3 or 4 esophagitis than sCRT. Consequently, cCRT is only given to patients with minimal or no comorbidities, a good general condition, and who are relatively young. Decelerated approaches such as sCRT may be a valuable alternative for patients who are not eligible for cCRT (De Ruysscher et al 2009).

Despite longer survival benefit comparing with sCRT, the majority of patients who receive cCRT inevitably progress (PFS is usually short; approximately 8 months), and 5-year OS is approximately 15% (Butts et al 2014). Though advances have been made in improving

survival from Stage III NSCLC by optimising local control, evidence suggests that cCRT also does not reduce the risk of distant relapse.

With fewer cycles and, in some cases, lower doses of chemotherapy being delivered in the concurrent setting, several studies have assessed whether delivering induction or consolidation treatment will improve survival. A pooled analysis of 41 Phase II/III trials confirmed that there remains no evidence to suggest that consolidation chemotherapy after cCRT improves survival for patients with Stage III NSCLC, and current guidelines continue to recommend cCRT alone for the treatment of inoperable Stage III NSCLC (Bayman et al 2014). However, intensification of both radiotherapy and concurrent chemotherapy may result also into excessive toxicity or incomplete treatment. There is still, therefore, a significant unmet medical need for additional treatment options for use in this patient population to improve on PFS and OS (see Section 2.2).

The consolidation setting post CRT may be ideal to evaluate the efficacy of immunotherapy, which is aimed at boosting the ability of the patient's immune system to eliminate cancer cells. Both chemotherapy and radiotherapy can up-regulate the expression of PD-L1 (Zhang et al 2008b, Deng et al 2014) due to the release of cytokines and other inflammatory molecules, which could therefore make such tumours sensitive to a PD-L1-directed therapy. Durvalumab, an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects and therefore enhance the cytotoxic activity of antitumour T cells. Emerging clinical data from the PACIFIC study have proven this concept (see Section 2.3.1) by providing early, statistically significant evidence of clinical activity and a manageable safety profile. This study will further evaluate durvalumab in patients with unresectable Stage III NSCLC in both cCRT and sCRT to ascertain if the success of cCRT can also be applied to sCRT.

Durvalumab will be compared against placebo in this study as although durvalumab demonstrated a PFS benefit in this setting, it is not yet available (i.e approved and/or reimbursed) as a treatment option in countries where this study is conducted. Furthermore the 2:1 randomised allocation ensures there is more opportunity for participants to receive durvalumab than placebo in this study.

4.2.1 Timing of treatment with durvalumab relative to concurrent or sequential chemoradiation therapy

Non-clinical data show that both chemotherapy and ionising radiation up-regulate PD-L1 expression (Deng et al 2014, Zhang et al 2008b). In addition, chemotherapy and radiotherapy both release new antigens, leaving the cancer to act as an in situ vaccine that can elicit tumour-specific T cells. The PACIFIC study showed that the subset of patients who started durvalumab <14 days after CRT had superior results than the subset of patients who started 14 to 42 days after CRT. Thus, starting durvalumab as close as possible to the completion of the

CRT when antigen release and PD-L1 expression are most likely to be at their maximum will hypothetically result in the most optimal benefit.

4.2.2 Predictive biomarkers and rationale for an unselected population in Study D933YC00001

For this study, we propose not to exclude any biomarker-defined subpopulation and, where possible, to carefully assess these patient characteristics in the context of this study, and other studies.

Tumour biopsies and viable tissue may be difficult to obtain post CRT. Tumours evolve with time and in response to treatment, and PD-L1 expression is likely to be different, post CRT. In addition, non-clinical data show that both chemotherapy and ionising radiation up-regulate PD-L1 expression (Deng et al 2014, Zhang et al 2008b). Therefore, PD-L1 expression from a biopsy sample prior to CRT may not accurately reflect the state of disease at the time the participant enrols in this study and is randomised to either durvalumab or placebo. In addition, tumours that are poorly immunogenic or that have become immunosuppressive can likely be made immunogenic through administration of pro-immunogenic therapies designed to increase antigen release from the cancer cell Therefore, as stated, we propose not to restrict inclusion in this study based on PD-L1 expression from tissue samples available prior to CRT, but to prospectively evaluate the relevance of PD-L1 expression to outcome.

Findings from the PACIFIC study comparing durvalumab and placebo in an all-comers population of participants with Stage III NSCLC did not demonstrate PD-L1 to be a predictive marker. Participants with high (≥25%) or low (<25%) or negative (<1%) PD-L1 expression experienced clinical meaningful improved PFS over placebo (PD-L1 high: HR 0.41 [95% CI: 0.26, 0.65]; PD-L1 low: HR, 0.59 [95% CI: 0.43, 0.82]; PD-L1 negative: HR 0.73 [95% CI: 0.48, 1.11]) (Paz-Ares L 2020). In light of these results, this study target to recruit all comer population reflecting natural PD-L1 prevalence.

AstraZeneca has committed to identifying the right drug for the right patient; therefore, exploratory analyses of emerging immuno-oncology biomarkers are critical to this field. Recent studies have shown that tumours with higher CCI respond to checkpoint inhibition. The hypothesis is that tumours with CCI that can be recognized by the immune system. Improved ORR, PFS, and durable clinical benefit were observed in patients with high somatic nonsynonymous mutation burden in NSCLC patients who received pembrolizumab (Rizvi et al 2015b). Recently, CCI was examined as part of an exploratory analysis of the Checkmate 026 study, which compared nivolumab with platinum doublet chemotherapy in first-line metastatic NSCLC. For patients with a high CCI, the response rate was higher in those who received nivolumab versus chemotherapy (47% versus 28%), and PFS was improved (9.7 versus 5.8 months) (Carbone et

al 2017). Due to these observations, we will be evaluating CCI in relation to clinical response in this study.

4.2.3 Rationale for study endpoints (efficacy)

The primary aim of this study is to determine the efficacy of durvalumab (1500 mg q4w via iv infusion) compared with placebo in terms of PFS (mITT). PFS may serve as a surrogate endpoint for OS when differences between treatment arms are of sufficient magnitude and are clinically important (FDA Guidance 2011, Pazdur 2008). In certain settings, the utility of survival as an endpoint may potentially be confounded by subsequent therapies. Specifically, a number of agents targeting the PD-1/PD-L1 pathway in advanced NSCLC have been approved and are available on the market while this study is ongoing. This poses challenges in being able to fully characterise effects on OS if participants subsequently receive these immunotherapeutic agents. Therefore, PFS (mITT) will be the primary endpoint. Given that tumour response to immunotherapy may differ from typical responses, OS (mITT) will be a key secondary endpoint.

Antitumour activity will be assessed according to RECIST 1.1 guidelines, with the understanding that in the context of post-radiation changes, tumour assessment may be difficult and may need to be repeated over time to reach a clear determination regarding responses and PD (see Section 8.1). The primary analysis of PFS will be based on programmatically derived PFS based on BICR assessments. Sensitivity analyses will also be performed using study site Investigator's tumour data from all scans based on RECIST 1.1. Exploratory analysis may also be performed for data obtained from the BICR using irRECIST (Nishino et al 2013), which may be presented outside the main CSR.

Response to immunotherapy may differ from typical responses observed with cytotoxic chemotherapy, including the following differences (per Wolchok et al 2009):

1 Response to immunotherapy may be delayed.

2 Response to immunotherapy may occur after PD by conventional criteria.

3 SD while on immunotherapy may be durable and represent clinical benefit.

Use of Confirmation of Radiological Progression criteria as described (Appendix E) may discourage the early discontinuation of study drug and provide a more complete evaluation of its antitumour activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Notably, clinically significant deterioration is considered to be a rapid tumour progression that necessitates treatment with anticancer therapy other than durvalumab or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, and spinal cord compression).

The secondary symptoms and overall health related quality of life (HRQoL) endpoints assessed using the European Organisation for Research and Treatment of Cancer 30-item core quality-of-life questionnaire (EORTC QLQ-C30), version 3 and the complementary 13-item self-administered questionnaire for lung cancer (QLQ-LC13), will show the overall influence of the benefits and toxicity of the treatment from the participant's perspective and will aid in understanding the benefit/risk evaluation. These PRO questionnaires are well-established instruments that have been previously included in cancer clinical studies.

4.2.4 Rationale for study endpoints (other exploratory endpoints)

Biological samples will be used to explore potential CCI [redacted], which may influence the progression of cancer (and associated clinical characteristics) and/or response to treatment.

The assessment of health economic resource use data and derivation of health state utility will provide important information for payers and will be used within economic evaluations of durvalumab.

4.3 Justification for dose

4.3.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in participants with advanced solid tumours and from a Phase I study performed in Japanese participants with advanced solid tumour CCI [redacted]

PK/pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg every 2 weeks (q2w) or 15 mg/kg every 3 weeks (q3w), durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near-complete target saturation (membrane-bound and soluble programmed death ligand 1 [sPD-L1]), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No participants have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB.)

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by area under the concentration-time curve at steady state (4 weeks). Median maximum concentration at steady state is expected to be higher with [CCI] (~1.5-fold), and median trough concentration at steady state is expected to be higher with 10 mg/kg q2w (~1.25-fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w, with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of participants; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of anti-drug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal anti-tumour activity in animal models.

Given the similar area under the serum drug concentration-time curve and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of [CCI]

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the [CCI] regimen.

4.3.2 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses=0.1 to [CCI]; solid tumours). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based ([CCI] and fixed dosing [CCI] of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of [CCI] was selected to approximate [CCI] (based on median body WT of ~75 kg). A total of 1000 participants were simulated using body WT distribution of 40 to 120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-participant variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of

reducing the between-participant variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to [redacted]) is included in the current study.

4.4 End of study definition

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last scheduled procedure shown in the SoA.

The study may be terminated at individual study sites if the study procedures are not being performed according to Good Clinical Practice, if recruitment is slow, or when there are no longer any participants being treated or if the OS Follow-up Period before the final DCO for the study has occurred and all queries at that study site have been resolved.

Participants may be withdrawn from the study if the study itself is stopped. The study may be stopped if, in the judgment of AstraZeneca, participants are placed at undue risk because of clinically significant findings.

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

Treatment after final DCO for the study

The final DCO is the latest DCO for any of the planned analyses. For further details about treatment and participant management after the final DCO for the study, see Section 6.6.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each participant should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures; refer to Section 5.4.

In this protocol, "enrolled" participants are defined as those who sign informed consent of tumour sample collection (part I screening ICF). "Randomised" participants are defined as those who undergo randomisation and receive a randomisation number.

For procedures for withdrawal of incorrectly enrolled participants, see Section 6.2.2.

5.1 Inclusion criteria

Part I screening

Participants are eligible to be included in the study only if all of the following inclusion criteria apply and none of the Part II screening exclusion criteria numbers 1-5, 7, 10, 16-20 apply:

Informed consent

1 Capability to give signed informed consent of tumour sample collection that includes compliance with the requirements and restrictions listed in the pre-screening informed consent form (part I screening ICF) and in this protocol

2 Provision of signed and dated written part I screening ICF prior to any mandatory study-specific procedures, sampling, and analyses

The ICF consenting process is described in Appendix A 3.

Age

3 Age ≥18 years at the time of Screening

Type of participant and disease characteristics

4 Histologically or cytologically documented NSCLC and present with locally advanced, unresectable (Stage III) disease (according to Version 8 of the (IASLC Staging Manual in Thoracic Oncology]). Positron emission tomography/CT, MRI of the brain, and endobronchial ultrasound with biopsy are highly encouraged at diagnosis.

5 Tumour sample requirements are as follows: Provision of a tumour tissue sample (newly acquired sample ≤ 3 months old is preferred; an archived sample ≤ 6 months old is acceptable) in a quantity sufficient to allow for analysis. (refer to Section 8.8.1 and the Laboratory Manual for details). A biopsy procedure during screening period is not allowed. Study subject should not have received any intervening systemic therapy other than chemoradiotherapy for Stage III disease as described above.

6 Tumor PD-L1 status, with the Ventana SP263 PD-L1 IHC assay determined by a reference laboratory, must be known prior to randomization. Participant with unknown PD-L1 status is not eligible for the study. “Unknown” refers to (1) insufficient sample which is not able to be analyzed, or (2) sample could be analyzed but results not interpretable.

7 Documented EGFR and ALK status (locally or centrally) at screening visit part I. If the local laboratory will perform the test, a well-validated, local regulatory-approved kit must be used.

EGFR and ALK status must be available prior to randomisation. After approximately 7% sensitizing EGFR (e.g., exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) or ALK mutant participants have been randomised, the incoming participants with sensitizing EGFR (e.g., exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) or ALK mutation will not be enrolled.

Part II screening

Participants are eligible to be included in the study only if all the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capability to give signed informed consent of study procedure that includes compliance with the requirements and restrictions listed in the Main informed consent form (Part II screening ICF) and in this protocol

2 Provision of signed and dated written Part II screening ICF prior to any mandatory study-specific procedures, sampling, and analyses

The ICF consenting process is described in Appendix A 3.

Type of participant and disease characteristics

4 Histologically or cytologically documented NSCLC and present with locally advanced, unresectable (Stage III) disease (according to Version 8 of the (IASLC Staging Manual in Thoracic Oncology]). Positron emission tomography/CT, MRI of the brain, and endobronchial ultrasound with biopsy are highly encouraged at diagnosis.

5 Receipt of concurrent or sequential chemoradiation therapy, which must be completed within 1 to 28 days prior to first dose of IP in the study.

- For cCRT, participants must have received at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy. The last dose of chemotherapy must be prior to, or concurrent with, the final dose of radiation. Consolidation chemotherapy after radiation is not permitted, but no more than 2 cycles of induction chemotherapy prior to cCRT is acceptable.
- For sCRT, participants must have received at least 2 cycles of platinum-based chemotherapy before radiation therapy. The interval between administration of the last dose of chemotherapy regimen and start of RT must be no more than 6 weeks. Consolidation chemotherapy after radiation is not permitted.
  - Note: If a participant receives only 1 cycle of platinum-based chemotherapy concurrent with radiation treatment, this participant will be eligible for the study to participate in the sCRT stratum.
- The platinum-based chemotherapy regimen must contain cisplatin or carboplatin and 1 of the following agents: etoposide, vinblastine, vinorelbine, a taxane (paclitaxel or docetaxel), or pemetrexed, according to the local SoC regimens. (Gemcitabine is not included.)
- Participants must have received a total dose of radiation of 60 Gy ±10% (54 to 66 Gy) to be randomised as part of the chemoradiation therapy. Study sites are encouraged to adhere to the following mean organ radiation dosing:
  - Mean lung dose must be <20 Gy, and/or V20 must be <35%
  - Mean oesophagus dose must be <34 Gy
  - Heart V45 must be <35%, or V30 must be <50%
- Study sites should be aware of the recent RTOG 0617 Trial data demonstrating that doses higher than 60 Gy may be associated with greater toxicity and worse efficacy.

6 No progression following definitive, platinum-based, concurrent or sequential chemoradiation therapy

7 World Health Organization (WHO) PS of 0 or 1 at enrolment

8 No prior exposure to any anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines

9 Adequate organ and marrow function as defined below. Absolute neutrophil count, platelet count, and haemoglobin criteria cannot be met with transfusion or growth factor support administered within 14 days before randomisation.

- Haemoglobin ≥9 g/dL
- Absolute neutrophil count >1.5 × 10^9/L (1500 per mm^3)
- Platelet count >100 × 10^9/L (100000 per mm^3)
- Serum bilirubin ≤1.5× the upper limit of normal (ULN). This will not apply to participants with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of evidence of haemolysis or hepatic pathology), who will be allowed in consultation with their primary physician.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5× ULN
- Serum creatinine clearance (CL) >40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine CL

Males

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

Females:

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

10 Life expectancy of at least 12 weeks at Day 1

11 WT >30 kg

5.2 Exclusion criteria

Part I screening: Participants should not enter the study, if any of 1-5, 7, 10, and 16-20 exclusion criteria are fulfilled.

Part II screening: Participants should not enter the study if any of the following exclusion criteria are fulfilled.

Medical conditions

1 History of allogeneic organ transplantation

2 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g. colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis syndrome, or

Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

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

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

4 History of another primary malignancy except for

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of investigation product (IP) and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease

5 History of active primary immunodeficiency

6 Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive hepatitis B virus [HBV] surface antigen [HBsAg] result), **hepatitis C** (HCV), or **human immunodeficiency virus** (positive human immunodeficiency virus [HIV] 1/2 antibodies). Participants with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

7 Mixed small cell and NSCLC histology, sarcomatoid variant

8 Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 from the prior chemoradiation therapy. Participants with irreversible toxicity that is not reasonably expected to be exacerbated by study treatment may be included (eg, hearing loss) after consultation with the

AstraZeneca Study Physician. Grade 2 AE of laboratory abnormality for inclusion criteria 12 related lab parameters may be included as long as within the specified range in inclusion criteria 12.

9 Participants with Grade ≥2 pneumonitis from prior chemoradiation therapy

10 Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients

Prior/concomitant therapy

11 Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment other than those under investigation in this study

12 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP.
Note: Participants, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

13 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent and placement of vascular access are acceptable.

14 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)
- Systemic steroid administration required as prophylaxis against or to manage toxicities arising from chemotherapy and/or radiotherapy delivered as part of the chemoradiation therapy for locally advanced NSCLC

Prior/concurrent clinical study experience

15 Participation in another clinical study with an IP administered in the last 4 weeks prior to randomization.

16 Previous IP assignment in the present study

17 Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the Follow-up Period of an interventional study

18 Prior randomisation or treatment in a previous durvalumab ± tremelimumab clinical study regardless of treatment arm assignment

Other exclusions

19 Female participants who are pregnant or breastfeeding or male or female participants of reproductive potential who are not willing to employ effective birth control from Screening to 90 days after the last dose of durvalumab monotherapy

20 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements. Or the participant is not willing to/can not continue screening procedures during the screening period.

21 Meet any of the study protocol specified capping criteria.

Procedures for withdrawal of incorrectly enrolled participants are provided in Section 6.2.2.

Participant who is not willing or not able to continue screening is considered as screen failure but not withdrawal.

5.3 Lifestyle restrictions

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

1 Female participant of childbearing potential

- Female participants of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilised male partner must use at least 1 **highly** effective method of contraception (Table 3) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilised male partners of a female participant of childbearing potential must use a male condom plus spermicide (or male condom in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female participants should refrain from breastfeeding throughout this period.

2 Male participants with a female partner of childbearing potential

- Non-sterilised male participants who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide (or male condom in countries where spermicides are not approved) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation throughout this period.

– Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 3).

Please note, females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.
- Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table 3. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper-containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 3 Highly effective methods of contraception (<1% failure rate)

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

[a] This is also considered a hormonal method.

3 All participants: Participants should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

4 Restrictions relating to concomitant medications are described in Section 6.4.

5.4 Screen failures

Screen failures are participants who have signed the part I screening ICF or part I screening ICF plus part II screening ICF and do not fulfil the eligibility criteria for the study. These participants should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (i.e. participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (i.e. not randomised participants). Participants may be re-screened a single time, but they may not be re-randomised.

If a participant who has failed screening is re-screened, a new E-code must be assigned. Participants will reconfirm their consent to participate in the study by signing and dating a new consent form(s).

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

6 STUDY TREATMENTS

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to durvalumab or placebo.

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca will supply durvalumab (MEDI4736). The saline solution for the placebo will be supplied locally. See Table 4 Study treatments for study treatment details.

Table 4 Study treatments

	Treatment 1	Placebo
Study treatment name:	Durvalumab (MEDI4736)	Saline solution
Dosage formulation:	500-mg vial solution for infusion after dilution, 50 mg/mL	Sterile solution of 0.9% (w/v) sodium chloride for injection
Route of administration	iv	iv
Dosing instructions:	iv infusion over approximately 60 minutes (±5 minutes), q4w (see Section 6.1.2)	iv infusion over approximately 60 minutes (±5 minutes), q4w (see Section 6.1.2)
Packaging and labelling	Study treatment will be labelled in accordance with GMP Annex 13 and per country regulatory requirement[a]	Sourced locally by site
Provider	AstraZeneca	Sourced locally by site

[a] Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

GMP Good Manufacturing Practice; iv Intravenous; q4w Every 4 weeks.

6.1.1.1 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), CCI histidine/histidine-hydrochloride, CCI trehalose dihydrate, and CCI polysorbate 80; it has a CCI. The nominal fill volume is 10.0 mL. IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Preparation of durvalumab (MEDI4736) doses for administration with an iv bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or study site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)

- 4 hours at room temperature

A dose of 1500 mg (for participants >30 kg in weight) will be administered using an iv bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to [CCI], and delivered through an iv administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500 mg of durvalumab [MEDI4736]) to the iv bag. The iv bag size should be selected such that the final concentration is within 1 to [CCI] Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. The IV bag should be covered with a translucent colored or opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover should be secured (e.g. using stapling, heat-sealing), to maintain double-blind conditions.

If weight falls to ≤30 kg, weight-based dosing at [CCI] will be administered using an iv bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to [CCI], and delivered through an iv administration set with a 0.2- or 0.22-µm in-line filter.

Standard infusion time is 1 hour. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The iv line will be flushed with a volume of iv diluent equal to the priming volume of the infusion set used, after the contents of the iv bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

6.1.1.2 Placebo

Sterile solution of 0.9% (w/v) sodium chloride for injection will be added to an iv bag containing 0.9% (w/v) saline or 5% (w/v) dextrose. The volume of saline solution added will be 30.0 mL for durvalumab placebo. The iv bag should be covered with a translucent coloured or opaque sleeve after preparation by the unblinded pharmacist and/or other appropriate unblinded site staff prior to dispensing to other study personnel, sleeve cover should be secured (e.g. using stapling, heat-sealing), to maintain double-blind conditions. Infusion time is 1 hour and should be delivered through an iv administration set with a 0.2- or 0.22-µm in-line filter.

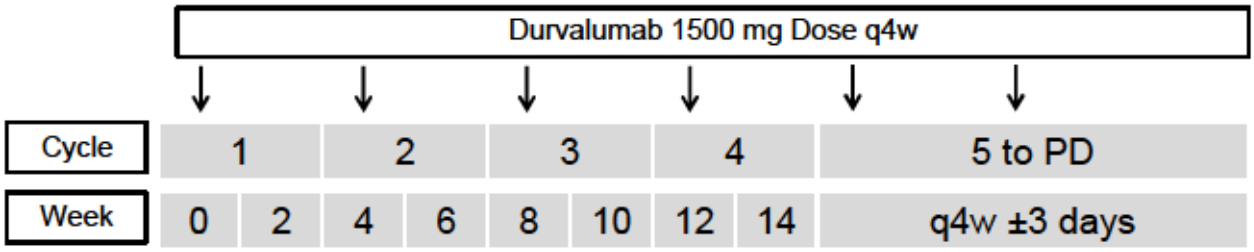
6.1.2 Dose and treatment regimens

6.1.2.1 Durvalumab (MEDI4736) monotherapy

Participants in the durvalumab monotherapy treatment arm will receive 1500 mg durvalumab via iv infusion q4w until confirmed radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion (Section 7.1) is met. See Figure 2. (Please note, if a participant's weight falls to 30 kg or below the participant should receive weight-based dosing equivalent to CCI of durvalumab q4w after consultation between the Investigator and Study Physician, until the weight improves to >30 kg, at which point the participant should start receiving the fixed dosing of durvalumab 1500 mg q4w).

The standard infusion time is 60 minutes. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Figure 2 Durvalumab monotherapy dosing schedule



q4w Every 4 weeks.

6.1.2.2 Placebo

The treatment regimen for placebo is the same as described for durvalumab monotherapy (Section 6.1.2.1), including the dosing schedule shown in Figure 2.

6.1.3 Duration of treatment

All treatment will be administered beginning on Day 1 until confirmed radiological progression (refer to Appendix E), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion (Section 7.1) is met.

During the Treatment Period, participants who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study treatment at the discretion of the Investigator and participant. A follow-up scan is to be collected after the initial RECIST 1.1-defined radiological PD, no less than 4 weeks after the prior assessment of PD and no later than the next regularly scheduled imaging visit, and this follow-up scan is evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix E. Participants with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, or spinal cord compression) will not be eligible for continuing study treatment.

At the request of the Investigator, following discontinuation of IP and RECIST 1.1- defined progression of disease plus the additional regularly scheduled follow-up scan participant can be unblinded. Participants may not receive any further study treatment (durvalumab or placebo) after this point and they will be counselled on other anticancer therapy options.

For all participants who are treated through progression, the Investigator should ensure that participants do not have any significant, unacceptable, or irreversible toxicities that indicate continuing would not further benefit the participant.

Participants in placebo arm will no longer receive any further placebo treatment after the study is unblinded.

Crossover within the study will not be permitted.

The participant ICF will specify that treatment beyond initial evidence of PD during follow up is not the SoC and that alternative treatment options, either locally licensed treatments or other clinical trials, are available for this participant population.

Participants with confirmed PD who continue to receive study treatment at the discretion of the Investigator and participant (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit, and tumour assessments should continue on their regular imaging schedule for the duration of treatment.

6.1.4 Storage

The Investigator, or an approved representative (e.g., pharmacist), will ensure that all IP is stored in a secured area, in refrigerated temperatures (2°C to 8°C) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

6.2 Measures to minimise bias: randomisation and blinding

6.2.1 Participant enrolment and randomisation

All participants will be centrally assigned to randomised study treatment using an interactive voice response system (IVRS)/interactive web response system (IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each study site.

If a participant withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn participants will not be replaced.

Investigators should keep a record (i.e. the participant screening log) of participants who entered Screening.

At Screening part I visit (Days -84 to -1), the investigator or suitably trained delegate will:

- Obtain signed informed consent form of use of tumour sample. A biopsy procedure during screening period is not allowed, and an irradiated sample is not acceptable.
- Obtain a unique 7-digit enrolment number (E-code), through the IVRS/IWRS in the following format (ECCNNXXX: CC being the country code, NN being the centre number, and XXX being the participant enrolment code at the centre). This number is the participant's unique identifier and is used to identify the participant on the electronic case report forms (eCRFs).
- Obtain tumour sample and send for centralised PD-L1 testing. Obtaining the tumour biopsy samples should be given the highest priority and, as such, the sample may be obtained and sent for PD-L1 expression status evaluation. If EGFR and ALK status is unknown, the archived or newly acquired tumour sample can be used for central EGFR and ALK mutation testing along with PD-L1 testing. However, the EGFR and ALK result from the local laboratory is also acceptable, if it is accessed by a well-validated, local regulatory-approved kit.
- Determine participant eligibility (see Sections 5.1 and 5.2)

At Screening part II visit/Baseline (Days -28 to -1), the Investigator or suitably trained delegate will:

- After participants complete CRT, obtain signed informed consent of study procedures before any study specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing inform consent of study procedure, these can be used for screening purposes with consent of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days of randomisation. For participants with a single target lesion, if screening biopsy is collected prior to screening imaging for baseline tumour assessment, allow approximately 2 weeks before imaging scans are acquired.
- Determine participant eligibility (see Sections 5.1 and 5.2).

At randomisation, once the participant is confirmed to be eligible, the Investigator or suitably trained delegate will perform the following:

- A unique randomisation number will be generated via the IVRS/IWRS, when randomization transaction is completed. Numbers will start at 001 and will be assigned

strictly sequentially by IVRS/IWRS as participants are eligible for entry into the study. The system will randomise the eligible participant to 1 of the 2 treatment arms. (PD-L1 expression status results need to be received from the central laboratory by the IVRS/IWRS prior to randomisation.)

- If the participant is ineligible and not randomised, the IVRS/IWRS should be contacted to terminate the participant in the system.

Participants will begin treatment on Day 1. Treatment should start no more than 3 days after being randomised. Participants must not be randomised and treated unless all eligibility criteria have been met.

6.2.2 Procedures for handling incorrectly enrolled or randomised participants

Participants who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Participants who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented and that the potential benefit: risk profile remains positive for the participant.

6.2.3 Methods for assigning treatment arms

The actual treatment given to participants will be determined by the randomisation scheme in the IVRS/IWRS. The randomisation scheme will be produced by a computer software program that incorporates a standard procedure for generating randomisation numbers. One randomisation list will be produced for each of the randomisation strata. A blocked randomisation will be generated, and all centres will use the same list in order to minimise any imbalance in the number of participants assigned to each treatment arm.

Participants will be identified to the IVRS/IWRS per country regulations. Randomisation codes will be assigned strictly sequentially, within each stratum, as participants become eligible for randomisation. The IVRS/IWRS will provide the kit identification number to be allocated to the participant at the randomisation visit and subsequent treatment visits.

Participants will be randomised in a 2:1 ratio to either durvalumab (1500 mg q4w) or placebo. Participants will be stratified at randomisation based on the level of PD-L1 expression (PD-L1 <1% or PD-L1 ≥1%) and prior therapy (cCRT or sCRT).

Every effort should be made to minimise the time between randomisation and starting study treatment. It is recommended that participants commence study treatment as soon as possible after randomisation (ie, on the same day after randomisation in the IVRS system).

The IVRS/IWRS may not be available after the final DCO for the study. In this case, a manual process will need to be followed.

6.2.4 Methods for ensuring blinding

The study will be conducted in a double-blind manner. The reconstituted durvalumab solution and its matching placebo will be identical in colour, and the iv bags used for administration will be identical with regards to size. All study treatment will be blinded using a translucent colored or opaque sleeve, after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover should be secured (e.g. using stapling, heat-sealing*),* to maintain double-blind conditions.

The IVRS/IWRS will provide to the pharmacists and/or other appropriate site staff the kit identification number to be allocated to the participant at the dispensing visit. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS. Investigators will remain blinded to each participant's assigned study treatment until the time of final analysis of the primary endpoint. To maintain this blind, a pharmacist and/or other appropriate site staff will be unblinded and responsible for the reconstitution and dispensation of all study treatment and will endeavour to ensure that there are no differences in time taken to dispense following randomisation. The unblinded pharmacist and/or other appropriate site staff will be monitored by unblinded study monitors all of whom will have no further role in the management of study participants or data collection and will not have access to the study database. All other site personnel will be blinded for the dispensation of all study treatments.

In the event that the treatment allocation for a participant becomes known to the Investigator or other study staff involved in the management of participants, or needs to be known to treat an individual participant for an AE, the Sponsor must be notified promptly by the Investigator and if possible, before unblinding.

The IVRS/IWRS will be programmed with blind-breaking instructions. The treatment code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. Additionally, at the request of the Investigator, following discontinuation of IP and RECIST 1.1-defined progression of disease plus the additional regularly scheduled follow-up scan the participant can be unblinded. In the setting of rapid clinical progression, unblinding should be discussed with the AstraZeneca Global Study Physician and Study Statistician.

The Sponsor must be notified before the blind is broken unless identification of the study

treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual participant have been made and documented. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities.

The IDMC will be provided with unblinded data for their review, but AstraZeneca and designee staff and Investigators involved in the study will remain blinded.

6.3 Treatment compliance

Any change from the dosing schedule, dose delays/interruptions, and dose discontinuations should be recorded in the eCRF. Treatment compliance will be assured by study site reconciliation of medication dispensed.

The Investigational Product Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the participant has returned all unused IP.

The administration of all study treatments (including IPs) should be recorded in the appropriate sections of the eCRF. The Investigator or pharmacy must retain records of all study treatments administered. The Study Monitor will check these records to confirm the compliance with the protocol administration schedule.

Use of IP in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.4 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of part II screening until the end of the clinical treatment phase of the study including the 90-day safety Follow-up Period following the last dose of study drug.

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose, unit, and frequency

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

Restricted, prohibited, and permitted concomitant medications are described in the following tables (Table 5 and Table 6). Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

Table 5 Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage:**
For all treatment arms	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the participant is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the participant is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic, or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the participant is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the study treatment infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study treatment-related AEs • Short-term premedication for participants receiving SoC CRT, in which the prescribing information or local guidance for the agent requires the use of steroids for documented hypersensitivity reactions, nausea/vomiting, or prophylaxis • Use in participants with contrast allergies In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroid treatment will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the participant (eg, chronic obstructive pulmonary disease, radiation, or nausea).

Prohibited medication/class of drug:	Usage:
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days after the last dose of durvalumab. Increased incidences of pneumonitis (with third-generation EGFR TKIs) and increased incidence of transaminase increases (with first-generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies that may have immune-modulating and/or anticancer effects	Should not be given concomitantly unless agreed by the Sponsor

AE Adverse event; EGFR Epidermal growth factor receptor; mAb Monoclonal antibody; PD-1 Programmed death 1; PD-L1 Programmed death ligand 1; TKI Tyrosine kinase inhibitors.

Table 6 Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management	Should be used, when necessary, for all participants
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.4.1 Other concomitant treatment

Medications other than those described above that are considered necessary for the participant's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.4.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either pre-clinically or in participants. As durvalumab is a monoclonal antibody and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug-metabolising cytochrome P450 pathways. As a result, there are no expected PK drug-drug interactions. The mechanism of action of durvalumab involves binding to PD-L1, and therefore, significant pharmacodynamic drug-drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate

clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

6.4.3 Rescue medication

As a result of immune-mediated adverse events (imAEs) that could potentially be experienced by participants on durvalumab, steroids and other immunosuppressant rescue medication has to be made available to this participant population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis). AstraZeneca supply chain will only be responsible for sourcing these 2 rescue medications to the study sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy-related toxicities. These rescue medications must be receipted, controlled, and administered by the unblinded pharmacist and/or other appropriate unblinded site staff and stored according to the labelled storage conditions, with temperature excursions reported accordingly by the unblinded pharmacist and/or other appropriate unblinded site staff. If required for use as a result of an imAE, then the IVRS/IWRS will provide to the unblinded pharmacists and/or other appropriate unblinded site staff the kit identification number to be allocated to the participant at the time, when the rescue medication is centrally supplied by AstraZeneca supply chain. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS.

6.5 Dose modification

Dose delays are permitted for immuno-oncology therapy (see Dosing Modification and Toxicity Management Guidelines in Section 8.4.5). However, **dose reduction is not permitted**.

6.6 Treatment after the end of the study

After the final DCO for this study, AstraZeneca will continue to supply open-label durvalumab monotherapy to participants who received durvalumab monotherapy until PD occurs as judged by the investigator. Tumour assessment scans will be performed in accordance with local clinical practice.

For participants continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the participants continue the scheduled site visits and investigators monitor the participants' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participants currently receiving treatment may be transitioned to such a study, and the current study would reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be proposed to move to such a study would be given a new informed consent, as applicable.

Dependent on the analysis results of the study, a decision may be made to continue further data collection for a longer period with intent to analyse long-term OS and safety data to fulfil any other potential Health Authority requirements. Any additional long-term analysis may be further clarified through addendum to main statistical analysis plan, which will be developed before DCO for the long-term analysis.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

An individual participant will not receive any further IP (durvalumab or placebo) if any of the following occur in the participant in question:

- Withdrawal of consent from further treatment with IP. The participant is, at any time, free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5)
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmed radiological progression (refer to Appendix E) or Clinical progression and Investigator determination that the participant is no longer benefiting from treatment with IP

Withdrawal of consent for biological sampling is included in Section 8.8.6.

7.1.1 Procedures for discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the participant's participation in the study. A participant who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The participant should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the participant, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Participants who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Participants who are permanently discontinued will enter Follow-up (see the SoAs).

Participants who permanently discontinue drug for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 scans performed every 8 weeks (q8w) ±1 week for the first 48 weeks (relative to the date of randomisation), and then every 12 weeks (q12w) ±1 week thereafter until RECIST 1.1-defined radiological PD plus an additional follow-up scan or death (whichever comes first) regardless of whether or not the participants started a subsequent anticancer therapy as defined in the SoAs.

If a participant is discontinued for RECIST 1.1-defined progression, then the participant should have 1 additional follow-up scan performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD.

All participants will be followed for survival until the end of the study.

Participants who decline to return to the study site for evaluations should be contacted by telephone as indicated in the SoAs as an alternative.

Participants who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

7.2 Lost to follow-up

Participants will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time. Participants who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-

establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

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

· The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

· Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

· Should the participant continue to be unreachable, he/she will be considered to have been lost to follow-up.

· Site personnel, or an independent third-party, will attempt to collect the vital status of the participant during survival follow-up within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

In order to support key endpoints of PFS and OS analyses, the survival status of all participants in the intent-to-treat and the safety analysis sets (SAS) should be re-checked; this includes those participants who withdrew consent or are classified as "lost to follow-up."

- Lost to Follow-up – study site personnel should check hospital records, the participants' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable eCRF modules will be updated.)
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant can be obtained by study site personnel from publicly available death registries (if available) where it is possible to do so under

applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

7.3 Withdrawal from the study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.

A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).

A participant who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a participant withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow-up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples (see Section 8.8.6)

Withdrawn participants will not be replaced.

Vital status (ie, whether a participant is dead or alive), based on public available sources, will be investigated at the scheduled study end.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoAs (Table 1 and Table 2).

The Investigator will ensure that data are recorded on the eCRFs. The Web Based Data Capture system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Whenever feasible, participants must first be confirmed to have documented PD-L1 expression status (<1% or ≥1%), EGFR and ALK status before proceeding with the rest of screening procedures. Screening/baseline evaluations may be performed over more than 1 visit.

Inform consent form of tumour samples collection should be signed in order to permit tumour biopsy samples acquisition.

8.1 Efficacy assessments

This study will evaluate the primary endpoint of PFS (mITT). Efficacy assessments of PFS, ORR, DoR, PFS12, PFS18, and time to death or distant metastasis (TTDM) will be derived (by AstraZeneca) using BICR RECIST 1.1 assessments. Time from randomisation to second progression (PFS2) will be assessed by the Investigator according to local standard clinical practice. OS and proportion of participants alive at 24 months from randomisation (OS24) will also be assessed.

Tumour assessments utilise images from CT (preferred) or MRI, each preferably with iv contrast, of the chest and abdomen (including the entire liver and both adrenal glands), collected during part II screening/Baseline and at regular (Follow-up) intervals during the study. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual participants. It is important to follow the tumour assessment schedule as closely as possible (refer to the SoAs). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Treatment continues until confirmed radiological progression (refer to Appendix E) or other discontinuation criterion (Section 7.1) is met; and scanning/tumour assessments continue until RECIST 1.1-defined radiological progression plus 1 or more additional follow-up scans for confirmation of progression (if clinically feasible).

The RECIST 1.1 guidelines (Appendix E) provide a method of assessment of change in tumour burden in response to treatment. Part II screening/baseline imaging should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and Non-Target Lesions (NTLs). On-study images are evaluated for TLs and NTLs chosen at Baseline, and for New Lesions (NLs) when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall timepoint responses (CR, PR, SD, PD, or Not Evaluable [NE]).

A follow-up scan is to be collected after the initial RECIST 1.1-defined radiological PD, no less than 4 weeks after the prior assessment of PD and no later than the next regularly scheduled imaging visit and; this follow-up scan is evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix E. If the subsequent scan confirms the immediate prior radiological PD, no additional scans are required; however, if the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST 1.1-defined radiological PD, which in turn will require a subsequent scan evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix E.

If a participant has initial progression but changes to another anticancer treatment before that progression is confirmed, the follow-up scan should still be acquired on the regular imaging schedule.

8.1.1 Central reading of scans

The primary analysis for this study will be based on PFS (mITT) from BICR using assessment of tumours using RECIST 1.1. All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed contract research organisation for QC and storage. Guidelines for image acquisition, de-identification, storage at the investigative study site as source data, and transfer to the imaging contract research organisation will be provided in a separate document. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of participants will be based in part on the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter (also referred to as “Imaging Charter”).

In addition, an exploratory analysis of PFS from BICR by assessment of tumours using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) 1.1 (Wolchok et al 2009, Nishino et al 2013) may be presented outside of the main CSR.

8.1.2 Survival assessments

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

In addition, participants on treatment or in survival Follow-up will be contacted following the DCO for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the DCO.

8.1.3 Second progression

Following the first progression event used for the primary variable, PFS (the first progression), the site will be asked on a regular basis (q8w ±1 week for the first 48 weeks [relative to the date of randomisation], and then q12w ±1 week) if the participant has had a second progression event. A participant's progression status is defined according to local standard clinical practice and may involve any of the following: objective radiological progression, symptomatic progression, or death. The date of PFS2 assessment and Investigator's opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the PFS2 eCRF.

8.1.4 Clinical outcome assessments

A Clinical Outcome Assessment (COA) is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. Patient Reported Outcomes (PROs) is one of the types of COAs. PROs is an umbrella term referring to all outcomes that are directly reported by the participant. The following PRO instruments will be administered in this study: EORTC QLQ-C30 v3 (core questionnaire), EORTC QLQ-LC13 (lung cancer module), and EQ-5D-5L; see Appendix G.

Timings of the assessments for PRO are presented in Table 1 (Screening and the Treatment Period) and Table 2 (Follow-up).

If participants have scans at an outside facility or missed a scheduled data collection, PRO questionnaires need to be administered at the next visit.

8.1.4.1 EORTC QLQ-C30 and QLQ-LC13

The EORTC QLQ-C30 is a 30-item self-administered questionnaire (Appendix G). There are 9 multiple item scales: 5 scales that assess aspects of functioning (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health status/quality of life (QoL) scale. There are 5 single-item measures assessing additional symptoms commonly reported by cancer participants (dyspnoea, loss of appetite,

insomnia, constipation, and diarrhoea) and a single item concerning perceived financial impact of the disease.

For NSCLC participants, a disease-specific, 13-item, self-administered questionnaire for lung cancer was developed (QLQ-LC13; Appendix G) to be used in conjunction with the EORTC QLQ-C30 (Bergman et al 1994). It comprises both multi-item and single-item measures of lung cancer-associated symptoms (ie, coughing, haemoptysis, dyspnoea, and pain) and side effects from conventional chemotherapy and radiotherapy (ie, hair loss, neuropathy, sore mouth, and dysphagia).

All but 2 questions have 4-point scales: "Not at all," "A little," "Quite a bit," and "Very much." The 2 questions concerning global health status/QoL have 7-point scales with ratings ranging from "Very poor" to "Excellent." Final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater health status/QoL, or greater level of symptoms (Aaronson et al 1993).

8.1.4.2 EQ-5D

The EuroQoL 5-dimension utility index (EQ-5D) is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems) that reflect increasing levels of severity (EuroQoL 2013).

Since 2009, the EuroQoL group has been developing a more sensitive version of the EQ-5D (the EuroQoL 5-dimension, 5-level health state utility index [EQ-5D-5L]), which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5L version improves upon the properties of the 3L measure in terms of reduced ceiling effect, increased reliability, and an improved ability to differentiate between different levels of health (Janssen et al 2008a, Janssen et al 2008b, Pickard et al 2007).

The participant will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the participant will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

The assessment of health state utility will provide important information for payers and will be used within economic evaluations of durvalumab.

8.1.4.3 Administration of patient-reported outcomes questionnaires

Participants will perform the PRO assessments using an electronic tablet (ePRO) during clinic visits and will take approximately 10 minutes to complete.

Each center must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be administered and completed at the clinic as per the SoAs.

It is important that the site staff explains the value and relevance of PRO data: to hear directly from participants how they feel. The following best practice guidelines should be followed:

- It is preferred that PRO questionnaires are completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid biasing the participant's responses to the questions.
- PRO questionnaires must be completed in private by the participant.
- Participant should be given sufficient time to complete the PRO questionnaires at their own speed.
- If the participant is unable to read the questionnaire (e.g. is blind or illiterate), that participant should be exempted from completing PRO questionnaires but may still participate in the study. Participants exempted in this regard should be flagged appropriately by the site staff in the source documents.
- The research nurse or appointed site staff should stress that the information is confidential. Therefore, if the participant has any medical problems, he or she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the participant on how to use the ePRO device using the materials and training provided in the ePRO device.
- The research nurse or appointed site staff must remind participants that there are no right or wrong answers and avoid introducing bias by not clarifying items. The participant should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.
- All PRO questionnaires are to be completed using an ePRO device. If technical or other device-related issues prohibit completion on the device, an appropriate back-up option may be considered with prior approval from the study team.

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

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the SoAs.

8.2.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the study site. Pregnancy tests may be performed at the study site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

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

The laboratory variables to be measured are presented in Table 7 (clinical chemistry), Table 8 (haematology), and Table 10 (urinalysis).

Other safety tests to be performed at part II screening include assessment for HBsAg, HCV antibodies, and HIV antibodies.

The following laboratory variables will be measured:

Table 7 Clinical chemistry

Albumin	Lipase[a,b]
Alkaline phosphatase[c]	Magnesium[d]
ALT[c]	Potassium
Amylase[a,b]	Sodium
AST[c]	Total bilirubin[c]
Bicarbonate[d]	Total protein
Calcium	TSH[e]
Chloride[d]	T3 free[f] (reflex)
Creatinine[d]	T4 free[f] (reflex)
Gamma glutamyltransferase[d]	Urea or blood urea nitrogen, depending on local practice
Glucose	Uric acid[b]
Lactate dehydrogenase	

[a] It is preferable that both amylase and lipase parameters are assessed. For study sites where only 1 of these parameters is routinely measured, either lipase or amylase is acceptable.
[b] Amylase, lipase, and uric acid are tested at Screening, Day 1 (unless part II screening laboratory assessments are performed within 3 days prior to Day 1) and every 4 weeks thereafter.
[c] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
[d] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at Baseline, on Day 1 (unless all part II screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.
[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.
[f] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WT Body weight.

Table 8 Haematology

Absolute neutrophil count[a]	Absolute lymphocyte count[a]
Haemoglobin	Platelet count
Total white blood cell count	

[a] Should be recorded as absolute counts other than percentages.

Table 9 Coagulation Parameters

Activated partial thromboplastin time[a]	International normalised ratio[a]

[a] Can be recorded as absolute counts or as percentages. Total white blood cell count therefore has to be provided.

Note: For coagulation parameters, activated partial thromboplastin time and international normalised ratio are to be assessed at part II screening and as clinically indicated.

Table 10 Urinalysis

Bilirubin	Ketones
Blood	pH
Colour and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis should be done at Baseline (part II screening), and then as clinically indicated.
Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red and white blood cells.

If a participant shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix D for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they

meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfil any of the SAE criteria.

All participants should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week), and 3 months (±1 week) after permanent discontinuation of IP (see the SoAs).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.7.

All participants with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.2.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at part II screening only. Targeted physical examinations are to be utilised by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

8.2.3 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the SoAs. WT is also recorded at each visit along with vital signs.

First infusion

On the first infusion day, participants will be monitored and vital signs collected/recorded in eCRF prior to, during, and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from participants before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent infusions

BP, pulse, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of the infusion. Participants should be carefully monitored, and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.7. For any AEs of infusion reactions, the vital signs values should be entered into the CRF.

8.2.4 Electrocardiograms

Resting 12-lead ECGs will be recorded at part II screening and as clinically indicated throughout the study (see the SoAs). ECGs should be obtained after the participant has been in a supine position for 5 minutes and recorded while the participant remains in that position.

In case of clinically significant ECG abnormalities, including a QT interval corrected for heart rate using Fridericia's formula (QTcF) value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 8.3.7.

8.2.5 WHO/ECOG performance status

WHO/Eastern Cooperative Oncology Group (ECOG) PS will be assessed at the times specified in the assessment schedules (see the SoAs) based on the following:

1 Fully active; able to carry out all usual activities without restrictions
2 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)
3 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
4 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
5 Completely disabled; unable to carry out any self-care and totally confined to bed or chair
6 Dead

Any significant change from Baseline or part II screening must be reported as an AE.

WHO/ECOG PS should also be collected at other study site visits that the participant attends, if appropriate study site staff are available to collect such information. In addition, WHO/ECOG PS should be provided when information on subsequent anticancer therapy is provided, where possible.

8.2.6 Other safety assessments

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease (ILD) is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

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

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc) including auscultation for lung field
- Saturation of peripheral oxygen (SpO_2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - ILD Markers (KL-6 and surfactant-associated protein) and β-D-glucan
    - Tumour markers: Particular tumour markers that are related to disease progression
    - Additional Clinical chemistry: C-reactive protein, lactate dehydrogenase

8.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs, see Section 8.3.3.

8.3.1 Method of detecting adverse events and serious adverse events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting adverse event and serious adverse event information

AEs and SAEs will be collected from the time of the participant signing the ICF of study procedure (part II screening) until the Follow-up Period is completed (90 days after the last dose of study drug). If an event that starts post the defined safety Follow-up Period noted above is considered to be due to a late onset toxicity to study drug, then it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant’s last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator should notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up.

Any AEs that are unresolved at the participant’s last visit in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 90 days after the last dose of durvalumab), but without further recording in the eCRF. AstraZeneca retains the right

to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8.3.5
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Any non-serious AE that is ongoing at the time of the final DCO is to be followed up at the discretion of the Investigator, per local practice, and in alignment with the toxicity

management guidelines (refer to Section 8.4.5) of this protocol. Data will not be captured for the purposes of this study outside of being recorded in the participants' source documents.

8.3.5 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer "yes" or "no" to the question, "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

A guide to the interpretation of the causality question is found in Appendix B.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff, "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR). Deterioration as compared to Baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Asymptomatic Grade 3 or 4 increases in amylase or lipase resulting in interruption of dosing (refer to Section 8.4.5) should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study; see Section 8.3.8 and Section 8.3.9.

8.3.8 Hy's Law

Cases in which a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.9 Disease-under study

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

8.3.10 Disease progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing, metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

8.3.11 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the participant's inclusion in this study.

8.3.12 Deaths

All deaths that occur during the study Treatment Period, or within the protocol-defined Follow-up Period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a

comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE, and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Participant Safety or its representative within the usual timeframes.

Deaths occurring after the protocol-defined safety Follow-up Period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety Follow-up Period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

8.3.13 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this IP.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs/imAEs observed with anti PD-1/PD-L1 agents such as durvalumab include:

- Diarrhoea/colitis and intestinal perforation
- Pneumonitis/ILD
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, and type I diabetes mellitus)
- Hepatitis/transaminase increases

- Nephritis/blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Rash/dermatitis
- Myocarditis
- Myositis/polymyositis
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated aetiology include, but are not limited to, haematological events, neuropathy/neuromuscular toxicity (eg, Guillain-Barré and myasthenia gravis), non-infectious encephalitis, non-infectious meningitis, pericarditis, rheumatological events, sarcoidosis, skin events, uvetitis [and other events involving the eye] and vasculitis.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

8.3.14 Safety data to be collected following the final data cutoff of the study

For participants continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the participants continue the scheduled study site visits and Investigators monitor the participant's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). All data post the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) after the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other study site personnel inform the appropriate AstraZeneca representatives within 1 day (ie, immediately or **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Participant Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other study site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the IB for durvalumab.

After the final DCO for the study, any SAEs occurring in the 90-day safety Follow-up Period after receiving the last dose of durvalumab are to be recorded in a paper CRF and reported directly to the AstraZeneca Participant Safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For further guidance on the definition of a SAE, see Appendix B.

8.4.2 Pregnancy

All pregnancies including pregnancy in the partner of male participants and outcomes of pregnancy should be reported to AstraZeneca representative except:

- If the pregnancy is discovered before the patient has received any study treatment

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

Following the final DCO for the study, Investigators or other study site personnel shall report all pregnancy outcomes to AstraZeneca Participant Safety.

8.4.2.1 Maternal exposure

If a participant becomes pregnant during the course of the study, IP should be discontinued immediately and the pregnancy reported to AstraZeneca.

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

If any pregnancy occurs in the course of the study, then the Investigator or other study site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately or **no later than 24 hours** of when he or she becomes aware of it).

If any pregnancy occurs after the final DCO for the study, Investigators or other study site personnel must inform AstraZeneca Participant Safety immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Participant Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.4.1) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy, and the PREGOUT is used to report the outcome of the pregnancy. Paper-based modules will be available to study sites following final DCO for the study.

8.4.2.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of durvalumab monotherapy should, if possible, be followed up and documented in the medical record and provided to the AstraZeneca Participant Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the participant's partner. Therefore, the local study

team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

Participants who are permanently discontinued from further receipt of IP, regardless of the reason, will enter Follow-up (see the SoAs).

8.4.3 Overdose

Use of durvalumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab, and possible symptoms of overdose are not established.

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Participant Safety data entry site within one or 5 calendar days for overdoses associated with an SAE (see Section 8.4.1) and within 30 days for all other overdoses.

If an overdose on an AstraZeneca study treatment occurs after the final DCO for the study, then Investigators or other study site personnel shall inform AstraZeneca Participant Safety immediately, or **no later than 24 hours** of when he or she becomes aware of it.

8.4.4 Medication error

If an event of medication error occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error(see Section 8.3.2) and within 30 days for all other medication errors.

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.5 Management of IP-related toxicities

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

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

8.4.5.1 Specific toxicity management and dose modification information – durvalumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy are provided in the Dosing Modifications and Toxicity Management Guidelines. The most current version of these guidelines is to be maintained within the Site Master File.

Participants should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative aetiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 of this protocol and the Dosing Modification and Toxicity Management Guidelines).

Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

Dose modifications will not be required for AEs that are clearly not attributed to study treatment (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dosing may continue despite concurrent vitiligo of any AE grade.

8.5 Pharmacokinetics

Drug concentration information that may unblind the study will not be reported to investigative study sites or blinded personnel until the study has been unblinded.

8.5.1 Collection of samples

Blood samples for determination of durvalumab concentration in serum will be obtained according to the SoAs.

Samples for determination of durvalumab concentration in serum will be analysed by a designated third party on behalf of AstraZeneca. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

8.5.1.1 Collection of samples to measure for the presence of antidrug antibodies

The presence of ADAs will be assessed in serum samples taken according to the SoAs.

Samples will be measured for the presence of ADAs and ADA-neutralising antibodies using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titre assay components, and positive-negative cut points previously statistically determined from drug-naïve validation samples will be employed.

8.5.2 Storage and destruction of pharmacokinetic/antidrug antibody samples

PK and ADA samples collected in China will be destroyed after the finalisation of the Bioanalytical Reports. PK/ADA samples collected will be stored and disposed of according to local laws and regulations.

Durvalumab PK and ADA samples collected in rest of world may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the CSR. Durvalumab PK samples collected in the rest of the world will be disposed of 6 months after final study Bioanalytical report. Durvalumab ADA samples collected in the rest of the world will be destroyed within 5 years of CSR finalization.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Validation Report.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6.1 Collection of samples

Pharmacodynamic samples will not be taken during the study.

8.6.2 Storage, reuse, and destruction of pharmacodynamic samples

Pharmacodynamic samples will not be taken during the study.

8.7 Genetics

Not applicable.

8.8 Biomarkers

By participating in this study the participant consents to the mandatory collection and use of donated biological samples as described here.

Pre-treatment tumour PD-L1 expression will be evaluated in all screening participants, and CCI will be evaluated in all randomised participants. For randomised participants, data will be compared between arms to determine if baseline PD-L1 status and CCI is prognostic and/or predictive of outcomes associated with durvalumab. Baseline tumour requirements are briefly described in Section 8.8.1.

Based on availability of tissue, additional exploratory biomarkers may be evaluated as described in Section 8.8.2. Also, descriptions of exploratory, peripheral measures are described in this section. Samples will be obtained according to the assessment schedules provided in the SoAs.

Details on the collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy as described in the exploratory analyses section.

The results may be pooled with biomarker data from other durvalumab ± tremelimumab studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

8.8.1 Collection of participant selection biomarker data

At part I screening, there is 1 mandatory provision of tissue to be used for determination of PD-L1 (EGFR mutation and ALK mutation assessments will be tested, if there's no available result from local laboratories). After PD-L1 is tested and participants are eligible and randomized, the remaining sample will be used to assess CCI :

- MANDATORY: Provision of a tumour biopsy, formalin fixed and embedded in paraffin, for the purpose of PD-L1 expression analyses (and for enabling CCI analyses, if the participants are randomized). A newly acquired tumour biopsy sample ≤ 3 months old is strongly preferred; however, if not feasible with an acceptable clinical risk, an archival sample taken ≤ 6 months prior to part I screening can be submitted. A biopsy procedure during screening period is not allowed. Archived or newly acquired tumour sample must be obtained before CRT. Any irradiated sample is not acceptable.
- Samples should be collected via an image-guided core needle (at least 18 gauge) or by excision. Where institutional practice, in this setting, uses a smaller gauge needle, samples should be submitted with tissue adequate to ensure that a valid result can be achieved (i.e. total tissue quantity submitted should be similar to core needle or excisional biopsy requirements described briefly here and outlined in the lab manual).
- Effort should be made to maximize material for downstream analyses. Sample acquired before screening period is expected to be collected in two cores, using an 18-gauge or larger needle, for determining PD-L1 expression. Unstained tissue sections will be collected for PD-L1 expression. It is mandated that sufficient tissue for both PD-L1 analyses and CCI analysis should be obtained and processed as described in the Laboratory Manual/Pathology Manual.

The tumour specimen submitted should be of sufficient quantity to allow for PD-L1 immunohistochemistry (IHC) analyses and determination of CCI (see the Laboratory Manual). Newly acquired or archived specimens with limited tumour content and fine needle aspirates are inadequate for defining tumour PD-L1 status. CCI is an optional test in China.

Tumour lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy, and in this instance only core needle (not excisional/incisional) biopsy is allowed. For participants with a single target lesion, if screening biopsy is collected prior to screening imaging for baseline tumour assessment, allow approximately 2 weeks before imaging scans are acquired.

Additional tumour biopsies collected as part of clinical care (e.g. for mixed responses or upon PD) can be submitted for further analysis. This sample will not be collected in China.

See the Laboratory Manual for further details of requirements including sample quality control and shipping.

The Ventana PD-L1 (SP263) IHC assay will be used to determine PD-L1 status in all specimens.

A panel of genes, such as the [redacted], will be utilized to assess [redacted] in the subject specimens from the trial.

To meet the requirement of global regulatory approval of a diagnostic, sections of the tumour will be retained in all regions that allow this for potential additional studies, as requested by the regulatory agencies, to support potential test approval.

8.8.2 Exploratory biomarkers

Blood and tumour samples for exploratory biomarker analyses will be obtained according to the schedules presented in the SoAs. Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Baseline measures will be correlated with outcomes. Note that samples will be obtained from participants randomised to each treatment arm. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with durvalumab therapy.

Additional sample collections and analyses may be completed at select study sites by site-specific amendment. All samples collected for such exploratory analyses will be stored at the study site, a reference laboratory, or at AstraZeneca's facilities and may be used for subsequent research relevant to evaluating response to immunotherapy.

The exploratory biomarker plan is described by sample type below.

[redacted]

This sample will not be collected in China.

[redacted]

CCI [redacted]

Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to participants, their family members, any insurance company, an employer, clinical study Investigator, general physician, or any other third party, unless required to do so by law. The participant's samples will not be used for any purpose other than those described in the study protocol.

Individual participants will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the participant's name nor any other personal identifiers will appear in any publication or report.

8.8.3 Storage, reuse, and destruction of biomarker samples

Samples collected in China will be disposed of according to local laws and regulations. . Samples collected in the rest of the world will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab ± tremelimumab to generate hypotheses to be tested in future research.

Biological samples collected will be stored and disposed of according to local laws and regulations.

8.8.4 Labelling and shipment of biological samples

The Principal Investigator will ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix C "International Airline Transportation Association (IATA) 6.2 Guidance Document."

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved participants unless agreed upon with AstraZeneca and appropriate labelling, shipment, and containment provisions are approved.

8.8.5 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The Principal Investigator at each study site will keep full traceability of collected biological samples from the participants while in storage at the study site until shipment or disposal (where appropriate) and will keep documentation of sample shipments.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival.

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

Except in China, samples retained for further use will be registered in the AstraZeneca-assigned Biobank during the entire life cycle.

8.8.6 Withdrawal of informed consent for donated biological samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples have already been analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the participant's withdrawal of informed consent to the use of donated samples
- Ensure that biological samples from that participant, if stored at the study site, are immediately identified, disposed of or destroyed and the action documented
- Ensure that the organisation(s) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the site informed.

Ensure that the participant and AstraZeneca are informed about the sample disposal.

8.9 Health economics

For the purposes of economic evaluation, it is necessary to capture health care resource use related to the treatment and the underlying disease. Within the study, the following will be captured:

- Hospital episodes including the type of contact (hospitalisations, outpatient, or day case), reason, length of stay by ward type (including intensive care unit), and concomitant medications and procedures
- Treatment related to AEs (including the method of delivery of the treatment)
- Treatment not related to the study

The above resource use data will mainly come from the participant's medical record and will be captured in the eCRF.

The assessment of health economic resource use data will provide important information for payers and will be used in economic evaluations of durvalumab.

Frequency and estimates of resource use, including length of stay and number of hospital admissions, will be derived from the health resource use information.

9 STATISTICAL CONSIDERATIONS

The primary aim of the study is to compare the efficacy of durvalumab compared with placebo in terms of BICR PFS (mITT).

- All personnel involved with the analysis of the study will remain blinded until database lock for the final analysis and protocol deviations identified.
- Analyses will be performed by AstraZeneca or its representatives.
- Refer to the statistical analysis plan (SAP) for details.

The mITT, ITT and the Safety Analysis Set described below will be applied to the randomised participants.

9.1 Statistical hypotheses

The formal statistical analysis will be performed to test the main hypotheses:

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

The research hypothesis for this study is that durvalumab (1500 mg q4w via iv infusion) will show improved efficacy compared with placebo when given as consolidation therapy to participants with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based, concurrent or sequential chemoradiation therapy.

This will be assessed via the primary objective of this study, which is to assess the efficacy of durvalumab treatment compared with placebo in terms of BICR PFS (mITT). In order to strongly control the type I error at 5% (2 sided), PFS (mITT) will be tested first with a significance level of 5% and the study will be considered positive (a success) if the PFS (mITT) analysis result is statistically significant. The secondary efficacy endpoints included in the multiple testing procedure are (in order): OS (mITT), PFS (ITT) and OS (ITT). The details on the multiple testing procedure for controlling the type I error rate can be found in Section 9.5.7. Other secondary efficacy objectives include evaluation of OS24, ORR, DoR, PFS12 and PFS18, PFS2, and TTDM. Other secondary objectives include an assessment of safety and tolerability, durvalumab PK exposure, immunogenicity, and PROs. Exploratory objectives are also included.

9.2 Sample size determination

The study will randomise approximately 400 participants in the ITT population and approximately 375 participants in the mITT population. Participants who received prior cCRT or sCRT and have not progressed following definitive chemoradiation therapy will be randomised in a 2:1 ratio to receive durvalumab and placebo. Study will recruit at least CCI of participants who received prior cCRT with the majority of participants to be recruited in China.

The final (primary) PFS (mITT) analysis for superiority will be performed when either of the following conditions have been met first:

- Reaching approximately CCI BICR progression-free survival events across the durvalumab and placebo treatment arms (approximately CCI maturity) in the mITT population

OR

- Approximately CCI months follow-up from last participant randomized to the study

If the true PFS HR is CCI, with an estimated CCI BICR PFS events in the mITT, the study will provide at least CCI power to demonstrate a statistically significant difference for PFS with a 2-sided significance level of 5%; this translates to an approximately 3-month benefit in median PFS over CCI months on placebo. The smallest treatment difference that would be statistically significant is a HR of CCI. A recruitment period of approximately CCI months and a follow-up period of CCI months are expected for the PFS (mITT) final analysis.

The overall alpha level for the statistical testing of the secondary key endpoint OS CCI for durvalumab versus placebo will be CCI if PFS (mITT) analysis is significant. The final planned overall survival analysis data cutoff will occur when reaching approximately CCI death events (CCI maturity) or approximately CCI months follow-up from the last participant randomization in the mITT, whichever occurs first. If the true OS HR is CCI with an estimated CCI OS events, this study will provide CCI power to demonstrate a statistically significant difference for OS, assuming a CCI 2-sided significance level (with overall 2-sided alpha for OS as CCI This translates to a CCI-month benefit in median OS over CCI months on placebo. The smallest treatment difference that would be statistically significant is a HR of CCI Up to two interim analyses for OS will be conducted: 1) at the same time as primary PFS analysis and 2) at approximately CCI months after the OS first interim analysis, with approximately CCI and CCI of the target events respectively. If the expected DCO for OS final analysis is within CCI months after the OS first interim analysis, the OS second interim analysis may be removed. A recruitment period of approximately CCI months and a follow-up period of CCI months are expected for the final analysis of OS endpoint.

9.3 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 11.

Table 11 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
PFS	mITT and ITT [a]
OS, OS24, ORR, DoR, PFS12, PFS18, PFS2, PRO endpoints, and TTDM	mITT and ITT [a]
Demography	mITT and ITT [a]
PK data	PK analysis set

Outcome variable	Populations
Safety data	
Exposure	Safety analysis set
Adverse events	Safety analysis set
Laboratory measurements	Safety analysis set
Vital Signs	Safety analysis set

[a] ITT is the secondary population for efficacy analysis, and the analysis to be performed in the ITT population will be detailed in the SAP.
DoR Duration of response; ITT Intent-to-treat; mITT Modified Intent-to-treat set; ORR Objective response rate; OS Overall survival; OS24 Proportion of participants alive at 24 months from randomisation; PFS Progression-free survival; PFS2 Time from randomisation to second progression; PFS12 Proportion of participants alive and progression free at 12 months from randomisation; PFS18 Proportion of participants alive and progression free at 18 months from randomisation; PK Pharmacokinetic; PRO Patient-reported outcomes; TTDM Time to death or distant metastasis.

9.3.1 Intent-to-treat set

The ITT will include all randomised participants. The ITT will be used as secondary population for efficacy analyses (including PROs). Treatment arms will be compared on the basis of randomised study treatment, regardless of the treatment actually received. Participants who were randomised but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomised.

9.3.2 Modified intent-to-treat set

The mITT will include all randomised participants in the ITT who are without sensitizing EGFR mutations or ALK rearrangements. Unless otherwise specified, the mITT will be used as primary population for all efficacy analyses (including PROs). Treatment arms will be compared based on randomized study treatment, regardless of the treatment actually received.

9.3.3 Safety analysis set

The SAS will consist of all participants who received at least 1 dose of study treatment (durvalumab or placebo). Safety data will not be formally analysed but summarised using the SAS according to the treatment received; that is, erroneously treated participants (eg, those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

When assessing safety and tolerability, summaries will be produced based on the SAS.

9.3.4 PK analysis set

All participants who receive at least 1 dose of durvalumab per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set. The

population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of efficacy variables

9.4.1.1 RECIST 1.1-based endpoints

The analysis of the primary endpoint PFS (mITT), and the analyses of the secondary endpoints, PFS (ITT), ORR, DoR, PFS12, PFS18, and TTDM, will be based on BICR assessments using RECIST 1.1. In addition, the other secondary endpoints, OS, OS24, and PFS2, will also be evaluated.

Blinded Independent Central Review

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a participant discontinues study treatment or receives another anticancer therapy.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each participant, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). If a participant has had a tumour assessment that cannot be evaluated, then the participant will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (of PFS, ORR, and DoR) will be derived from the overall visit response date and the scan dates.

Further details of the BICR will be documented in the Imaging Charter.

Investigator RECIST 1.1-based assessments

An Investigator assessment of radiological scans will be performed on all participants to confirm the robustness of the PFS endpoint.

At each visit, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days before the day of randomisation. If a participant has had a tumour assessment that cannot be evaluated, then the participant will be assigned a visit response of not evaluable (NE; unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Appendix E for the definitions of CR, PR, SD, and PD.

9.4.1.2 Primary endpoint

The primary endpoint is PFS (mITT). PFS (per RECIST 1.1 as assessed by the BICR) will be defined as the time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdraws from randomised therapy or receives another anticancer therapy prior to progression (ie, [date of event or censoring – date of randomisation] + 1). Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the participant progresses or dies after 2 or more missed visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the participant has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of Baseline, which then will be treated as an event with date of death as the event date.

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

RECIST 1.1 assessments/scans contributing towards a particular visit may be performed on different dates within the imaging visit window. The following rules will be applied:

- For BICR assessments, date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans that indicates progression for the adjudicated reviewer selecting PD, or where both reviewers select PD as a timepoint response and there is no adjudication, then the assessments of the reviewer who completed their baseline assessments first are used for the PD timepoint.
- For Investigator assessments, the date of progression will be determined based on the earliest of the RECIST 1.1 assessment/scan dates of the component that indicates progression.
- When censoring a participant for PFS, the participant will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Note: At each imaging visit, an overall timepoint response is algorithmically derived according to assessments of target lesions, non-target lesions, and new lesions (refer to Appendix E). For target lesions, only the latest scan date is recorded in the RECIST 1.1 eCRF out of all scans performed within an imaging visit window used for the assessment of target lesions, and similarly for non-target lesions only the latest scan date is recorded out of all scans performed within an imaging visit window used for the assessment of non-target lesions. For new lesions, only the first scan date is recorded in the RECIST eCRF out of all scans performed within an imaging visit window used for the assessment of new lesions.

A sensitivity analysis of PFS will be performed using Investigator assessments according to RECIST 1.1. If applicable, another sensitivity analysis will be performed by excluding sCRT

participants with 1 concurrent chemotherapy and radiation cycle using BICR tumour data (RECIST 1.1).

9.4.1.3 Key secondary objective (Overall survival)

OS (mITT) is a key secondary endpoint of this study. OS is defined as the time from the date of randomisation until death due to any cause. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Note: Survival calls will be made in the week following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If participants are confirmed to be alive or if the death date is after the DCO date, these participants will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

9.4.1.4 Proportion of participants alive at 24 months after randomisation

The OS24 will be defined as the Kaplan-Meier (KM) estimate of OS at 24 months after randomisation.

9.4.1.5 Objective response rate

ORR (per RECIST 1.1 as assessed by BICR) is defined as the number (%) of participants with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Participants who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

9.4.1.6 Duration of response

DoR (per RECIST 1.1 as assessed by BICR) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of CR or PR. If a participant does not progress following a response, then his or her DoR will be censored at the PFS censoring time. DoR will not be defined for those participants who do not have documented response.

9.4.1.7 Progression-free survival at 12 and 18 months

The PFS12 and PFS18 will be defined as the KM estimate of PFS (per RECIST 1.1 as assessed by BICR) at 12 and 18 months, respectively.

9.4.1.8 Time from randomisation to second progression

Time from randomisation to second progression or death (PFS2) will be defined as the time from the date of randomisation to the earliest of the progression event subsequent to first subsequent therapy, or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Second progression status will be reviewed (q8w ±1 week for the first 48 weeks [relative to the date of randomisation], and then q12w ±1 week (the first progression)) and status will be recorded. Censoring details for this endpoint will be defined in the SAP.

9.4.1.9 Time to death or distant metastasis

TTDM will be defined as the time from the date of randomisation until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST 1.1 or proven by biopsy. Participants who have not developed distant metastasis or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the participant has distant metastasis or dies after 2 or more missed visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the participant has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of Baseline, which then will be treated as an event with date of death as the event date.

9.4.1.10 Best objective response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST 1.1 assessment, as described in Appendix E. It is the best response a participant has had during their time in the study up until RECIST 1.1 progression or the last evaluable assessment in the absence of RECIST 1.1 progression.

Categorisation of BoR will be based on RECIST 1.1 (Appendix E) using the following response categories: CR, PR, SD, PD, and NE.

BoR will be determined programmatically based on RECIST 1.1 using all BICR assessments up until the first progression event. For participants whose progression event is death, BoR will be calculated based on all evaluable RECIST 1.1 assessments prior to death.

For participants who die with no evaluable RECIST 1.1 assessments, if the death occurs ≤17 weeks (ie, 16 weeks + 1 week to allow for a late assessment within the assessment window) after randomisation, then BoR will be assigned to the progression (PD) category. For participants who die with no evaluable RECIST 1.1 assessments, if the death occurs >17 weeks (ie, 16 weeks + 1 week) after the date of randomisation, then BoR will be assigned to the NE category.

9.4.2 Calculation or derivation of safety variables

9.4.2.1 Adverse events

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 participants. Data from all cycles of treatment will be combined in the presentation of safety data. "On treatment" will be defined as assessments between date of start dose and 90 days following discontinuation of IP (ie, the last dose of durvalumab monotherapy or placebo). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

AEs observed up until 90 days following discontinuation of IP or until the initiation of the first subsequent therapy following discontinuation of 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 treatment are likely to be attributable to subsequent therapy. However, to assess the longer-term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of IP (ie, without taking subsequent therapy into account). Any events in this period that occur after a participant has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

The SAS will be used for reporting of safety data.

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

Any AE occurring before treatment with study treatment will be included in the data listings but will not be included in the summary tables of AEs.

9.4.2.2 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examinations, the baseline value will be the latest result obtained prior to the start of study treatment.

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

QTcF = QT/RR^ (1/3) where RR is in seconds

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

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

The denominator used in laboratory summaries will only include evaluable participants, ie, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from Baseline, evaluable participants would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from Baseline to be evaluable, the participant need only have 1 post-dose value recorded.

The denominator in vital signs data should include only those participants with recorded data.

9.4.3 Calculation or derivation of patient-reported outcome variables

All PRO questionnaires will be scored according to published scoring guidelines or the developer's guidelines, if published guidelines are not available. All PRO analyses will be based on the mITT (primary population), and separately on the ITT population.

9.4.3.1 EORTC QLQ-C30 and QLQ-LC13

Symptoms and overall quality of life will be assessed using EORTC QLQ-C30 and QLQ-LC13 (secondary endpoints).

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual items (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea), and a global measure of health status. The QLQ-LC13 is a lung cancer-specific module from the EORTC for lung cancer comprising 13 questions to assess lung cancer symptoms (cough, haemoptysis, dyspnoea, and site-specific pain), treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication. With the exception of a multi-item scale for dyspnoea, all are single items. The dyspnoea scale will only be used if all 3 items have been scored; otherwise, the items are treated as single-item measures.

An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, the functional scales, and the global health status/QoL scale according to the EORTC QLQ-C30 Scoring Manual (EORTC QLQ-C30 Scoring Manual, Third Edition) and EORTC QLQ-LC13 instructions.

Higher scores on the global health status/QoL and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity. Changes in score compared with baseline will be evaluated. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number

of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimised.

Definition of clinically meaningful changes

Changes in score compared with Baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change in the score from Baseline of ≥10 for scales/items from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from Baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from Baseline of ≥10. At each post-baseline assessment, the change in symptoms/functioning from Baseline will be categorised as improvement, no change, or deterioration, as shown in Table 12 in Section 9.4.3.3.

Time to symptom deterioration (QLQ-C30 and QLQ-LC13)

Time to deterioration in symptoms, functioning and global health status/QoL will be evaluated, more details will be specified in the SAP.

Symptom improvement rate (QLQ-C30 and QLQ-LC13)

The symptom improvement rate will be defined as the number (%) of participants with 2 consecutive assessments, at least 14 days apart, that show a clinically relevant improvement (a decrease ≥10) in that symptom from Baseline.

The denominator will consist of a subset of the mITT/ITT who have a baseline symptom score of ≥10.

QoL/function improvement rate (QLQ-C30)

The QoL/function improvement rate will be defined as the number (%) of participants with 2 consecutive assessments, at least 14 days apart, that show a clinically relevant improvement (an increase score ≥10) in that scale from Baseline.

The denominator will consist of a subset of the mITT/ITT who have a baseline QoL/function score of ≤90.

CHANGE FROM BASELINE

Change from baseline in key symptom scores of dyspnea, cough, chest pain, fatigue and appetite loss will be analysed using a mixed model for repeated measures (MMRM) analysis.

9.4.3.2 Calculation or derivation of patient-reported health state utility (EQ-5D-5L)

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from 5 possible options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where value sets are not available, the EQ-5D-5L to EuroQoL 5-dimension, 3-level health state utility index crosswalk will be applied (van Hout et al 2012, van Reenen and Janseen 2015). In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

9.4.3.3 Analysis of EORTC QLQ-C30 and QLQ-LC13

Symptoms and overall quality of life will be assessed using EORTC QLQ-C30 and QLQ-LC13 (secondary endpoints). Questionnaires will be scored according to published guidelines or the developer's guidelines, if published guidelines are not available. PRO analyses will be based on the mITT (primary population), and separately on the ITT. Further details of the statistical analyses including details of Mixed effect Models for Repeated Measures (MMRM) modelling and the analysis to be performed in the ITT will be given in the SAP.

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), and a global measure of health status. The QLQ-LC13 is a lung cancer-specific module from the EORTC for lung cancer comprising 13 questions to assess lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication. With the exception of a multi-item scale for dyspnea, all are single items. The dyspnea scale will only be used if all 3 items have been scored; otherwise, the items are treated as single-item measures.

An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, the functional scales and the global health status/QoL scale according to the EORTC QLQ-C30 Scoring Manual (EORTC QLQ-C30 Scoring Manual, Third Edition) and EORTC QLQ-LC13 instructions.

Higher scores on the global health status/QoL and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity. Changes in score compared with baseline will be evaluated. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Definition of compliance and evaluability rates

Compliance rates for the PRO questionnaires should be 85%, this rate will be monitored as the trial goes on. Compliance with the EORTC QLQ-C30 and EORTC QLQ-LC13 will be calculated, separately for each questionnaire:

$$\text{Compliance rate} = \frac{\text{number of evaluable forms}}{\text{number of expected forms}} \times 100$$

Evaluability rates for the EORTC QLQ-C30 and EORTC QLQ-LC13 will also be calculated, separately for each questionnaire:

$$\text{Evaluability rate} = \frac{\text{number of evaluable forms}}{\text{number of received forms}} \times 100$$

An expected form = a questionnaire that is expected to be completed at a scheduled assessment time, i.e. a questionnaire from a participant who has not withdrawn from the study at the scheduled assessment time but excluding participants in countries with no available translation.

An evaluable form = a questionnaire with a completion date and at least one subscale that is non-missing.

A received form = a questionnaire that has been received and has a completion date and at least one individual item completed.

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically relevant change is defined as a change in the score from baseline of ≥10 for scales/items from the QLQ-C30 and the QLQ-LC13 (Osoba et al 1998). For example, a clinically relevant deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline (defined as Day 1, pre-dose) of ≥10. A clinically relevant improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from

baseline of ≥10. At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable, or worsening as shown in Table 11. Participants with no baseline data will be excluded from analyses.

Table 12 Visit response for symptoms and HRQoL

Score	Change from baseline	Visit response
QLQ-C30/QLQ-LC13 symptom scales/items	≥+10	Worsened
	≤-10	Improved
	Otherwise	Stable
QLQ-C30 functional scales and global health status/QoL	≥+10	Improved
	≤-10	Worsened
	Otherwise	Stable

HRQoL Health-related quality of life; QLQ-C30 30-item core quality of life questionnaire; QLQ-LC13 13-item lung cancer quality of life questionnaire.

Time to symptom and HRQL/function deterioration (QLQ-C30 and QLQ-LC13)

Time to deterioration in symptoms, functioning and global health status/QoL will be evaluated, more details will be specified in the SAP.

Improvement in symptom and HRQL (QLQ-C30 and QLQ-LC13)

Improvement in symptoms, functioning and global health status/QoL will be evaluated, more details will be specified in the SAP.

9.4.4 Calculation or derivation of pharmacokinetic variables

9.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modelling approach in participants with NSCLC. The impact of physiologically relevant participant characteristics (covariates) and disease on PK will be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints will be evaluated. The results of such an analysis will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

9.4.4.2 Pharmacokinetic non-compartmental analysis

The actual sampling times will be used in the PK calculations. PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. PK parameters will be determined using standard non-compartmental

methods. The following PK parameters will be determined after the first and steady-state doses: peak concentration and trough concentration (as data allow). Samples below the lower limit of quantification will be treated as missing in the analyses.

9.4.4.3 Immunogenicity analysis

Immunogenicity results will be analysed descriptively by summarising the number and percentage of participants who develop detectable ADAs against durvalumab. The immunogenicity titre and presence of neutralising ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

9.4.5 Calculation or derivation of biomarker variables

Biomarker(s) will be assessed for evaluable participants in each treatment arm according to prespecified criteria that will be detailed in the SAP.

9.4.6 Calculation or derivation of health economic variables

Frequency and estimates of resource use, including length of stay and number of hospital admissions, will be derived from the health resource use information.

9.5 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalised before database lock and will describe the participant populations to be included in the analyses and the procedures to account for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. Relevant listings will be generated as needed. More details will be provided in the SAP.

9.5.1 Efficacy analyses

The study has been sized to characterise the PFS benefit of durvalumab versus placebo.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be

summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables, Baseline is defined as the last visit prior to randomisation.

All data collected will be listed. Efficacy and PRO data will be summarised and analysed based on the mITT (primary population), and separately on the ITT, more details will be specified in the SAP. PK data will be summarised and analysed based on the PK analysis set. Safety data will be summarised on the SAS.

Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

Table 13 details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint. Note, all endpoints compare durvalumab versus placebo in randomised participants in the mITT/ITT, unless otherwise indicated.

Table 13 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analysed	Notes
Progression-free survival	Stratified log-rank tests for: Primary analysis using BICR tumour RECIST 1.1 assessments Sensitivity analyses using BICR tumour data (RECIST 1.1) 1 Interval censored analysis – evaluation time bias 2 Analysis using alternative censoring rules – attrition bias 3 Analysis by excluding sCRT participants with 1 concurrent chemotherapy and radiation cycle Sensitivity analysis stratified log-rank test using study site Investigator tumour data (RECIST 1.1) – ascertainment bias
Overall survival	Stratified log-rank test
Proportion of participants alive at 24 months from randomisation	Kaplan-Meier estimates of survival at 24 months
Objective response rate	Logistic regression for: Secondary analysis using BICR tumour data (RECIST 1.1) Sensitivity analysis using study site Investigator tumour data (RECIST 1.1)
Duration of response	Analysis following the method described by Section 9.5.1.5 using BICR tumour data (RECIST 1.1)

Endpoints analysed	Notes
Progression-free survival at 12 and 18 months from randomisation	Kaplan-Meier estimates of progression-free survival at 12 and 18 months
Time from randomisation to second progression	Stratified log-rank test
Time to death or distant metastasis	Stratified log-rank test using BICR tumour data (RECIST 1.1)
Symptom improvement rate (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Logistic regression
HRQoL/Function improvement rate (EORTC QLQ-C30 endpoints)	Logistic regression
Time to HRQoL/Function deterioration (EORTC QLQ-C30 endpoints)	Stratified log-rank test
Time to symptom deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Stratified log-rank test
Change from Baseline in key symptoms (EORTC QLQ-C30 and QLQ-LC13)	Mixed model repeated measures analysis

BICR Blinded Independent Central Review; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; HR Hazard ratio; KM Kaplan-Meier; QoL Quality of Life; QLQ-LC13 13-item self-administered questionnaire for lung cancer; RECIST 1.1 Response Evaluation Criteria In Solid Tumors Version 1.1.

All outputs will be summarised by treatment arm for randomised participants in the mITT/ITT.

9.5.1.1 Primary endpoint: Progression-free survival

The primary PFS analysis will be based on the programmatically derived RECIST 1.1 using the BICR tumour assessments in the mITT. The analysis will be performed using a stratified log-rank test adjusting for the level of PD-L1 expression (PD-L1<1% or PD-L1≥1%) and prior therapy (cCRT or sCRT). The effect of durvalumab versus placebo treatment will be estimated by the HR together with its corresponding 95% CI and p-value.

KM plots of PFS will be presented by treatment arm. Summaries of the number and percentage of participants experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment.

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable RECIST 1.1 assessment will be analysed using a log-rank test. For participants whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust even in highly asymmetric assessment schedules (Sun and Chen 2010).

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of participants who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumour assessments will be included. In addition, participants who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a KM plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

A sensitivity analysis will be performed by analysing the Investigator assessments. The stratified log-rank test will be repeated on these data. The HR and 95% CI will be presented.

If applicable, a sensitivity analysis will be performed by excluding sCRT participants with 1 concurrent chemotherapy and radiation cycle using BICR tumour data (RECIST 1.1). The stratified log-rank test will be repeated on these data. The HR and 95% CI will be presented.

The assumption of proportionality will be assessed first by examining plots of complementary log-log (event times) versus 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 will 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 KM curve along with landmark analyses (eg, 1-year PFS rate) will also help in understanding the treatment benefit.

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using BICR assessments) between durvalumab versus placebo in the following (but not limited to) subgroups:

- Prior therapy (cCRT or sCRT)
- Sex (male versus female)
- Age at randomisation (<65 versus ≥65 years)
- Stage (IIIA versus IIIB/C)
- Time from last dose of radiation to randomisation (<14 days versus ≥14 days)

- PD-L1 status (tumour cells [TCs] ≥ 1% vs TCs < 1%)
- Histology (squamous versus non-squamous)
- Smoking (smoker versus non-smoker [never smoker])
- Race (Asian versus non-Asian)
- EGFR/ALK status (positive vs negative) (only applicable for analyses in the ITT population)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

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

Cox proportional hazards modelling will be employed to assess the effect of covariates on the HR estimate. A model will be constructed, containing treatment and the stratification factors, to ensure that any output from the Cox modelling is likely to be consistent with the results of the stratified log-rank test.

Interactions between treatment and stratification factors will also be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985.

For each subgroup, the HR (durvalumab:placebo) and 95% CI will be calculated from a Cox proportional hazards model with treatment as the only covariate. These will be presented on a Forest plot including the HR and 95% CI from the overall population.

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 PFS will not be formally analysed. In this case, only descriptive summaries will be provided.

The analysis of PFS will be performed in the mITT (primary population), and separately in the ITT, more details will be specified in the SAP.

9.5.1.2 Overall survival

The key secondary endpoint of OS (mITT) will be analysed using stratified log-rank tests, using the same methodology as described for the primary PFS endpoint. The effect of durvalumab versus placebo will be estimated by the HR together with its corresponding CI and p-value. KM plots will be presented by treatment arm. Summaries of the number and percentage of participants 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 OS for each treatment.

The analysis of OS will be performed in the mITT (primary population), and separately in the ITT, more details will be specified in the SAP.

9.5.1.3 Proportion of participants alive at 24 months

OS24 will be summarised (using the KM curve) and presented by treatment arm based on the mITT (primary population), and separately on the ITT.

9.5.1.4 Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using the BICR tumour data. The ORR will be compared between durvalumab versus placebo using logistic regression models adjusting for the same factors as the primary endpoint (the level of PD-L1 expression [PD-L1<1% or PD-L1≥1%] and prior therapy [cCRT or sCRT]). The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 95% CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). This analysis will be performed in the mITT (primary population), and separately in the ITT.

This analysis of ORR will be repeated using the results of the programmatically derived site Investigator data from all scans based upon RECIST 1.1 as a sensitivity analysis to confirm the results of the primary analysis derived from the BICR data.

Summaries will be produced that present the number and percentage of participants with a tumour response (CR/PR). Overall visit response data will be listed for all participants (ie, the ITT). For each treatment arm, BoR will be summarised by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

9.5.1.5 Duration of response

Descriptive data will be provided for the DoR based on BICR assessments according to RECIST 1.1 in responding participants, including the associated KM curves (without any formal comparison of treatment arms or p-value attached). This analysis will be performed in the mITT (primary population), and separately in the ITT.

9.5.1.6 Progression-free survival at 12 and 18 months

The PFS12 and PFS18, will be summarised (using the KM curve) and presented by treatment arm.

These analyses will be performed in the mITT (primary population), and separately in the ITT.

9.5.1.7 Time from randomisation to second progression

Second progression (PFS2) will be analysed using a stratified log-rank tests, using the same methodology as described for the primary PFS endpoint. The effect of durvalumab versus

placebo will be estimated by the HR together with its corresponding 95% CI and p-value. KM plots will be presented by treatment arm. Summaries of the number and percentage of participants who have an event as well as those who were censored will be provided along with the medians for each treatment.

For supportive purposes, the time to the start of subsequent therapy will be analysed using the same methodology and model. The HR for the treatment effect together with its 95% CI will be presented. In addition, a KM plot of the time to the start of subsequent therapy will be presented by treatment arm, and the time between progression and starting subsequent therapy will be assessed. No multiplicity adjustment will be applied, as these are viewed as supportive endpoints.

A summary table of first subsequent therapies by treatment arm will be provided, as well as response to first subsequent therapy by treatment arm, if applicable.

This analysis will be performed in the mITT (primary population), and separately in the ITT.

9.5.1.8 Time to death or distant metastasis

TTDM will be analysed using identical methods as outlined for the analysis of PFS and adjusting for the same set of covariates, but no subgroup analysis will be performed. Medians and KM plots will be presented to support the analysis. The sensitivity analysis outlined in Section 9.5.1.1 will not be repeated for TTDM, with the exception of a KM plot of the time to censoring where the censoring indicator of TTDM is reversed. This analysis will be performed in the mITT (primary population), and separately in the ITT.

9.5.1.9 Patient-reported outcomes: EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L

PRO is a secondary objective. PRO analyses will be based on the mITT (primary population), and separately on the ITT, more details will be provided in the SAP.

Five symptoms have been identified as primary PRO endpoints:

- Dyspnoea: multi-item scale based on 3 questions (“Were you short of breath when you rested; walked; climbed stairs?” – QLQ-LC13)
- Cough: 1 item (“How much did you cough?” – QLQ-LC13)
- Chest pain: 1 item (“Have you had pain in your chest?” – QLQ-LC13)
- Fatigue: multi-item based on 3 questions (“Did you need rest?; Have you felt weak?; Were you tired?” – QLQ-C30)
- Appetite loss: 1 item (“Have you lacked appetite?” – QLQ-C30)

The physical functioning and overall health status domains of the EORTC QLQ-C30 are furthermore pre-specified endpoints of interest.

Mixed models repeated measures (MMRM) analysis

Change from baseline in dyspnea, cough, and chest pain scores as assessed by the EORTC QLQ-LC13 and fatigue and appetite loss as assessed by the EORTC QLQ-C30 will be the primary analysis and assessment of PRO outcome measures. The analysis will be performed using a linear mixed model for repeated measures (MMRM) analysis of change from baseline in the scores for each assessment timepoint and the Bonferroni-Holm procedure for adjusting the significance level will be used to aid interpretation. Therefore, the 5 endpoints will be tested at a 1% significance level.

Time to deterioration

Time to symptom and function/HRQoL deterioration will be analysed for each of the symptom scales/items, function scales, and global health status/QoL in EORTC QLQ-C30 and QLQ-LC13. This will be achieved by comparing between treatment arms using a stratified log-rank test as described for the primary analysis of PFS. The HR and 95% CI for each scale/item will be presented graphically on a forest plot.

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

Symptom and function/HRQoL improvement rate

A summary of the symptom improvement rate for all symptom scales/items in EORTC QLQ-C30 and QLQ-LC13 will be produced. Similarly, a summary of function/HRQoL improvement rate for each of the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL will be produced.

Symptom improvement rates will be analysed by comparing between treatment arms using a logistic regression model. The odds ratio and 95% CI for each scale/item will be presented graphically on a forest plot. If there are very few responses in 1 treatment arm, a Fisher's exact test will be considered.

Change from baseline

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score, and each functional domain will be reported by assessment timepoint for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of participants in each response category at each assessment timepoint for each ordinal item (in terms of the proportion of participants in the categories of improvement, stable, and deterioration as defined in Table 12) will also be produced for each treatment arm.

EuroQol-5-Dimension 5-Level questionnaire

The change from Baseline in health state utility values and the visual analogue scale will be compared between treatment arms at each visit using a mixed model repeated measures analysis, which adjusts for the same factors as the primary analysis and also the baseline health state utility value/visual analogue scale as appropriate. Adjusted mean differences between treatments and 95% CIs from these analyses will be presented, but, as this analysis is exploratory in nature, p-values will not be calculated.

Descriptive statistics will be reported for the health state domain (eg, proportion in each domain) and the visual analogue scale by visit, as well as the change in the visual analogue scale value and the derived utility index value from Baseline. To support future economic evaluations, additional appropriate analyses may be undertaken, for example, mean health state utility pre- and post-treatment, and pre- and post-progression.

9.5.1.10 Health care resource use

An exploratory health economic analysis of hospital episodes including type of contact (hospitalisation, outpatient, or day case), reason, length of stay by ward type (including intensive care unit), procedures, and tests may be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of durvalumab, and will be outlined in the payer analysis plan. This would include providing descriptive statistics as appropriate, including means, median, and ranges.

9.5.2 Safety analyses

Safety is a secondary objective. Safety and tolerability data will be presented by treatment arm using the safety population.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities preferred terms and CTCAE grade) will be listed individually by participant. The number of participants experiencing each AE will be summarised by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced.

Other safety data will be assessed in terms of physical examination, clinical chemistry, haematology, vital signs, and ECGs. Exposure to durvalumab and placebo will be summarised. Time on study, durvalumab and placebo dose delays will also be summarised. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.5.3 Pharmacokinetic data

PK concentration data will be listed for each participant and each dosing day, and a summary will be provided for all evaluable participants.

9.5.4 Immunogenicity data

Immunogenicity results will be listed by participant, and a summary will be provided by the number and percentage of participants who develop detectable anti-durvalumab antibodies. The immunogenicity titre and neutralising ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab antibodies.

The effect of immunogenicity as well as the effect of its neutralising properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the AstraZeneca Clinical Pharmacology group or designee.

9.5.5 Pharmacokinetic/pharmacodynamic relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modelling approach.

9.5.6 Biomarker data

The relationship of PD-L1 expression and, if applicable, of exploratory biomarkers to clinical outcomes (including but not restricted to) of PFS, OS, ORR, and DoR will be presented.

PD-L1 expression determined by IHC will be reported in the CSR. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.5.7 Methods for multiplicity control

The multiple testing procedure (as shown in Figure 3) will define which significance levels should be applied to the interpretation of the raw p-values for the primary endpoint of PFS (mITT) and the key secondary endpoint OS (mITT), and CCI [redacted]

There will be up to 3 DCO timepoints in the study.

The final (primary) PFS analysis (first analysis) for superiority will be performed in the mITT population when whichever of the following conditions have been met first:

- Reaching approximately CCI BICR progression-free survival events across the durvalumab and placebo treatment arms (approximately CCI maturity)

OR

- Approximately CCI months follow-up from last participant randomized to the study.

The first OS interim analysis in the mITT will be conducted at the same time as primary PFS analysis (with approximately CCI OS events, CCI maturity). The DCO for the second interim OS analysis in the mITT will be performed at approximately CCI months after the OS first

interim analysis (approximately CCI OS events in the CCI with CCI maturity), which may be removed as specified in section 9.2. The DCO for the final OS analysis in the CCI will be performed when reaching approximately CCI OS events (CCI maturity) or approximately CCI months follow-up from the last participant randomization, whichever occurs first.

If the null hypothesis is rejected in PFS (mITT) final analysis, CCI alpha level will be recycled to OS (CCI) analysis. The CCI alpha level allocated to OS will be controlled at the interim and final analysis by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach. If CCI of the OS events required at the time of the final OS analysis is available at the time of the interim analysis (ie, CCI or CCI OS events have occurred), the 2-sided significance level to be applied for the OS interim analysis would be CCI and CCI, respectively, and the 2-sided significance level to be applied for the final OS analysis would be CCI. Note that the actual allocation of alpha across the three analysis times will be driven by the actual information fraction associated with the analysis and alpha allocation for OS first interim analysis will assume that the OS second interim and final analysis will take place. If second interim analysis is removed after the first interim analysis is complete, the alpha has been spent for first interim analysis will not be changed, the remaining alpha will be calculated based on actual information fraction and allocated for OS final analysis.

If the null hypothesis is rejected in either OS CCI interim or final analyses, CCI alpha level will be further recycled to PFS CCI analysis. To strongly control the type I error rate, the DCO for PFS CCI analysis will be fixed at the same time as that of primary PFS (CCI analysis and approximately CCI BICR PFS events are expected in the CCI population at this time.

If the null hypothesis is rejected in PFS CCI analysis, CCI alpha level will be finally recycled to OS CCI analysis. The CCI alpha level will be controlled at the interim and final analyses by using the Lan DeMets method described as above. At the time of interim and final analyses (same time as the OS (mITT) analysis), the number of OS events is expected to be approximately CCI maturity), CCI maturity), and CCI maturity), respectively, which corresponds to an information fraction of approximately CCI at each analysis, the resulting alpha was calculated to be CCI at subsequent analyses. The alpha allocation for OS interim and final analysis in the ITT population will follow the same rule and consideration above for the analysis in the mITT population.

9.6 Interim analyses

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

Up to two interim analyses of OS will be performed. The DCO for the first interim analysis of OS will occur at the same time as primary PFS analysis. The second interim analysis of OS will be conducted at approximately CCI months after the first OS interim analysis (approximately CCI OS events in the CCI with CCI maturity), which may be removed as specified in section 9.2.

If the interim results do not meet the criterion of stopping for superiority for a given hypothesis, then follow-up will continue until the final analysis, following which the hypothesis will be re-tested.

The multiplicity introduced by including OS interim analyses for superiority has been accounted for, using the method as specified in section 9.5.7.

9.6.1 Data monitoring committee

This study will use an external IDMC to assess ongoing safety analyses:

- The IDMC will review the safety data periodically in accordance with the IDMC charter.
- Additional reviews of the safety data may be requested by the IDMC at additional points during the study.

This committee will be composed of therapeutic area experts and biostatisticians, who are not employed by AstraZeneca and do not have any major conflict of interest.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way. 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 rest with the sponsor.

A separate IDMC charter will be developed, which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with the Participant Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the clinical study protocol and letters to Investigators.

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