AstraZeneca

Statistical Analysis Plan

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A Phase II, Open-Label, Multi-Centre, International Safety Study of Durvalumab Following Sequential Chemotherapy and Radiation Therapy in Patients with Stage III, Unresectable Non-Small Cell Lung Cancer (PACIFIC 6)

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Study Statistician

PPD (PAREXEL) Date

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Statistical Science Director

PPD (AstraZeneca) Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACS	Abnormal clinically significant
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BoR	Best Objective Response
BP	Blood Pressure
cCRT	Concurrent chemoradiation therapy
CI	Confidence interval
COVID-19	Corona virus disease-2019
CR	Complete Response
CrCl	Creatinine Clearance
CRT	Chemoradiation therapy
CS	Clinically significant
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CCI	[redacted]
DBL	Database lock
DBP	Diastolic blood pressure
DCO	Data cut-off
DoR	Duration of response
EA	Early assessment
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
eCRF	Electronic Case Report Form
CCI	[redacted]
ePRO	Electronic patient-reported outcome assessment
CCI	[redacted]
ESE	Early Safety Evaluation
GI	Gastrointestinal
Gy	Gray
HL	Hy's Law
CCI	[redacted]
IASLC	International Association for the Study of Lung Cancer
IASLC 2016	IASLC Staging manual version 8
ICH	International conference of harmonisation
ICH 1995	ICH guidelines version dated 1995
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IP	Investigational product
IPD	Important protocol deviations
IV	Intravenous
kg	Kilogram
LLQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
msec	Milliseconds
MSSO	MedDRA Maintenance and Support Service Organization
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-target lesion
ORR	Overall response rate
OS	Overall survival

Abbreviation or special term	Explanation
OS12	Proportion of patients alive at 12 months
OS24	Proportion of patients alive at 24 months
PD	Progressive disease
CCI	[redacted]
PET	Positron emission tomography
PFS	Progression-free survival
PFS12	Proportion of progression-free and alive patients at 12 months
PFS24	Proportion of progression-free and alive patients at 24 months
PR	Partial response
PRAE	Possibly related adverse event
PRO	Patient reported outcome
CCI [redacted]	CCI [redacted]
PS	Performance status
PT	Preferred term
q12w	Every twelve weeks
q4w	Every four weeks
QoL	Quality of life
CCI [redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDI	Relative dose intensity
RECIST1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1
RS	Raw score
RTOG	Radiotherapy Oncology Group
RTOG 0617	RTOG version 0617
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBP	Systolic blood pressure
sCRT	Sequential Chemoradiotherapy

Abbreviation or special term	Explanation
SD	Stable disease
SI	International system (of units)
SOC	System organ class
T3	Tri-iodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TNM	Tumour, node and metastasis
TL	Target lesion
TRAE	Treatment-related adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
24 October 2018	Initial version 1.0

13 November 2020	Version 2.0 includes the following changes from V1.0:
	• updates arising from amendments to the clinical study protocol version 3.0 including:
	  • a change in the number of subjects (Sections 1.2 and 1.3)
	  • changes to the definition of inclusion criteria 6 and 7 and exclusion criterion 13, affecting the definition of Important Protocol Deviation 1 (Section 2.2.1)
	  • additional secondary endpoints for respiratory rate and temperature (Section 3.2.5)
	  • the inclusion of the early assessment analysis (Section 5)
	• additions or revisions:
	  • the removal of the exploratory objective and the analysis relating to CCI testing results (Sections 1.1.3, 3.5.3, 4.6.5, and 6).
	  • the inclusion of Important Protocol Deviation 4 considering effects of the COVID-19 pandemic on the study (Sections 2.2.1 and 4.2.2)
	  • changes to the monitoring of important protocol deviations (Section 2.2.2)
	  • changes to definitions and extra summaries for adverse events and immune-mediated adverse events (Sections 3.2.3 and 4.5.1),
	  • the use of the AZ project reference ranges for the primary interpretation of laboratory data (Section 3.2.6),
	  • inclusion of percentage intended dose as a variable relating to exposure to study treatment (Section 3.2.8)
	  • clarification of data used to assess when a patient was last known to be alive (Section 3.3.2)
	  • changes to the summaries of patient disposition (Section 4.2.1)
	  • changes to the summaries of demography and baseline characteristics (Section 4.2.3)
	  • the definition and analysis of best objective response (Sections 3.3.4 and 4.4.3)
	  • definitions and summaries of compliance for patient reported outcomes (Sections 3.4.1 and 4.6)
	  • changes to the description of baseline characteristics (Section 3.5.1),
	  • the handling of missing data for values below LLQ (Section 4.1.3),
	  • the definition of visit windows for survival follow-up (Section 4.1.4.1)

Date	Brief description of change
	• the assessment of thyroid and renal function tests (Sections 4.5.4.2 and 4.5.4.3) • Extra summaries for exposure (Section 4.5.5)
1 October 2021	Version 3.0 includes the following changes from V2.0: • Added explanation for equivalence of SAF and FAS in section 2.1.1 • Added shift table for Assessment of Thyroid Function Test Results to section 4.5.4.2 • Added rule to identify two missed visits for censoring for progression-free survival in section 3.3.1 • Added estimates for Month 36 (Day 1095) in section 4.4.5 • Removed Total Protein and Corrected Calcium from analysis by CTCAE grading in section 4.5.4 • Removed section 4.5.4.3 Assessment of Renal Function Test Abnormalities • Added text for Covid-19 pandemic in section 3.2.3.4, 4.1.1, 4.2.1 and 4.2.2, 4.2.3, 4.4.1, 4.4.2, 4.5.1.2 • Updates from amendment to the clinical study protocol version 4.0.

1. STUDY DETAILS

This study is being conducted to provide safety, efficacy, and quality of life (QoL) data to complement the results of the PACIFIC (D4191C00001) Study, which assessed treatment with durvalumab (MEDI4736) in patients with unresectable Stage III non-small cell lung cancer (NSCLC) who had not progressed after concurrent chemoradiation therapy (cCRT). The study will expand on the data currently available from the PACIFIC Study by assessing the clinical profile of durvalumab in patients who have not progressed after sequential chemoradiation therapy (sCRT), and in patients of World Health Organisation/Eastern Cooperative Oncology Group Performance Status 0 to 1 and 2 (WHO/ECOG PS 0 to 1 and 2).

1.1 Study Objectives

1.1.1 Primary Objective

Primary Objective	Endpoint / Variable
To assess the safety and tolerability profile of durvalumab as defined by Grade 3 and Grade 4 treatment-related adverse events (TRAEs[a]) within six months from the initiation of durvalumab treatment	Grade 3 and Grade 4 TRAEs[a]

Note: Toxicities will be classified as per CTCAE grading system NCI CTCAE version 4.03.

TRAE: treatment-related adverse event; CTCAE: Common Terminology Criteria for Adverse Event; NCI: National Cancer Institute.

a. TRAEs and PRAEs are used interchangeably and "possibly related adverse events" (PRAEs) will be reported in this SAP, tables, figures, listings, and CSR.

1.1.2 Secondary Objectives

Secondary Efficacy Objectives	Endpoints / Variables
To assess the efficacy of durvalumab treatment in terms of progression-free survival (PFS) and overall survival (OS)	Median PFS according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) as assessed by the Investigator PFS12 and PFS24 according to RECIST 1.1 as assessed by the Investigator Median OS, OS12, OS24, and OS36
To further assess the efficacy of durvalumab treatment in terms of objective response rate (ORR) and duration of response (DoR)	ORR according to RECIST 1.1 as assessed by the Investigator DoR according to RECIST 1.1 as assessed by the Investigator
To assess the efficacy of durvalumab treatment in terms of lung cancer mortality	Lung cancer mortality

Secondary Safety Objectives	Endpoints / Variables
To further assess the safety and tolerability profile of durvalumab treatment, including all adverse events (AEs)	AEs, serious adverse events (SAEs), adverse events of special interest (AESIs), immune-mediated adverse events (imAEs), physical examinations, vital signs including blood pressure (BP) and pulse rate, respiratory rate, temperature, ECGs, and laboratory findings including clinical chemistry, haematology and urinalysis

Note: Analysis of ORR and DoR will be based upon Investigator assessment according to RECIST 1.1. Prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

Note: An AESI is an AE of scientific and medical interest specific to understanding of the durvalumab. 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.

Note: An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology.

AE: adverse event; AESI: adverse event of special interest; BP: blood pressure; DoR: duration of response; CTCAE: Common Terminology Criteria for Adverse Event; ECG: electrocardiogram; imAE: immune-mediated adverse event; ORR: objective response rate; OS: overall survival; OS12, OS24, OS36: proportion of patients alive at 12 months, 24 months, 36 months, respectively, from first date of treatment; PFS: progression-free survival; PFS12, PFS24: proportion of patients progression-free at 12 months and 24 months, respectively, from first date of treatment; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SAE: serious adverse event.

1.1.3 Exploratory Objectives

Exploratory Objectives	Endpoints / Variables
CCI	
CCI	
CCI	
CCI	

CCI

CCI

a. CCI

b. CCI

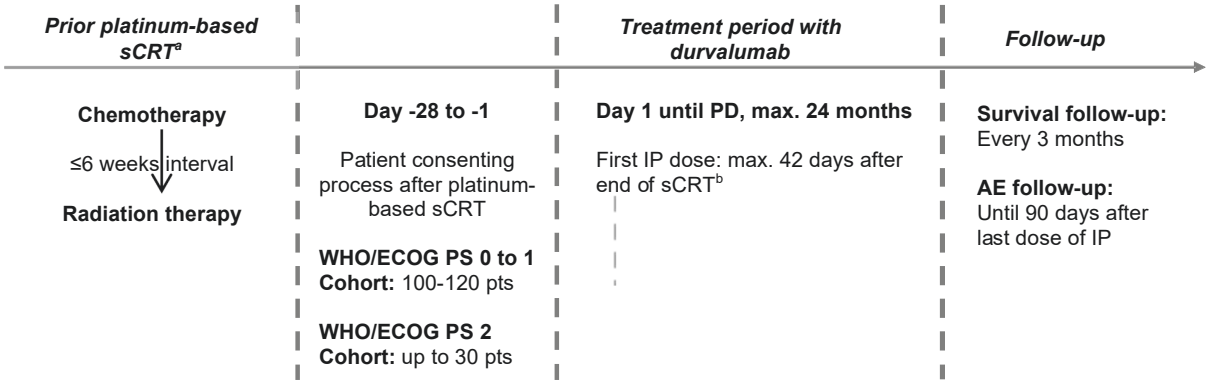
CCI

1.2 Study Design

This is a Phase II, open-label, multi-centre study to determine the safety of a fixed dose of durvalumab 1500 mg monotherapy dose in patients with unresectable Stage III NSCLC who have not progressed following definitive, platinum-based sCRT.

The general study design is summarised in Figure 1.

Figure 1 Study Design



a Patients 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 radiation therapy must be no more than 6 weeks. Consolidation chemotherapy after radiation is not permitted. If the patient's platinum-based chemotherapy contained gemcitabine, no overlap between chemotherapy and radiation therapy is permitted. If the patient's platinum-

based chemotherapy contained cisplatin or carboplatin and etoposide, vinblastine, vinorelbine, a taxane (paclitaxel or docetaxel), or pemetrexed (ie, an agent other than gemcitabine), an overlap of 1 cycle of chemotherapy and radiation therapy is acceptable.

b Treatment initiation within the first 14 days after sCRT therapy is highly encouraged.

AE: adverse event; IP: investigational product; PD: progressive disease; sCRT: sequential chemoradiotherapy; WHO/ECOG PS: World Health Organisation/Eastern Cooperative Oncology Group Performance Status.

Up to 150 patients will be treated with the study drug in Europe and North America in two cohorts: one cohort of between 100 and 120 patients with WHO/ECOG PS=0 or 1, and a second cohort of up to 30 patients with WHO/ECOG PS=2.

Patients must not have progressed following definitive, platinum-based sCRT; radiation therapy must be completed within 42 days prior to first dose administration of durvalumab. The last dose of radiation therapy is defined as the day of the last radiation treatment session.

Patients must have histologically- or cytologically-documented NSCLC and locally-advanced, unresectable Stage III disease (according to the International Association for the Study of Lung Cancer [IASLC] Staging Manual Version 8 [IASLC 2016])

1.2.1 Study Treatment

Patients will receive 1500 mg durvalumab administered via intravenous (IV) infusion, starting on Week 1 after confirmation of eligibility, every four weeks (q4w) for a maximum of 24 months from Cycle 1 Day 1. Study drug should be discontinued prior to 24 months if there is progressive disease according to RECIST 1.1 criteria (PD; unless the investigator considers the patient continues to receive benefit from the durvalumab), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Patients may delay dosing due to TRAEs which are either immune-mediated AEs (imAEs) or non-imAEs, or for reasons other than TRAEs.

- In case of a TRAE (imAEs or non-imAEs), dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (see annex to the protocol).
- If dosing must be delayed for reasons other than TRAEs, dosing will resume as soon as feasible.
- The duration of delays will be accounted for, as a non-exposure duration, when deriving actual duration of exposure to study treatment (See Section 3.2.8)

The schedule of assessments including safety, tolerability, efficacy using RECIST version 1.1 and patient reported outcomes (PROs) based on questionnaires are detailed in the study assessment schedule in Appendix A.

If the dosing is delayed, the laboratory and physical assessments scheduled for that treatment cycle will also be delayed accordingly. The tumour efficacy and PRO assessments dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of first administration of durvalumab (not the date of the study therapy per cycle).

All other scheduled assessments must be performed relative to the start of the dosing cycle such that all procedures required for dosing (eg, collection of laboratory samples) should be

performed within 3 calendar days prior to dosing.

The assessment of electrocardiogram (ECG), urinalysis and coagulation are scheduled to be performed as clinically indicated.

If the recording of vital signs, ECG and blood draws for laboratory tests are scheduled at a visit, they will always be performed in the order: ECG, vital signs and blood draws. In case only two measurements are scheduled, this order will be maintained.

1.2.2 Tumour Response Assessments

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

1.2.3 Overall Survival Assessments

Patients will be followed for survival status every 12 weeks (q12w) following treatment discontinuation, until death, withdrawal of consent or the end of the study. These contacts may be conducted by phone and the survival data collected will be reported in the clinical database for the final study analysis.

1.3 Number of Subjects

This is a safety study and no formal sample size calculation has been performed. Up to 150 patients will be treated with the study drug in 2 cohorts: Between 100 and 120 patients in the WHO/ECOG PS 0 to 1 Cohort and up to 30 patients in the WHO/ECOG PS 2 Cohort.

The primary analysis will be performed when the last patient dosed had the opportunity to receive durvalumab (MEDI4736) for six months. If, as observed in the PACIFIC study, Grade 3 or 4 TRAEs were to occur in 8.3% of the 120 patients in this study (ie, 10 patients), the 95% Clopper-Pearson confidence interval (CI) for this incidence would be 4.1% to 14.8% (approximately ±5.35%). Furthermore, if Grade 3 or 4 TRAEs were to occur in 12% of 100 patients in the WHO/ECOG PS 0 to 1 cohort (ie, 12 patients, the 95% CI would be 6.4% to 20.0% (approximately ±6.8%), if they occurred in 13.3% of 30 patients in the WHO/ECOG PS 2 cohort (ie, in 4 patients), the 95% CI would be 3.8% to 30.7% (approximately ±13.5%).

A further illustration of the estimated incidence rate and Clopper-Pearson 95% CI for varying numbers of subjects observed with Grade 3 or 4 TRAEs for all patients and within each WHO/ECOG PS 2 Cohort is provided in Table 1.

Table 1 Precision of estimation of varying incidence rates of Grade 3 or 4 TRAEs

All Patients (n=120)	Number of subjects with a Grade 3 or 4 TRAEs	8	10	14	18	24
	Estimated Incidence (%)	6.7	8.3	11.7	15.0	20.0

	95% CI (%)	2.9, 12.7	4.1, 14.8	6.5, 18.8	9.1, 22.7	13.3, 28.3
WHO/ECOG PS 0 to 1 Cohort (n=100)	Number of subjects with a Grade 3 or 4 TRAEs	7	8	12	15	20
	Estimated Incidence (%)	7.0	8.0	12.0	15.0	20.0
	95% CI (%)	2.9, 13.9	3.5, 15.1	6.4, 20.0	8.7, 23.5	12.7, 29.2
WHO/ECOG PS 2 Cohort (n=30)	Number of subjects with a Grade 3 or 4 TRAEs	2	3	4	5	7
	Estimated Incidence (%)	6.7	10.0	13.3	16.7	23.3
	95% CI (%)	0.8, 22.1	2.1, 26.5	3.8, 30.7	5.6, 34.7	9.9, 42.3

Note: Clopper-Pearson confidence intervals are shown.

AE: Adverse event; CI: Confidence interval; n: Number of patients; TRAE: Treatment-related adverse event; WHO/ECOG PS: World Health Organisation/Eastern Cooperative Oncology Group Performance Status.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

With the exception of some summaries of patient disposition and particular individual patient data listings, which will be produced for all patients who provided informed consent and who were enrolled in the study, the Safety Analysis Set (SAF) will be used for listings, summaries, and analyses in the study.

2.1.1 Safety Analysis Set (SAF)

The SAF will consist of all patients who received at least one dose (partial or in full) of durvalumab.

In this study, Full Analysis Set (FAS) will consist of all patients who received at least one dose (partial or in full) of durvalumab. Therefore, the SAF and FAS would be equivalent in this study and for the purpose of results presentation all endpoints will be analysed using SAF.

2.2 Protocol Deviations

2.2.1 Important Protocol Deviations

According to ICH E3 guidelines version dated 1995 (ICH 1995),

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

For this study, the following 4 general categories will be considered IPDs and will be summarized in the CSR:

- Deviation 1: Patients who received treatment and who deviated from the following key entry criteria in CSP:
  - Inclusion Criterion 5: Histologically- or cytologically-documented NSCLC with locally-advanced, unresectable Stage III disease (according to the IASLC 2016]). Positron emission tomography (PET)/CT, MRI of the brain, and endobronchial ultrasound with biopsy are highly encouraged at diagnosis.
  - Inclusion Criterion 6: Receipt of sCRT which must have been completed within 42 days prior to first dose administration of durvalumab in the study.

    (a) 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. Platinum-based chemotherapy containing cisplatin or carboplatin and gemcitabine is permitted under certain conditions – refer to bullet point 6(b).

    (b) Patients 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 radiation therapy must be no more than 6 weeks. Consolidation chemotherapy after radiation is not permitted.

    (i) If the patient's platinum-based chemotherapy contained gemcitabine, no overlap between chemotherapy and radiation therapy is permitted.

    (ii) If the patient's platinum-based chemotherapy contained any of the agents listed in 6(a) other than gemcitabine, an overlap of 1 cycle of chemotherapy and radiation therapy is acceptable.

    (c) Patients must have received a total dose of radiation of 60 Gray (Gy) ±10% (54 Gy to 66 Gy). Sites are encouraged to adhere to mean organ radiation dosing as follows:

    (i) Mean lung dose <20 Gy and/or V20 <35%;

    (ii) Mean oesophagus <34 Gy;

    (iii) Heart V45 <35% or V30 <30%.

    Note: Sites should be aware of the recent Radiotherapy Oncology Group (RTOG) version 0617 (RTOG 0617) Study data demonstrating that doses higher than 60 Gy may be associated with greater toxicity and worse efficacy.

    (d) Patients with WHO/ECOG PS 2 or chronic lung disease (pulmonary emphysema or chronic obstructive pulmonary disease) must have received a V20 <25%.
  - Inclusion Criterion 7: Patients must not have progressed following platinum-based sCRT, as per Investigator-assessed RECIST 1.1 criteria. In order to assess disease progression, the baseline imaging (CT/MRI) used for Screening purposes should be compared against the most recently performed scan that allows physician assessment as per RECIST 1.1 criteria (i.e. fulfils the RECIST 1.1 defined imaging acquisition parameters). If an intermediate scan taken between chemotherapy and radiotherapy is available and that scan is suitable for physician assessment as per RECIST 1.1

criteria, then this scan should be used.

(a) Patients with measurable disease and/or non-measurable and/or no evidence of disease (NED) assessed at baseline by CT/MRI will be entered in this study.

(b) Prior irradiated lesions may be considered measurable and selected as TLs provided they fulfil the other criteria for measurability.

- Inclusion Criterion 9: WHO/ECOG PS ≤2.
- Exclusion Criterion 1: Patients with locally-advanced NSCLC whose disease has progressed following platinum-based sCRT.
- Exclusion Criterion 2: Patients who have disease considered for surgical treatment as part of their care plan, such as Pancoast or superior sulcus tumours.
- Exclusion Criterion 3: Mixed small-cell lung cancer and NSCLC histology.
- Exclusion Criterion 6: Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, Interstitial lung disease (ILD), serious chronic Gastrointestinal (GI) 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 patient to give written informed consent.
- Exclusion Criterion 13: Patients who have received cCRT for locally-advanced NSCLC, or who received sCRT with at least 2 concomitant CRT cycles. Prior surgical resection (ie, Stage I or II) is permitted.

  Note: Patients whose platinum-based chemotherapy contained gemcitabine and who received sCRT with at least 1 concomitant CRT cycle are excluded from this study.
- Exclusion Criterion 16: Prior exposure to immune-mediated therapy, including but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.

- Deviation 2: The patient met discontinuation criteria but did not discontinue durvalumab (eg, patient withdrew consent, patient became pregnant).
- Deviation 3: The patient received a prohibited concomitant medication or procedure as detailed in Section 6.4 of the CSP or any other concomitant medication or procedure which, upon physician review of all medications and procedures prior to database lock (DBL), is considered to have a potential effect on study outcomes.
- Deviation 4: Missed visits, assessments, or treatments that, in the opinion of the principal investigator,
  - were due to the 2020 COVID-19 global pandemic and
  - there was a significant effect on either completeness, accuracy, and/or reliability of the patient's data, or the patient's rights, safety or well-being.

2.2.2 Monitoring of Important Protocol Deviations

Programmable PDs will be detected from the data recorded in the clinical database and will be reviewed at regular PD review meetings. At this meeting, the programmatically-derived PDs will be checked to ensure that they have been correctly classified as major or minor PDs.

On an ongoing basis throughout the study, monitoring notes or summaries will also be reviewed to determine any important post-entry deviations that are not identifiable via programming.

If the number of deviations which are considered to have the potential to impact the primary analysis is considered important, sensitivity analyses may be performed on subgroups. This will be decided during the data review meeting and before the database lock.

The final classification of IPDs will be made prior to database lock or data cut-off (DCO) for final analysis. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

3. ANALYSIS VARIABLES

3.1 Derivation of RECIST Visit Responses

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

The baseline radiological tumour assessment is part of the screening procedure and should be performed within 42 days after the end of sCRT, no more than 28 days before the start of durvalumab treatment, and ideally as close as possible to the start of study treatment. Tumour assessments will begin at 8 weeks ± 1 week after durvalumab initiation and continue every 8 weeks ± 1 week through 52 weeks (relative to the date of durvalumab initiation), and then every 12 weeks ± 1 week thereafter until disease progression. An additional follow-up scan will be performed if clinically feasible.

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

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

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

response will be assigned as PD).

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

3.1.1 Site Investigator Assessments Using RECIST 1.1

3.1.1.1 Target Lesions

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

A maximum of five measurable lesions (with a maximum of two lesions per organ), representative of all lesions involved and suitable for accurate repeated measurement, should be identified as target lesions (TLs) at baseline. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In which circumstance the next largest lesion, which can be measured reproducibly, should be selected. If more than one baseline scan is recorded, then measurements from the one that is closest and prior to initiation of durvalumab will be used to define the baseline sum of TLs.

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

For patients who do not have measurable disease at entry (ie, no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see Section 3.1.1.3 for further details). If a patient does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

Table 2 Target Lesion Visit Responses

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

CR: Complete response; NA: Not applicable; NE: Not evaluable; PD: Progressive disease; PR: Partial response; SD: Stable Disease; TL: target lesion

Rounding of Target Lesion Data

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

Missing TL Data

For a visit to be evaluable then all target lesion measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred

- A new lesion is recorded
- A NTL visit response of PD is recorded
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared

Note: the nadir can only be taken from assessments where all the TLs had a LD recorded.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

If all TL measurements are missing, then the TL visit response is NE. Overall visit response

will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

Lymph Nodes

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

Target Lesion Visit Responses Subsequent to Complete Response

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

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

Target Lesion Too Big to Measure

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

Target Lesion Too Small to Measure

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

Irradiated Lesions/Lesion Intervention

A previously irradiated lesion may be selected as a TL, provided that it fulfils the criteria for reproducible measurability and is the only lesion available.

Any TL (including lymph nodes), which has had intervention in addition to study treatment during the study (eg, irradiation / palliative surgery / embolization), should be handled in the

following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours:

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

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

Scaling of the Sum of Target Lesions

Scaling of the sum of target lesion diameters is used when one or more target lesion diameter is missing because of on-study target lesion intervention.

If more than one third of target lesion measurements are missing (because of intervention) then target lesion response will be NE, unless the sum of diameters of non-missing target lesion would result in PD (ie, if using a value of 0 for missing lesions, the sum of diameters has still increased by > 20% or more compared to nadir and the sum of target lesions has increased by ≥5mm from nadir).

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

Example of Scaling

Lesion	Longest diameter (mm) at nadir visit	Longest diameter (mm) at follow-up visit
1	16	18
2	14	16
3	14	16
4	18	18
5	12	Intervention
Sum	**74**	**68**

Lesion 5 has had an intervention at the follow-up visit. The sum of the Baseline measures is 74 mm. The sum of lesions 1-4 at the follow-up is 68 mm. The sum of the corresponding lesions at nadir visit is 62 mm. Scale up as follows to give an estimated follow-up visit TL sum of 81mm:

$$\frac{68}{62} \times 74 = 81mm$$

Lesions that Split in Two or more Parts

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

Lesions that Merge

If two or more target lesions merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL sizes should be recorded as 0mm.

Change in Method of Assessment of Target Lesions

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

Note, if a change in method involves clinical examination (eg, CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.1.1.2 Non-Target Lesions and New Lesions.

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

Non-target lesion response will be derived based on the Investigator's overall assessment of NTLs as follows:

Table 3 NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of one or more NTLs with no evidence of progression.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if there are no NTLs at baseline.

CR: Complete response; NA: Not applicable; NE: Not evaluable; NTL non-target lesion; PD: Progressive disease; PR: Partial response; SD: Stable Disease; TL: target lesion

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

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

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

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

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

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

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

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour

assessments where possible until objective disease progression is observed.

3.1.1.3 Overall Visit Response

Table 4 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 4 Overall Visit Responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR (or NA)	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-PD	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**
NA	NA	No (or NE)	**NED**

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

3.2 Safety Variables

Safety and tolerability will be assessed in terms of AEs (including SAEs, AESIs), deaths, physical examinations, laboratory data, vital signs, ECGs and exposure. These will be collected for all patients throughout the study.

3.2.1 Primary Safety Endpoint

The primary endpoint of this study is the incidence of Grade 3 and Grade 4 TRAEs (see Section 3.2.3.1) which occur within the first six months (ie, up to and including the 183rd day) after the initiation of durvalumab. Any Grade 3 or Grade 4 TRAEs which started after the 183rd day of the study, or after the 90th day following discontinuation of durvalumab, or after the start of subsequent anti-cancer therapy will not be included. In the tables, listings and figures, the TRAEs are presented as “possibly related adverse events” as per the CRF and AZ standards.

3.2.2 Secondary Safety Endpoints

The secondary safety endpoints of this study include:

- TEAEs and SAEs
- AESIs (see Section 3.2.3.2) and imAEs (see Section 3.2.3.3)
- ECG
- Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, temperature, and respiratory rate
- Laboratory data including clinical chemistry, haematology and urinalysis
- Physical Examination

3.2.3 Adverse Events

Details of all AEs and SAEs will be collected for a patient from the signing of the informed consent form (ICF) up to 90 days after the last dose of durvalumab. If an event starts after this period and the Investigator considers that it is possible that it is due to a late onset toxicity to durvalumab, then it should be reported as an AE or SAE.

All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) providing the System Organ Class (SOC) and Preferred Term (PT).

In addition, all AEs will also be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE Version 4.03) allocating grades from Grade 1 to Grade 4 which will be used for the reporting. The meaning of these categories are as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

Treatment-emergent adverse events (TEAEs) are AEs that start after the first dose of durvalumab or which start prior to the first dose of durvalumab but worsen following the first dose of durvalumab, and where the start date/date of worsening is also no later than 90 days after the last dose of durvalumab or the initiation of the first subsequent therapy following discontinuation of durvalumab (whichever occurs first). Any TEAE will be included in the AE summaries as detailed in Section 4.5.1.

Missing start and stop dates for AEs will be imputed using the rules described in Section 4.1.3.

3.2.3.1 Treatment-Related Adverse Events

A TRAE is any AE with a relatedness to durvalumab of possible or probable, or where the

relatedness is missing. When the relatedness of an AE is missing on the eCRF, all efforts will be taken to ensure that the Investigator assigns his/her assessment of relatedness prior to database lock. In the tables, listings and figures, the TRAEs are presented as "possibly related adverse events" as per the CRF and AZ standards.

If relatedness of an AE is missing at the DBL, as given in Section 4.1.2, the AE will be considered as related to durvalumab.

3.2.3.2 Adverse Events of Special Interest

An AESI is defined as an AE of scientific and medical interest specific to durvalumab and may require close monitoring and rapid communication by the Investigator to the sponsor. An AESI can be either serious or non-serious. All AESIs will be programmatically derived.

An AstraZeneca medically qualified expert, after consultation with the Global Patient Safety Physician, has reviewed all AEs of interest and identified which PTs contribute to each AESI. A further review will take place prior to DBL to ensure any further terms not already included are captured within the categories. The final list of PTs for all AESIs will be completed before DBL and documented in the Study Master File.

3.2.3.3 Immune-Mediated Adverse Event

An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. In general, imAEs will include AESIs that are managed using steroids, immunosuppressants and/or hormone replacement therapy.

This document comprises the specification for the analysis of the imAEs as identified by the investigator (as recorded in CRF Adverse Events (AE)).

Time to event analyses for imAEs will be performed for the following definitions:

- Time to first onset of imAE: Start date of first imAE episode – First dose date + 1
- Time to first onset of imAE of Grade 3 or 4: First date of imAE episode that had CTCAE Grade 3 or 4 – First dose date + 1
- Time to resolution of imAE: End date of imAE episode – Start date of imAE episode + 1
- Time to resolution of Grade 3 or 4: End date of imAE episode that had CTCAE Grade 3 or 4 – First date imAE episode had severity of grade 3 or higher + 1

If an imAE does not resolve, then the time to resolution will be censored at earliest date of DCO, death date, or last dose date + 90 days. Patients who die prior to resolution of the imAE will be censored at the date of death.

Adjudication and statistical analysis for the imAEs will be performed by AstraZeneca. The results will be incorporated into and discussed in the CSR.

3.2.3.4 Confirmed/Suspected COVID-19 infections

Confirmed/Suspected Covid-19 infection is defined as an AE occurring during the pandemic timeframe (after 11th of March 2020) with preferred term within the AE search criteria

developed by the latest MedDRA maintenance and support service organization (MSSO) guidance.

3.2.4 Electrocardiograms

These measurements are recorded as detailed in the study schedule (See Appendix A). If vital signs, ECG and blood draws for laboratory tests are scheduled at a visit, they will always be performed in the order: ECG, vital signs and then blood draws.

At Screening, and as clinically indicated throughout the study, ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. From these resting 12-lead ECGs values of the QT and RR intervals and the QT interval corrected for heart rate using Fridericia's correction (QTcF) is derived using the following formula:

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

In case of clinically significant ECG abnormalities, 2 additional 12-lead ECGs will be performed. All three ECGs should include a value of QTcF over a brief period (eg, 30 minutes). A QTcF value >470 msec will confirm the ECG abnormality finding.

The value of QTcF will be re-derived from the values of RR and QT during the creation of the reporting database.

3.2.5 Vital Signs

Vital signs measurements will be collected at the start of each treatment cycle as detailed in the schedule of assessment (Appendix A).

Measurements will include SBP (mmHg), DBP (mmHg), pulse rate (breaths/min), weight (kg), body temperature (degrees Celsius), and respiratory rate (breaths/min).

3.2.6 Laboratory Data

Laboratory data (clinical chemistry, haematology and urinalysis) will be collected at the start of each treatment cycle as detailed in the schedule of assessment (Appendix A). Coagulation will be reported as clinically indicated. Laboratory data will be from local laboratories and will be converted to AZ preferred units, and AZ durvalumab project reference ranges will be used for the primary interpretation of laboratory data.

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

$$\text{Corrected calcium (mmol/L)} = \text{Total calcium (mmol/L)} + ([40 - \text{Albumin (g/L)}] \times 0.02)$$

3.2.7 Physical Examination

A physical examination will be performed at Screening and during the study. Findings in this

data will be reported as medical history at Screening. 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.

3.2.8 Exposure to Durvalumab

The total (or intended) exposure (weeks) of durvalumab is defined as:

- Total treatment duration (weeks) = Total treatment duration (days) / 7

  where:

  Total treatment duration (days) = [earliest of (last dose date where dose > 0mg + 27 days, death date, cut-off date [DCO])-first dose date] +1

The actual exposure (weeks) of durvalumab is defined as:

- Actual treatment duration (weeks) = [total treatment duration (days) – total duration of dose delays (days)] / 7.

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

As patients are scheduled to receive 1500 mg via IV infusion every 4 weeks (28 days), the duration of dose delays is the sum of all individual dose delays as follows:

- Total duration of dose delays (days) = sum of MAX[0, (date of dose [x+1] – date of dose [x] - 28 days)].

If no delays were encountered, the total duration of dose delays would sum up to 0.

Relative dose intensity (RDI) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation.

RDI is defined as follows:

RDI = 100% * d/D, where d and D are, respectively, the actual and intended cumulative doses delivered up to the date of durvalumab discontinuation or progressive disease or the data cut-off date, whichever occurs earlier. D is the total dose that would be delivered if there were no modification to dose or schedule.

Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to disease progression.

PID = 100% * d1/D1, where d1 is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or the data cut-off date and D1 is the intended cumulative dose up to the earlier of progression (or a censoring event) or the data cut-off date. D1 is the total dose that would be delivered, if there were no modifications to dose or schedule.

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

To illustrate the calculation of RDI, Table 5 shows an example of durvalumab dosing for 4 patients.

Table 5 Example dose intensity scenarios

		Study Day									
RDI	Patient	1	29	57	85	113	141	169	197	225	230
100%	1	X	X	X	X	X	X	X	X	X	PD
100%	2	X	X	X	X	X	X	X	X[D]		PD
56%	3	X		X		X	O	X	X		PD
67%	4	X	X	O	X	X	X	O	X	O	PD

X: Dose of 1500mg taken; O: Dose missed; [D]: Dose discontinued; PD: Progressive Disease

In this example, all 4 Patients progressed on Day 230, and so the intended dose through to progression was 9 * 1500mg of durvalumab = 13500mg (13.5g).

Patient 1 received a total of 13.5g of durvalumab, whereas other patients received less durvalumab due to:

- Early stopping prior to PD (Patient 2)
- Dosing delays (Patient 3)
- Missed doses (Patient 4)

For RDI the examples of Patients 2 and 4 illustrate that the end of actual dosing period is calculated based on the smallest recovery period after the last non-zero dose.

Patient 1: RDI = (9 * 1.5g)/ 13.5g = 100%

Patient 2: RDI = (8 * 1.5g)/ 12g = 100%

Patient 3: RDI = (5 * 1.5g)/ 13.5g = 56%

Patient 4: RDI = (6 * 1.5g)/ 13.5g = 67%

For the examples the PID differs from RDI for Patient 2 where the calculation is based on the intended cumulative dose up to disease progression regardless treatment discontinuation.

Patient 1: PID = (9 * 1.5g)/ 13.5g = 100%

Patient 2: PID = (8 * 1.5g)/ 13.5g = 89%

Patient 3: PID = (5 * 1.5g)/ 13.5g = 56%

Patient 4: PID = (6 * 1.5g)/ 13.5g = 67%

Exposure will also be measured by the number of cycles (doses) of durvalumab received. If a

cycle is prolonged due to toxicity this will still be counted as one cycle. A cycle will be counted if treatment is started, even if the full dose is not delivered.

3.3 Efficacy Variables

All RECIST assessments, whether scheduled or unscheduled, and regardless of whether a patient discontinues durvalumab treatment or receives another anti-cancer therapy will be included in the calculation of efficacy variables.

3.3.1 Progression-Free Survival

Progression-free survival is defined as the time from the date of first dose of durvalumab until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient discontinues durvalumab or receives another anticancer therapy prior to progression.

- PFS (days) = (date of PFS event or censoring) – (date of first dose of durvalumab) + 1.

Patients who have not progressed or died at the time of analysis will be censored at the date of their last evaluable tumour assessment (ie, this doesn't include NE or missing value).

If the patient progresses or dies after 2 or more missed visits, the patient will be censored at the date of the latest evaluable RECIST 1.1 assessment prior to the two missed visits.

Given the scheduled visit assessment scheme (i.e. eight-weekly for the first 48 weeks then twelve-weekly thereafter) the definition of 2 missed visits will change.

1. If the previous RECIST assessment is baseline then two missing visits will equate to 17 weeks since the previous RECIST assessment, allowing for a late visit (i.e. 2 x 8 weeks + 1 week for a late assessment = 17 weeks).
2. If the previous RECIST assessment is post baseline and less than study day 274 (i.e. week 39) then two missing visits will equate to 18 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks).
3. If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from eight-weekly to twelve-weekly this will equate to 22 weeks (i.e. take the average of 8 and 12 weeks which gives 10 weeks and then apply same rationale, hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks). The time period for the previous RECIST assessment will be from study days 274 to 344 (i.e. week 39 to week 49).
4. From week 49 onwards (when the scheduling changes to twelve-weekly assessments), two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

If the patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1 unless he/she dies within 2 visits of baseline, in which case the date of death is the event date.

3.3.2 Overall Survival

The OS is defined as the time from the date of first dose of durvalumab until death due to any cause.

- OS (days) = (date of death or censoring) – (date of first dose of durvalumab) + 1

Any patient not known to have died at the date of DCO will be censored at the last recorded date at which the patient was known to have been alive, or at date of DCO, if known afterwards.

The date that an individual patient was last known to be alive will be identified exclusively using the data recorded within the SURVIVE and DEATH modules of the electronic case report form (eCRF).

3.3.3 Objective Response Rate

The ORR is defined for the SAF as follows:

- The ORR is the proportion (%) of patients with an overall response of CR or PR (confirmed by a follow-up scan at least 4 weeks after showing CR or PR).

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging, preferably at the next regularly scheduled imaging visit, and not less than four weeks after the visit when the response was first observed, with no evidence of progression between the initial and CR/PR confirmation visit. Both visits contributing to the confirmed response must be prior to any subsequent anti-cancer therapy for the patient to be considered as a responder.

Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of the ORR. Responses that occur after the start of subsequent anti-cancer therapy must be excluded from the derivation of ORR (ie, only responses that occur prior to receiving subsequent therapy will be included in the numerator).

3.3.4 Best Objective Response

Best objective response (BoR) is the best response a patient has had after Day 1 up until progression, or the last evaluable assessment in the absence of progression. Responses that occur after the start of subsequent anti-cancer therapy must be excluded from the derivation. Categorization of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 8 weeks minus 1 week, ie, at least 49 days (to allow for an early assessment within the assessment window), after durvalumab initiation. For CR/PR, the initial overall visit assessment that showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For patients whose progression event is death, BoR will be calculated based upon all evaluable

RECIST assessments prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurs <= 9 weeks (ie, 8 weeks + 1 week to allow for a late assessment within the assessment window) after durvalumab initiation, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs > 9 weeks after Day 1 then BoR will be assigned to the NE category.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time following Day 1, prior to RECIST progression and prior to starting any subsequent cancer therapy.

3.3.5 Duration of Response

For patients who are classified as responders (see Section 3.3.3), the DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until the first date of documented progression or death in the absence of disease progression.

- DoR = (date of PFS event or censoring) – (date of start of response) +1

The date of the end of response will coincide with the date of disease progression or death from any cause used for the PFS endpoint (see Section 3.3.1). If a patient does not progress following a response, then their DoR will be censored at the date used in the PFS censoring. The date of the initial response will be defined as the latest of the dates contributing toward the first visit response of CR or PR that was subsequently confirmed. DoR will not be defined for those patients who do not have documented confirmed response.

DoR will also be obtained using the algorithm described above for the RECIST 1.1 site Investigator tumour data.

3.3.6 Lung Cancer Mortality

The lung cancer mortality (NSCLC-related death) is assessed using the deaths which are reported as 'NSCLC-related' and is defined as the time (days) from the date of first dose of durvalumab until date of death due to lung cancer as follows:

- Time to lung cancer mortality = (date of NSCLC-related death or censoring) – (date of first dose of durvalumab) + 1

Any patient not known to have died at the date of DCO will be censored at the last recorded date at which the patient was known to have been alive, or at date of DCO, if known afterwards.

The date that an individual patient was last known to be alive will be identified exclusively using the data recorded within the SURVIVE and DEATH modules of the electronic case report form (eCRF).

3.4 Exploratory Variables

CCI [redacted]

3.4.1 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

3.4.1.1 CCI

CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

3.4.1.2 CCI

CCI

[redacted]

3.4.1.3 CCI

CCI

[redacted]

CCI

3.4.2 CCI

CCI

3.5 Other Variables

3.5.1 Baseline Characteristics

Baseline characteristics that will be collected or derived are:

- Demographics: age (years), sex, race and ethnicity.
- Patient characteristics: weight, height, body mass index (BMI).
- Medical history: name of past and/or concomitant diseases (verbatim and coded using the latest or current version of the MedDRA dictionary), start and stop dates.
- Nicotine use: smoking status (current, former, never) and pack years.
- Characteristics of NSCLC at diagnosis: original diagnosis date, primary tumour location, histology type, TNM classification, American Joint Committee on Cancer (AJCC) staging.
- Extent of disease at entry of study: current AJCC staging, evidence of disease (yes/no), sites of locally advanced disease, recent progression (yes/no, date).
- Previous disease-related sequential chemoradiotherapy: Total dose, Radiotherapy treated location, Time from completion of radiotherapy to study treatment, Type of previous chemoradiotherapy, best response to previous chemoradiotherapy, Chemotherapy Class,

Chemotherapy regimen used for sequential chemoradiotherapy, Number of chemotherapy cycles.

- Previous treatments for early stage disease (prior to definitive CRT): Radiotherapy treated location, Treatment status, Chemotherapy regimen used for early stage disease prior to CRT.
- Relevant surgical history: surgical procedure (verbatim and coded using the latest or current version of the MedDRA dictionary) and date of surgery.

3.5.2 Prior and Concomitant Medications and Therapies

All therapies (drug or non-drug), including herbal preparations, whether prescribed or over-the-counter, that are used during the study will be recorded in the eCRF. Details include generic and/or brand names of medications, WHO drug dictionary encoding, reason for use, route, dose, dosing frequency, and start and stop dates.

Prior therapies are defined as those with at least one dose/treatment taken before the date of the first dose of study medication.

Concomitant therapies are defined as those with at least one dose/treatment taken between the date of first dose (inclusive) and the date of last dose (inclusive) of durvalumab.

Missing start and stop dates for medications will be imputed using the rules described in Section 4.1.3.

3.5.3 CCI

CCI

4. ANALYSIS METHODS

4.1 General Principles

4.1.1 General Statistical Considerations

The following general statistical considerations will be applied for the analyses and presentation of the data. In case of any specific deviations, methods will be specifically noted on the relevant output.

- All data, demography, baseline characteristics, safety, efficacy and biomarkers, will be summarized using descriptive statistics, as appropriate for the type of data, for the SAF. In addition, all efficacy and safety data and some selected relevant data (eg, patient disposition, demography and baseline characteristics) will be summarised separately for the WHO/ECOG PS 0 to 1 and 2 groups.
- Continuous variables will be summarized by the number of observations (n), mean,

standard deviation, median, minimum, and maximum.

- For the continuous data, the summary statistics will be displayed with the following accuracy (number of dps):
  - The minimum and maximum with same accuracy as the raw data.
  - The mean and median will be rounded to 1 additional dp more than the number of dps in the raw data.
  - The standard deviation will be rounded to 2 additional dps more than the number of dps in the raw data.
  - If the number of observation is 1, the SD will not be derived.
- Categorical variables will be summarized by frequency counts and percentages for each category and percentages will be rounded to one dp.
- As a default, percentages will be calculated using the number of patients who have non-missing data as the denominator. Therefore, percentages for missing data will not be presented in the results. If the denominator is different from this default, it will be explained in a footnote to the output.
- SAS® version 9.3 or higher will be used for all analyses.
- Exact CIs for proportions will be calculated using the Clopper-Pearson method.
- For percentiles of survival times based on the Kaplan-Meier method (eg, median survival), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, the Klein and Moeschberger extension of the Brookmeyer-Crowley method).
- For point-estimates of survival based on the Kaplan-Meier method (eg, for PFS12), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, using Greenwood's estimate of standard error and a log-log transformation).
- The data will be included in summaries/analyses using the following criteria:
  - All laboratory data, vital signs data that are recorded at unscheduled visits will be included in the summaries using the visit windows defined in Section 4.1.4.1.
  - The tumour measurements and PRO data should not be affected by any delays in treatment cycles/dates of start of treatment cycles as it is intended that they are only recorded at pre-scheduled time points. These data will be included in the summaries and analyses of the data using the visit windows defined in Section 4.1.4.2.
- All data collected including scheduled, delayed and unscheduled data will be listed in the patient data listings which are produced for all treated patients. They will be ordered by treatment/not treated, centre, WHO/ECOG PS group, patient and visit and, if relevant, timepoint when they were recorded. Patients who are included in the SAF will be flagged. Depending on the availability of the data, all data for the patients who are not treated will be listed separately. They will be ordered by centre, WHO/ECOG PS group, patient and visit and timepoint, if relevant.

- All adverse events will be coded using MedDRA and NCI CTCAE Grade and will be reported using SOC and PT, NCI CTCAE Grade, as appropriate.
- All concomitant and previous medications will be coded using WHO drug dictionary and will be reported using anatomical therapeutic chemical (ATC) classification and generic term.
- Baseline is defined as the last assessment of the variable under consideration prior to the first dose of durvalumab regardless of whether the assessment is on Day 1, Screening or unscheduled.
- Participants affected by the COVID-19 pandemic will be listed as recorded as protocol deviations, which were assessed as COVID-19 related. The study disruptions due to the pandemic will also be summarized. Subject disposition will be summarized including number (%) of patients who discontinued treatment due to the pandemic and who withdrew from study due to pandemic. Important protocol deviations will be summarized including number (%) of patients with at least one important protocol deviation related to the pandemic. Number and percentage of patients with confirmed/suspected COVID-19 infection along with demographic characteristics, medical history and adverse event of patients with confirmed/suspected COVID-19 infection will be presented. If the study has fewer than 5 and/or less than 2% of the patient population with confirmed/suspected COVID-19 infection, then a listing will be presented instead of summary.

4.1.2 General Considerations for Summary of Safety Data

The following considerations are for the summary of safety data.

- The missing values in vital signs, laboratory data, coagulation and urinalysis will not be imputed.
- If a laboratory value is reported as <LLQ (where 'LLQ' is the lower limit of quantification), then LLQ value will be used to impute '<LLQ' for the summary tables. In the data listings, this value will be listed as reported <LLQ.
- Any TEAEs with missing causality data will be considered as related to the durvalumab.
- Any partial dates will be presented as reported in the data listings. The partial dates will be imputed for the derivation of time to resolution, time to onset etc. using the criteria given in Section 4.1.3.

4.1.3 Handling of Missing Data

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

If the start date of the concomitant medication or AE is missing, the following rules will be

applied:

- If the year is missing, the year should be imputed as the year that patient received the first dose of durvalumab.
- If the year is available and the month and day are missing, then impute the month as January and the day as 01.
- If the year and month are available and the day is missing, impute the day as 01 (the first day of the month).
- If any of the above puts the date before the date of first dose of durvalumab, a conservative approach is followed and, the date is imputed using the date of first dose.

If the stop date of the concomitant medication or AE is missing, the following rules will be applied:

- If the year is missing, the year should be imputed as the year that patient received the last dose of durvalumab.
- If the year is available and the month and day are missing, then impute the month as December and the day as 31.
- If the year and month are available and the day is missing, impute the day as the last day of the month (eg, 28, 29, 30 or 31).
- If any of the above puts the date after the date of the last dose of durvalumab, a conservative approach is followed and, the date is imputed using the data cut-off date (DCO).
- It is not expected to have missing dates for unscheduled laboratory, diagnostics data. However, if there are missing dates, for any derivations, the dates should be imputed following the rules for concomitant medications and AEs

4.1.4 Definitions of Visit Windows

Time windows are defined for all summaries of vital signs, laboratory data, PRO around visits in Section 4.1.4.1 and for tumour assessments around the scheduled RECIST assessment time in Section 4.1.4.2

4.1.4.1 Visit Windows for Safety and PRO Assessments

The following conventions will apply for safety and PRO data:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data will have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first

post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day.

For example, the visit windows for vital signs data are:

- Week 1; nominal day 1, visit window Day 1
- Week 4; nominal day 29, visit window 2 – 42
- Week 8; nominal day 57, visit window 43 – 70
- Week 12; nominal day 85, visit window 71 – 98
- Week 16; nominal day 113, visit window 99 – 126
- Visits after treatment discontinuation will be assigned to the last treatment cycle for up to 15 days only. Visits after the 15 days will contribute to the following 30 days post treatment discontinuation interval, see below.

- Visits up to 90 days after last dose will be assigned similarly to the definition for the visits under treatment, but for 30 day intervals after treatment discontinuation, eg,:
  - 30 days after last dose, visit window 16 – 45
  - 60 days after last dose, visit window 46 – 75
  - 90 days after last dose, visit window 76 – 97
  - Data recorded after 97 days after last dose will not contribute to the analysis period of up to 90 days following the date of last dose, and will not be re-mapped
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.

For visit based summaries:

- If there is more than one value per patient within a time window then the closest value to the scheduled visit date should be used, or the earlier in the event the values are equidistant from the nominal visit date. If there are two values recorded on the same day and the parameter is CTCAE gradable then the record with the highest toxicity grade should be used. The listings should highlight the value for that patient that went into the summary table, wherever feasible. Note: in summaries of extreme values all on-treatment values collected are used including those collected at unscheduled visits.
- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a patient level statistic such as a maximum.

4.1.4.2 Visit Windows for Tumour Assessments

The following conventions will apply for tumour assessment data:

- All tumour assessments available during the study should be used for the efficacy analysis. A windowing rule will be applied and will follow the CSP allowed visit window; therefore, any RECIST assessment performed within ± 1 week of the CSP scheduled visit will be used for that visit.
- If there are any assessments outside these visit windows, they will also be included in the closest visit window following the intent-to-treat principle. The tumour assessments which are outside the visit windows will be flagged in the data listings.

The above could result in more than one tumour assessments within a window and in that case, the one closest to the scheduled assessment will be used.

4.2 Study Population

4.2.1 Patient Disposition

The following patient disposition summaries will be produced:

- The number and percentage of patients who were screened, who were screening failures, and who received and did not receive durvalumab will be summarised for all patients.
- Discontinuation from durvalumab and/or discontinuation from study, together with reason for discontinuation (including the reason due to COVID-19 Pandemic) will be summarised using the SAF.
- Disruptions due to COVID-19
- Summary of confirmed/suspected COVID-19 infection.

The date of the last contact (date of withdrew consent/lost to follow-up/died) will be listed in patient disposition listings. COVID-19 study disruptions will also be listed as recorded as protocol deviations, which were assessed as COVID-19 related.

4.2.2 Protocol deviations

Important protocol deviations are defined in Section 2.2 and will be listed and summarized for the SAF, including a summary of those identified as resulting from the COVID-19 pandemic.

The number and percentage of patients with any IPD will be summarized for each IPD category. Patients with more than one deviation in the same IPD category will be counted once for that IPD category. Any patients who have deviations in more than one IPD category will be counted once in the overall summary. The number of patients with at least 1 COVID-19 related important protocol deviation and the number of patients with at least 1 important protocol deviation, excluding COVID-19 will be presented by IPD category.

4.2.3 Demography and Baseline Characteristics

Demographic and other baseline characteristics (see Section 3.5.1) will be listed for all patients and summarised for the SAF, as:

- Demographics (age, age group [<50, >=50-< 65, ≥ 65-<75, and ≥ 75 years], sex, race and

ethnicity)

- Demographic characteristics in patients with confirmed/suspected COVID-19 infection.
- Patient characteristics at baseline (height, weight [prior to start of sCRT, and after sCRT at screening, and the change], weight groups [<40, >=40-< 75, ≥ 75-<90, ≥ 90-<120, and ≥ 120 kg], body mass index (BMI) after sCRT, and BMI groups [Underweight (<18.5), Normal weight (=18.5 - <25.0), Overweight (=25.0 - <30.0), Obese (=30.0)]
- Nicotine use and consumption
- A summary and a list of patients by site and country will be provided.
- Previous disease-related sequential chemoradiotherapy
    - Sequential, no chemotherapy overlap with radiotherapy
    - Sequential, 1 cycle chemotherapy overlap with radiotherapy
    - Concurrent, >1 cycle chemotherapy overlap with radiotherapy

    The number of cycles used for the classification will be derived by the number of days from the overlapping time interval from each specific chemotherapy regimen overlapping with radiotherapy, divided by 21 days, and rounded up to the next integer, and will subsequently be summed up by patient.
- Previous treatments for early stage disease

Medical history and relevant surgical history are coded using MedDRA and will be summarized by SOC and PT. Medical history will also be summarized for patients with confirmed/suspected COVID-19 infection.

4.2.4 Previous and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be listed for all patients in the SAF.

Concomitant medications will be summarized by chemical subgroup (ATC 4th level), and preferred WHO name for the SAF. Patients with the same concomitant medication/procedure multiple times will be counted once per medication/procedure. A medication/procedure that can be classified into more than one chemical and/or therapeutic subgroups will be presented in each subgroup.

4.2.5 Study drug administration

Individual patient data for study drug administration will be listed for all patients in the SAF.

4.3 Analysis of Primary Safety Endpoint

The primary endpoint of this study is the incidence of Grade 3 and Grade 4 TRAEs (see Section 3.2.3.1) which occur within the first six months (ie, up to and including the 183rd day) after the initiation of durvalumab. Any Grade 3 or Grade 4 TRAEs which started after the 183rd day of the study, or after the 90th day following discontinuation of durvalumab, or after the start of

subsequent anti-cancer therapy will not be included.

The number and percentage (and exact Clopper-Pearson 95% CI) of patients with NCI CTCAE Grade 3 or Grade 4 TRAEs, both overall and for those occurring within the first six months after initiation, will be summarized for the SAF for all patients and within the WHO/ECOG PS 0/1 and PS 2 groups. This summary will also be graphically presented as a bar chart. The number and percentages of patients with NCI CTCAE Grade 3 or Grade 4 TRAEs will also be summarized by SOC and PT.

4.4 Analysis of Secondary Efficacy Endpoints

4.4.1 Progression-Free Survival

Kaplan-Meier plots and descriptive statistics will be provided for PFS. Summary statistics will include lower and upper quartile and median PFS, PFS12 (Day 365) and PFS24 (Day 730).

Summaries of the number (%) of patients experiencing a PFS event (overall and also at Month 12 and Month 24) and the type of event (disease progression or death) will be provided.

All summary statistics will be presented with the appropriate 95% CI.

If necessary, a sensitivity analysis will be conducted to assess the potential impact of COVID-19 related deaths on PFS. That is, patients who had a PFS event due to death where the primary or secondary cause of death was COVID-19 infection or COVID-19 infection was reported as a fatal AE, will be censored at the last evaluable RECIST 1.1 assessment prior to COVID-19 infection related death.

4.4.2 Overall Survival

The following numbers (%) of patients in the SAF will be presented at 12month (Day 365) intervals and overall: those who have died, those still in survival follow-up, those lost to follow-up, those who withdrew consent, and those with censored OS.

Kaplan-Meier plots and descriptive statistics will be presented for OS. Summaries will include the lower and upper quartile and median OS, and estimates of OS12 (Day 365), OS24 (Day 730) and OS36 (Day 1095).

All summary statistics will be presented with the appropriate 95% CI.

If necessary, a sensitivity analysis will be conducted to assess the potential impact of COVID-19 related deaths on OS. That is, patients who had a death event where the primary or secondary cause of death was COVID-19 infection or COVID-19 infection was reported as a fatal AE, will be censored at the date of their COVID-19 infection related death.

4.4.3 Objective Response Rate

The ORR will be estimated for the SAF and will be presented with the corresponding exact 95% CIs.

The number (%) of patients with a confirmed response and the number (%) of patients with a single visit response (ie, an unconfirmed response) will also be presented.

Best objective response (BoR) will be summarised by n (%) for each category (CR, PR, SD, PD and NE).

4.4.4 Duration of Response

A Kaplan-Meier plot and descriptive statistics will be provided for the DoR and the respective Time to onset of first response for patients in the SAF who had responded to treatment (see Section 3.3.5). Summary statistics will include: lower and upper quartile and median DoR with appropriate 95% CIs.

4.4.5 Time to Lung Cancer Mortality (NSCLC-Related Death)

The following numbers (%) of patients in the SAF will be presented at Month 12 (Day 365) intervals and overall: those with an NSCLC-related death, those still in survival follow-up, those lost to follow-up, those who withdrew consent, and those with censored time to lung-cancer mortality (separately for those who died from a cause not related to NSCLC and other reasons for censoring, as well as overall).

Kaplan-Meier plots and descriptive statistics will be presented for time to NSCLC-related mortality. Summaries will include the lower and upper quartile and median lung cancer mortality and estimates at Month12 (Day 365), Month 24 (Day 730), and Month 36 (Day 1095).

All summary statistics will be presented with the appropriate 95% CI.

4.5 Analysis of Secondary Safety Endpoints

4.5.1 Adverse Events

All AEs reported up until 90 days following completion or discontinuation of durvalumab treatment or until the initiation of the first subsequent therapy (whichever occurs first) will be included in the summaries unless explicitly stated otherwise below.

All AEs will be summarised descriptively, in terms of number of patients (n) and percentage of patients (%) reporting the event by MedDRA SOC and PT.

Listings of AEs will include the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity, relationship to durvalumab, and NCI CTCAE Grade. Separate listings will be produced for all AEs, TRAEs, SAEs, AESIs, imAEs, AEs with outcome of death, AEs leading to discontinuation of durvalumab, AEs leading to discontinuation of study. Listings of AESIs and imAEs will also include the additional information (eg, intervention, dose, duration of therapy etc.) recorded for these AEs. All AEs that are not treatment-emergent will be flagged in the data listings and the time of onset will be flagged as 'pre-treatment', 'post-treatment and no other anti-cancer therapy' and 'after initiation of other anti-cancer therapy'.

An overall summary of AE data will be presented including the number and percentage of patients reporting the following:

- At least one AE

- At least one TRAE
- At least one AE of CTCAE Grade 3 or Grade 4
- At least one TRAE of CTCAE Grade 3 or Grade 4
- At least one SAE
- At least one Serious TRAE
- At least one AE leading to discontinuation of study treatment
- At least one TRAE leading to discontinuation of study treatment
- At least one AE leading to treatment interruption
- At least one TRAE leading to treatment interruption
- At least one AE with outcome of death
- At least one TRAE with outcome of death
- At least one AESI
- At least one TRAE of special interest (AESI)
- At least one imAE (and exact Clopper-Pearson 95% CI)
- At least one immune-mediated TRAEs

The following summaries including the number and percent of patients by SOC and PT will be presented separately:

- All AEs / TRAEs
- All AEs / TRAEs of CTCAE Grade 3 or Grade 4
- All TRAEs of CTCAE Grade 3 or Grade 4 occurring within the six months of first dosed date
- All TRAEs which starts within 90 days after last dose of durvalumab (irrespective of start of subsequent anti-cancer therapy)
- All AEs
    - This summary will include an AE event rate (per 100 patient years) for each PT. The number of patients with an AE in each PT is divided by the sum of the actual exposure to durvalumab (days) (see section 3.2.8) over all patients. This is multiplied by 365.25 x 100 to create an event rate per 100 patient years.
- All AEs by maximum CTCAE Grade
- All AEs / TRAEs with outcome of death
- All SAEs / Serious TRAEs
- All AEs / TRAEs leading to discontinuation from durvalumab (Note: Reason for discontinuation recorded on the patient disposition page)
- All AEs / TRAEs leading to dose interruption/discontinuation of durvalumab (Note: Reason for discontinuation recorded on the patient disposition page)

A summary of most common AEs and another summary of most common AEs with CTCAE Grade 3 or higher, including all events that occur in at least 2.5% of patients overall will be presented by PT, by decreasing frequency. This cut-off may be modified after review of the data. The raw percentage will be compared to the cut-off, without applying any rounding to the percentage value (ie, a TEAE with frequency of 2.4% will not appear in the table if a cut-off is 2.5%).

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

- Number of deaths (NSCLC-related, non-related, and unknown)
  - Number of deaths during the on-treatment study period up until 90-day follow-up and prior to initiation of first subsequent therapy
  - Number of deaths occurring more than 90 days after the last dose of durvalumab or after initiation of first subsequent therapy

Listings of key patient information for Deaths and SAEs will be provided.

4.5.1.1 Adverse Events of Special Interest and Immune-Mediated Adverse Events

The following summaries of AESIs will be presented by AESI category and PT:

- All AESIs / TRAEs of special interest
- All serious AESIs
- All AESIs by maximum CTCAE Grade
- All AESIs by outcome
- All AESIs leading to treatment interruption
- All AESIs leading to treatment discontinuation
- All AESIs / TRAEs of special interest with fatal outcome
- All AESIs which required treatment
- All AESIs which required treatment with systemic steroids, and high dose steroids
- All AESIs which required treatment with immunosuppressants
- All AESIs which required treatment with endocrine therapy

Overall summaries will present the numbers and percentages of patients with at least one immune-mediated AE (imAE) by the following categories:

- AEs / TRAEs,
- AEs / TRAEs of CTCAE Grade 3 or Grade 4
- SAEs / Serious TRAEs
- AEs / TRAEs with outcome of death
- AEs which required treatment
- AEs which required treatment with systemic steroids, and high dose steroids
- AEs which required treatment with immunosuppressants
- AEs which required treatment with endocrine therapy
- AEs leading to treatment discontinuation
- AEs by outcome

Using the same categories above similar summaries will be presented by preferred term, and by SOC and PT.

Time to event analyses for immune-mediated AE (imAE) will be performed by AESI categories, for:

- Time to first onset of imAE
- Time to first onset of imAE of Grade 3 or 4
- Time to resolution of imAE
- Time to resolution of Grade 3 or 4

For patients with imAEs having multiple PTs within an AESI category the AEs will be collapsed to one event if the difference between end date of an imAE and subsequent start date of the next imAE is <=3 days. The time to onset will be based upon the first PT, whereas time to resolution used for KM analysis will be based on time of the worst imAE episode from that given patient.

At the AESI grouped term level for time to resolution outputs the worst imAE is defined in the order of the following:

- imAE with worst (highest) grade first
- For more than one imAE with the same highest grade take imAE which did not resolve before imAE which did resolve
- If multiple imAE and all resolved take imAE with longest duration

Summaries for imAEs and related data will be presented by imAE category and PT:

- At least one imAE
- At least one serious imAE
- At least one imAE by outcome
- At least one imAE leading to treatment interruption
- At least one imAE leading to treatment discontinuation
- At least one imAE by maximum CTCAE Grade
- At least one imAE causally related to study medication
- At least one imAE with fatal outcome

Post-baseline medications associated with imAEs will be presented by number and percent of patients by ATC-classification and PT.

Length of intervention with steroids, immunosuppressants and/or hormone replacement therapy for imAEs will be calculated based on treatment start and stop dates. Total treatment times will then be combined for each patient and summarised for patients experiencing at least one treatment-emergent imAE.

4.5.1.2 COVID-19 related Adverse events

The following summaries of AE data will be presented including the number and percentage of patients with:

- AEs in patients with confirmed/suspected COVID-19 infection
- AEs in patients without confirmed/suspected COVID-19 infection
- AEs by SOC, PT and maximum CTCAE grade in patients with confirmed/suspected COVID-19 infection
- AEs by SOC, PT and maximum CTCAE grade in patients without confirmed/suspected

COVID-19 infection

- AEs associated with COVID-19 infection by SOC and PT
- AEs excluding AEs associated with COVID-19 infection by SOC and PT
- AEs with confirmed/suspected COVID-19 infection by SOC and PT
- AEs excluding confirmed COVID-19 infection by SOC and PT
- AEs associated with COVID-19 infection and with outcome of death by SOC and PT
- AEs excluding associated with COVID-19 infection and with outcome of death by SOC and PT
- AEs associated with COVID-19 infection leading to discontinuation of investigational product by SOC and PT
- AEs excluding associated with COVID-19 infection leading to discontinuation of investigational product by SOC and PT

The summaries for COVID-19 related adverse events will only be performed when there is sufficient number of patients (e.g. ≥5 and/or ≥2% of the patient population) have confirmed/Suspected Covid-19 infection.

4.5.2 Electrocardiograms

The data for the ECG are used for safety monitoring and to identify AEs. No summaries or listings will be created.

4.5.3 Vital Signs

Box plots of the vital signs results by visit will be presented.

4.5.4 Laboratory Data

Laboratory data obtained up until the 90 days after last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first) will be used for reporting.

Absolute values and change from baseline for all continuous haematology and clinical chemistry laboratory parameters will be summarised by visit. If a patient does not have the baseline value of laboratory data or the value at visit, the change from baseline is considered as missing.

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

- Haematology: Haemoglobin, Leukocytes, Lymphocytes (absolute count), Neutrophils (absolute count), Platelets
- Clinical chemistry: Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), Total bilirubin, Sodium (hypo- and hyper-), Potassium (hypo- and hyper-), Glucose (hypo- and hyper-), and Creatinine

For categorical urinalysis parameters (Bilirubin, Blood, Glucose, Protein), a shift table will be produced comparing baseline value to maximum on-treatment value.

For the parameters with no CTCAE grading that are listed in the CSP the number and percentage of patients with laboratory values outside normal range will be summarized by shift tables from baseline to the post-baseline maximum and minimum value on-treatment.

4.5.4.1 Liver Enzyme Elevations and Hy's Law

The following summaries (n, %) of the laboratory data will be used to identify cases of Hy's law:

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

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

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

Plots of post-baseline ALT and AST vs. post-baseline total bilirubin will also be produced with reference lines at 3×ULN for ALT, AST, and 2×ULN for Total bilirubin. In each plot, total bilirubin will be in the vertical axis.

4.5.4.2 Assessment of Thyroid Function Test Results

Shift table for TSH test, baseline versus maximum value on treatment will be produced for the categories:

- Low
- Normal
- >1 to 2 x ULN
- >2 x ULN

The following summaries will include the number and percentage of patients who have elevated or low TSH:

- On-treatment elevated TSH > ULN
- On-treatment elevated TSH > ULN with TSH <= ULN at baseline
- On-treatment elevated TSH > ULN
    - With at least one T3 free/ T4 free < LLN
    - With all other T3 free/ T4 free >= LLN
    - With T3 free/ T4 free missing
- On-treatment low TSH < LLN
- On-treatment low TSH < LLN with TSH >= LLN at baseline
- On-treatment low TSH < LLN
    - With at least one T3 free/ T4 free > ULN
    - With all other T3 free/ T4 free <= ULN
    - With T3 free/ T4 free missing

4.5.5 Exposure

The following summaries will be presented for durvalumab exposure:

- Total (or intended) exposure
- Actual exposure
- Number of cycles received
- Number and Reasons for dose delays of durvalumab. Dose interruptions will be based on investigator initiated dosing decisions.
- Relative dose intensity

4.5.6 Therapy following discontinuation from durvalumab

All recorded details of anti-cancer therapies subsequent to the discontinuation of durvalumab will be listed.

4.6 Analysis of Exploratory Endpoints

CCI [redacted]

4.6.1 CCI [redacted]

CCI [redacted]

CCI

4.6.2 CCI

CCI

4.6.3 CCI

CCI

4.6.4 CCI

CCI

4.6.5 CCI

CCI

5. INTERIM ANALYSES

No formal interim analysis is planned for this study, although an early safety evaluation (ESE) will be conducted when 10 patients in the WHO/ECOG PS 2 cohort have either been treated for a maximum of six months or have discontinued treatment due to an AE or disease progression, whichever occurs first. The ESE will be conducted by the steering committee (SC). A SC Charter will be written with details of the timing of the ESE, the data to include, and analyses to be performed.

Safety data for patients in the WHO/ECOG PS 0 to 1 cohort, as well as the WHO/ECOG PS 2 cohort, will be analysed as of the DCO for the ESE, and provided to the SC for completeness as applicable.

In addition, an early assessment (EA) of study data may be conducted when a minimum of 50 patients in the WHO/ECOG PS 0 to 1 cohort or WHO/ECOG PS 2 cohort have had the opportunity to receive durvalumab (MEDI4736) for up to 6 months. The EA will be conducted for publication purposes for the first 50 patients included into the study and will comprise the analysis of the study data for these patients as specified for the ESE.

The primary analysis will be performed when the last patient dosed had the opportunity to receive durvalumab (MEDI4736) for six months. The final analysis will be performed when the last patient had the opportunity to receive durvalumab (MEDI4736) for a maximum of 24 months, followed by a 90-day safety follow-up period post the last dose of IP.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The analysis of the CCI testing as planned with the study protocol as exploratory objective will not be part for this analysis plan, with the option to be planned and carried out apart from this analysis in a separate addendum for this project.

The CCI was removed from the definition of the exploratory objectives in section 1.1.3 and is not mentioned with 8.1 Appendix A: Schedule of Assessments in this analysis plan.

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8. APPENDIX

8.1 Appendix A: Schedule of Assessments

Table 7 Schedule of Assessments for Screening and Treatment Period

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD (max. 24 months)[a,b]	
Week	**-4 to -1**	**1**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				**Final visit**
Informed consent							
Informed consent: Study procedures	X						
Informed consent: CCI (optional)[c]	X						
Study procedures							
Physical examination (full)	X						
Targeted physical examinations (symptomatic patients only)		X	X	X	X	X	X
Assessment of early toxicities (phone call)[d]		X	X	X			
Vital signs (temperature, respiratory rate, blood pressure, and pulse), body weight, and height[e]	X	X	X	X	X	X	X
ECG[f]	X	As clinically indicated					
Concomitant medications	←						→
Medical history	X						
Demography, including baseline characteristics and tobacco use	X						

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD (max. 24 months)[a,b]	
Week	**-4 to -1**	**1**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				**Final visit**
Eligibility criteria	X	X					
Laboratory assessments							
Clinical chemistry	X	X[g]	X[h]	X[h]	X[h]	X[h]	X
Haematology	X	X[g]	X[h]	X[h]	X[h]	X[h]	X
Coagulation		X[i]	As clinically indicated				
TSH (reflex free T3 or free T4)[g,j,k]	X	X[k]	X	X	X	X	X
Urinalysis	X	As clinically indicated					
Hepatitis B and C, HIV, and tuberculosis	X						
Pregnancy test[l]	X	X	X	X	X	X	X
Monitoring							
WHO/ECOG PS	X	X	X	X	X	X	X
AE/SAE assessment[m]	←					→	
Drug accountability		X	All visits				
IP administration							
Durvalumab (MEDI4736)[n]		X	X	X	X	X	X
QoL assessments							
CCI [redacted][o]	X	X	X	X	X	X	X
CCI [redacted][o]	X	X	X	X	X	X	X
Biomarker assessments							

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD (max. 24 months)[a,b]	
Week	**-4 to -1**	**1**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				**Final visit**
CCI [redacted]	X						
CCI [redacted]	X						
CCI [redacted])[r]	X	X	X	X			
CCI [redacted][c]		X					
Efficacy evaluations							
Tumour evaluation as per local institutional standard care (CT or MRI) (RECIST 1.1)[b,s]	X	The allowed window for the tumour assessment is ±7 days. On-study tumour assessments begin 8 weeks ±1 week after IP treatment initiation and continue q8w ±1 week through 52 weeks (relative to the date of IP treatment initiation) and q12w ±1 week thereafter (relative to the date of IP treatment initiation) until disease progression, plus an additional follow-up scan is performed if clinically feasible. The on-study imaging schedule of 8 weeks ±1 week through 52 weeks and then q12w ±1 week thereafter MUST be followed regardless of any delays in dosing. Additional scans can be completed per standard practice post disease progression.					

[a] These cycles refer to the 28-day cycles of administration of durvalumab (MEDI4736).

[b] The baseline assessment is part of the screening procedures and should be performed within 42 days after the end of sCRT and no more than 28 days before the IP treatment initiation. Patients with radiological PD by RECIST 1.1 (see footnote s) who continue to receive study drug at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit. For these patients the assessments should continue as indicated here. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessment at the next scheduled visit.

[c] The sample for CCI [redacted] will be obtained at Day 1 pre-dose. If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for CCI [redacted] during the study.

[d] Patients should be contacted every 2 weeks (±1 day) after receiving IP during the first 3 cycles (Cycle 1 Day 14±1, Cycle 2 Day 14±1, and Cycle 3 Day 14 ±1) to ensure early identification and management of toxicities. This contact should be documented in the medical record.

[e] Body weight is recorded in kg at each visit along with vital signs. Height is recorded at screening only.

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

[g] If screening laboratory assessments are performed within 3 days prior to Day 1 (first IP dose administration), they do not need to be repeated at Day 1.

[h] Samples for laboratory assessments may be obtained more frequently based on the local clinical practice or the Investigator's discretion if clinically indicated.

[i] Coagulation tests are only performed at baseline on Day 1 (unless performed within 3 days prior to Day 1) and as clinically indicated.

[j] 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.

[k] If TSH is measured within 14 days prior to Day 1 (first IP dose administration), it does not need to be repeated at Day 1.

[l] 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 IP and then prior to every dosing visit (within 3 calendar days prior to dosing). 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.

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

[n] Results for 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.

[o] Will be administered using a site-based electronic device. At screening, ePRO should be done after informed consent but before any other screening procedures. At C1D1, and following visits, ePRO should be done prior to any other assessments and before dosing that day.. PRO questionnaires should be completed as long as the patient continues with the study drug, until confirmed PD. Patients with confirmed PD who continue to receive the study drug at the discretion of the Investigator will follow the PRO assessments until the study drug is stopped.

[p] CCI .

[q] CCI

[r] Pre-dose only. Plasma will be used to evaluate CCI . The concentrations of a panel of relevant cytokines and chemokines may be assessed.

[s] RECIST 1.1 assessments will be performed based on local institutional imaging results, using CT/MRI assessments of the chest and abdomen (including the entire liver and both adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients, including new lesions at follow-up. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of IP treatment initiation). All confirmatory scans should be recorded in the database. For patients who are clinically stable and being treated through radiological progression, the follow-up scan performed after a RECIST 1.1-defined PD should be 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. For these patients the assessments should continue as indicated here. Special Confirmation of Radiological Progression Criteria apply for tumour assessments on the follow-up scan (Appendix F of CSP).

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

Note: If a patient has a delay to an infusion of study drug, the efficacy and PRO assessments should be conducted relative to the date of first IP dose administration.

AE: Adverse event; C: Cycle; CT: Computed tomography; CCI ; ECG: Electrocardiogram; CCI HIV: Human immunodeficiency virus; IP: Investigational product; LFT: Liver function test; max.: maximum; MRI: Magnetic resonance imaging; PD: Progression of disease; CCI ; PRO: Patient-reported outcomes; CCI ; q4w, q8w, q12w: Every 4, 8, 12 weeks, respectively; q28d; Every 28 days; QoL: Quality of life; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SAE: Serious adverse event; sCRT: Sequential chemoradiation therapy; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-stimulating hormone; WHO/ECOG PS: World Health Organisation/Eastern Cooperative Oncology Group Performance Status.

Table 8 Schedule of Assessments for Patients who have Discontinued Study Drug

	Time since last dose of IP					
	Day (±3)	Months (±1 week)				12 months and every 3 months (±2 weeks)
Evaluation	30	2	3	6	9	
Physical examination (full)	X					
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X					
Body weight	X	X	X			
Pregnancy test[a]	X	As clinically indicated				
AE/SAE assessment	X	X	X			
Concomitant medications	X	X	X			
WHO/ECOG PS[b]	At timepoints consistent with tumour assessments; at 30, 60, and 90 days after last IP dose; and then at initiation of subsequent anticancer therapy					
Subsequent anticancer therapy[c,d]	←					→
Survival status[e]		X	X	X	X	X
Haematology	X	X	X			
Clinical chemistry	X	X	X			
Urinalysis	As clinically indicated					
TSH (reflex free T3 or free T4)[f]	X	X	X			
CCI [redacted][g]	X	X	X			
CCI [redacted][g]	X	X	X			

	Time since last dose of IP					
	Day (±3)	Months (±1 week)				12 months and every 3 months (±2 weeks)
Evaluation	30	2	3	6	9	
Tumour assessment as per local institutional standard care (CT or MRI) (RECIST 1.1)[h]	Additional scans to be completed per standard practice post progression. Patients who permanently discontinue IP for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 assessments performed q8w ±1 week beginning 8 weeks after IP treatment initiation for the first 52 weeks and q12w ±1 week thereafter until clinical progression/deterioration or 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).					

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

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

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

[d] For patients who discontinue the IP following progression, available readings of CT/MRI from local practice will be collected from patients' medical charts while information on subsequent anticancer treatment is collected.

[e] Patients who decline to return to the site for evaluations should be contacted by telephone as an alternative. In addition to the regularly scheduled survival follow-up, patients may be contacted in the week following DCO to confirm survival status. Every effort should be made to contact patients by telephone to follow and record survival status.

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

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

[h] Only for patients yet to progress, RECIST 1.1 assessments 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 should be image-based on signs and symptoms of individual patients. For patients who are clinically stable and being treated through radiological progression, the follow-up scan performed after a RECIST 1.1-defined PD should be 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; special Confirmation of Radiological Progression Criteria apply for tumour assessments on the follow-up scan (Appendix F of CSP). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of IP treatment initiation). The modality of tumour assessment should be the same throughout the study.

AE: Adverse event; CT: Computed tomography; DCO: Data cut-off; eCRF: Electronic case report form; CCI European CCI IP: Investigational product; IV: Intravenous; MRI: Magnetic resonance imaging; NSCLC: Non-small cell lung cancer; PD: Progression of disease; PRO: Patient-reported outcomes; CCI ; q8w, q12w: Every 8, 12 weeks, respectively; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SAE: Serious adverse event; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-stimulating hormone; WHO/ECOG PS: World Health Organisation/Eastern Cooperative Oncology Group Performance Status.

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