Statistical Analysis Plan
Study Code D4194C00009
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Date 12 January 2024

A Phase II, Open-label, Multicenter, International Study of Durvalumab Following Radiation Therapy in Patients with Stage III, Unresectable Non- Small Cell Lung Cancer Who Are Ineligible for Chemotherapy (DUART)

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AstraZeneca

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AEPI	Adverse event of possible interest
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
Anti-HBc	Hepatitis B core antibody
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
BED	Bioequivalent dose
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
CRF	Case Report Form
CRT	Chemoradiation therapy
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CCI	CCI
DBL	Database lock
DBP	Diastolic blood pressure
DCO	Data cut-off
DoR	Duration of response

Abbreviation or special term	Explanation
Dp	Decimal place
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
Gy	Gray
HBsAg	Hepatitis B virus surface antigen
HIV	Human immunodeficiency virus
HL	Hy's Law
CCI	CCI
IASLC	International Association for the Study of Lung Cancer
IASLC 2016	IASLC Staging manual version 8
IB	Investigator's Brochure
ICF	Informed Consent Form
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
LD	Longest diameter
LLQ	Lower limit of quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mOS	Median overall survival

Abbreviation or special term	Explanation
MRI	Magnetic resonance imaging
MSSO	Maintenance and Support Service Organization
Msec	Milliseconds
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
OR	Objective response
ORR	Objective response rate
OS	Overall survival
OS12	Proportion of patients alive at 12 months
PD	Progressive disease
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PFS6	Proportion of progression-free and alive patients at 6 months
PFS12	Proportion of progression-free and alive patients at 12 months
CCI	CCI
CCI	CCI
PID	Percentage intended dose
PR	Partial response
PRAE	Possibly related adverse event
CCI	CCI
CCI	CCI
PS	Performance status
PT	Preferred Term
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation therapy
q12w	Every twelve weeks

Abbreviation or special term	Explanation
q4w	Every four weeks
CCI	CCI
CCI	CCI
CCI	CCI
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDI	Relative dose intensity
RECIST1.1	Response Evaluation Criteria in Solid Tumors, 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
SC	Steering Committee
SD	Stable disease / standard deviation
SI	International system (of units)
simAE	Suspected imAE
SOC	System Organ Class
T3	Tri-iodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TL	Target lesion
CCI	CCI
TNM	Tumor, node and metastasis
PRAE	Possibly related adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WHO	World Health Organization
WHO/ECOG PS	World Health Organisation/Eastern Cooperative Oncology Group Performance Status

AMENDMENT HISTORY

Date	Brief description of change
19th June 2020	Initial version 1.0
18 November 2020	Abbreviation for AEPI is added in list of abbreviations
	Updated from 3 to 4 general categories of IPD in section 2.2.1
	Text 'and from time of the patients signed the informed consent and 30 days following last dose of the standard of care agents.' removed from section 3.2.3
	Duration of dose delays updated in section 3.2.8
	Text added for unexpected questionnaires in section 3.4.1
	CCI [redacted]
	CCI [redacted] .
	Text added for previous disease-related radiotherapy and previous disease-related cancer therapy in section 3.5.1
	Added text for definition of visit windows for survival follow-up (4.1.4.1)
	Units added for height, weight and bmi in section 4.2.3
	Changed to TEAE from AE in section 4.5.1
	Sign changed from >= to ≥ and =< to ≤ in section 4.2.3 and 4.5.4.2 in order to make it consistent.
	CCI [redacted]
	Section 5: Interim analysis text has been added
11th February 2021	In section 2.1.1 text for safety analysis is modified and patient reported safety analysis set (PROAS) is removed. PROAS removed from section 4.6 added updated text. PROAS removed from section 6 New text added for rescreened patients in section 4.1.1

Date	Brief description of change
9th March 2021	Section 3.2.3.3 updated based on AZ confirmation of internal adjudication of immune mediated AEs by AZ. Section 4.5.1.2 to remove wording for imAE charter
7th May 2021	Removed infection AEs (previous section 4.5.1.2)
	A new section 4.5.2 (Electrocardiogram) added to state that no summary or listing of ECG parameters will be presented.
	In section 6 (Changes of Analysis from Protocol) it is mentioned that ECG outputs will not be produced and only box plot for vitals will be presented.
	Section 4.5.5 (Therapy following discontinuation of Durvalumab) removed
	In section 4.2.1, more details added for last contact date.
	Cut-off for AE frequency has been changed from 5% to 2.5% in section 4.5.1
	Duration of AESI/AEPI and time to onset of first AESI/AEPI have been added in section 4.5.1.1
	Possibly related AESI/AEPI leading to discontinuation of study treatment has been added in section 4.5.1.1
18th May 2021 and 8th July 2021	New text added for Covid-19 in section 3.2.3.4, 4.1.1, 4.2.1 and 4.2.2, 4.2.3, 4.4.1, 0, 4.5.1.3
8th July 2021	CCI [redacted]
06 Jul 2023	Text added for Section 3.2.8 for dose delay
06 Jul 2023	Rules added for 2 missed visits for section 3.3.1
06 Jul 2023	Rules added for 2 missed visits for section 3.4.1.1
06 Jul 2023	Extra text added for handling of missing data in section 4.1.3
05 January 2024	Text and figure 1 updated in section 1.2 based on CSP V2.0
05 January 2024	Text updated for sample size section 1.3 based on CSP V2.0
05 January 2024	Text update for Section 5
05 January 2024	Removed the SOA tables (Tables 7 and 8) and referenced them in the protocol
05 January 2024	AJCC version and reference updated in section 7
05 January 2024	Signature page removed as it will be signed in Angel

1. STUDY DETAILS

Results from the PACIFIC Study in patients with Stage III unresectable non-small cell lung cancer (NSCLC) following concurrent chemoradiation therapy (cCRT) demonstrated a significant increase in median progression-free survival (PFS) and a significant increase in overall survival (OS) among patients who received durvalumab compared with placebo. Safety results from this study demonstrated that durvalumab monotherapy was well tolerated and had a manageable safety profile in this patient population. However, many patients with Stage III unresectable NSCLC are unable to undergo chemotherapy; these patients are therefore faced with fewer treatment options. This study is being conducted to assess the safety and tolerability of maintenance treatment with durvalumab (MEDI4736) following radiation therapy in this population. DUART will also assess the efficacy as secondary objective and CCI as exploratory objective.

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 possibly related adverse events (PRAEs) within six months from the initiation of durvalumab treatment	Grade 3 or Grade 4 PRAEs

Note: Toxicities will be classified as per CTCAE grading system NCI CTCAE version 5.0.

PRAE: Possibly related adverse event; CTCAE: Common Terminology Criteria for Adverse Event; NCI: National Cancer Institute.

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 Tumors version 1.1 (RECIST 1.1) as assessed by the Investigator PFS6 and PFS12 according to RECIST 1.1 as assessed by the Investigator Median OS and OS12
To further assess the efficacy of durvalumab treatment in terms of objective response rate (ORR) and duration of response (DoR)	Objective response (OR) 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, electrocardiograms (ECGs) and laboratory findings including clinical chemistry, haematology and urinalysis

Note: Analysis of OR 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 provided they fulfil the other criteria for measurability.

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

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; ECG: electrocardiogram; imAE: immune-mediated adverse event; OR: objective response; ORR: objective response rate; OS: overall survival; OS12: proportion of patients alive at 12 months from first date of treatment; PFS: progression-free survival; PFS6, PFS12: proportion of patients progression-free at 6 months and 12 months, respectively, from first date of treatment; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SAE: serious adverse event.

1.1.3 Exploratory Objectives

Exploratory Objectives	Endpoints / Variables
CCI	CCI
	CCI
CCI	CCI
CCI	CCI
CCI	CCI

CCI	CCI

Note: Analyses of some exploratory objectives may be presented outside of the clinical study report (CSR).

CCI

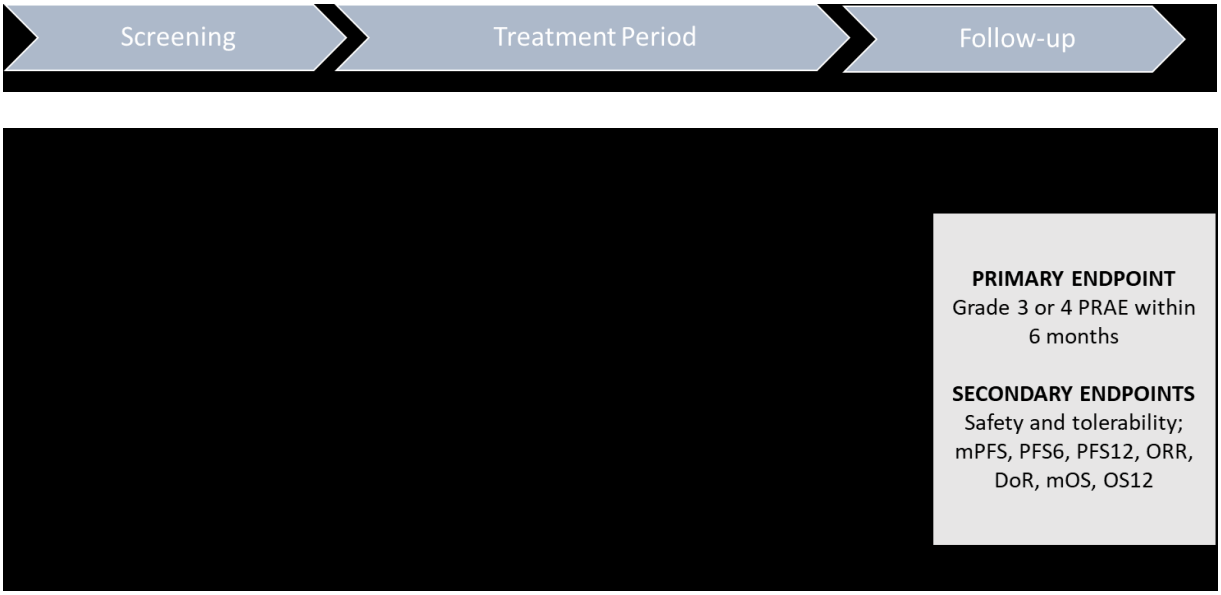
1.2 Study Design

This is a Phase II open-label, single-arm, multicenter, international study to evaluate the clinical activity of durvalumab (1500 mg q4w) in patients with Stage III unresectable NSCLC who have an ECOG PS of 0 to 2 and who were treated with radiotherapy but are ineligible for chemotherapy.

Patients will be enrolled into 2 cohorts according to radiotherapy pretreatment dose (Cohort A: standard radiation therapy [60 gray (Gy) ± 10% or hypofractionated bioequivalent dose (BED)]; Cohort B: palliative radiation therapy [40 to < 54 Gy or hypofractionated BED]).

The general study design is summarised in Figure 1

Figure 1 Study Design



BED = bioequivalent dose; DoR = Duration of response; ECOG = Eastern Cooperative Oncology Group; Gy = gray; m = Month; mOS = median overall survival; mPFS = median progression-free survival; NSCLC = Non-small cell lung cancer; ORR = Overall response rate; OS12 = Overall survival at 12 months; PD = Progressive disease; PFS6, PFS12 = Progression-free survival at 6, 12 months, respectively; PRAE = Possibly related adverse event; PS = Performance status; q4w = Every 4 weeks; RT = radiation therapy

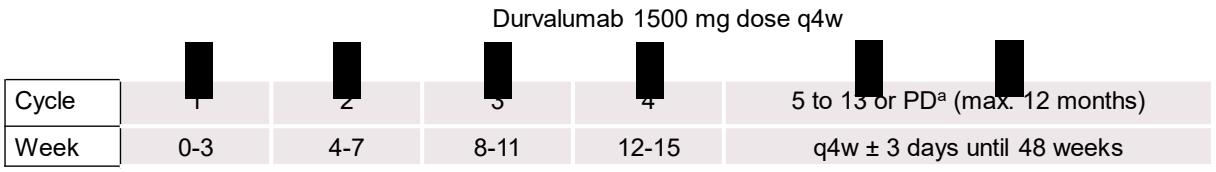
Approximately 102 patients will be treated with durvalumab in Europe and North America. Patients will be in complete response (CR), partial response (PR), or have stable disease (SD) following radiation therapy, as assessed by the Investigator and further supported by the screening imaging radiological assessment. Patients must not have progressed following radiation therapy, and radiation therapy must be completed within 6 weeks (42 days) prior to first durvalumab administration. The last dose of radiation therapy is defined as the day of the last radiation treatment session.

1.2.1 Study Treatment

All patients will receive 1500 mg durvalumab via intravenous (IV) infusion q4w for up to a maximum of 12 months (up to 13 doses/cycles). The last administration of durvalumab will be on week 48 unless there is clinical progression, RECIST 1.1-defined radiological progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. If a patient's weight falls to 30 kg or below, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between Investigator and Study Physician, until the weight improves to > 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w.

The standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Figure 2 Durvalumab monotherapy dosing schedule



max = Maximum; PD = Progression of disease; q4w = Every 4 weeks.

[a] Or until discontinuation of study drug due to any of the reasons

Patients may delay dosing under certain circumstances.

- Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1 of CSP), due to either immune-mediated adverse events (imAEs) or non-imAEs.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
- Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) and patient-reported outcomes (PRO) assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-life of durvalumab (see the current Investigator's Brochure [IB] for durvalumab).

One cycle of treatment with durvalumab is equal to 28 calendar days.

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

If imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening imaging results must have been obtained within 28 days prior to the first dose.

PRO and tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of the first dose (not the date of therapy).

All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc, required for dosing should be performed within 3 calendar days prior to dosing.

1.2.2 Tumor Response Assessments

Tumor 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 categorisation of objective tumor 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

All patients in the study should be followed up for survival at months 2, 3, 4, 6, 8, 10, and 12 following treatment discontinuation or completion, and then every 12 weeks until death, withdrawal of consent, or the end of the study.

1.3 Number of Patients

The primary objective of this study is to assess the safety and tolerability of durvalumab which is defined as Grade 3 and Grade 4 PRAEs observed within 6 months after the initiation of durvalumab treatment. In addition, safety and tolerability of durvalumab will be characterized for the cohorts of patients who received Standard Radiotherapy (60 Gy ± 10%) or hypofractionated BED and patients who received palliative radiotherapy (40 to < 54 Gy) or hypofractionated BED.

A total of approximately 102 patients are treated with durvalumab in 2 cohorts: approximately 59 patients in the Standard Radiotherapy Cohort and approximately 43 patients in the Palliative Radiotherapy Cohort. It is estimated that a sample size of a minimum 60 patients would be required to provide an adequate level of confidence in the estimated incidence of Grade 3 and 4 PRAEs occurring within 6 months after initiation of durvalumab treatment, which is the primary endpoint. With a sample size of 60 patients, the exact binomial 95% CI for an observed incidence rate of 12% would be 5% to 23%. If the underlying/true incidence rate was 12% as reported in PACIFIC (D4194C00006), on repeated implementations of this study, observing an incidence rate less than 5% or greater than 18.3% would be approximately 5% for each region/tail.

Furthermore, if there are 30 patients in each cohort (Standard Radiotherapy and Palliative Radiotherapy) and the true incidence of Grade 3 and Grade 4 PRAEs occurring within 6 months after initiation of durvalumab treatment is 12%, , the precision will be approximately ± 13.0% (95% CI: 3.1, 29.1) in each cohort.

An illustration of the precision around the varying incidence rate of Grade 3 and Grade 4 PRAEs for the patients overall and for each cohort (Standard Radiotherapy and Palliative Radiotherapy) is provided in Table 1.

Table 1 Precision around varying incidence of Grade 3 and Grade 4 Possibly-Related Adverse Events

Sample size	Grade 3 and Grade 4 PRAE Incidence Rate		
	10 %	12 %	15 %
60	3.8-20.5 (± 8.4)	5.0-23.0 (± 9.0)	7.1-26.6 (± 9.7)
30	2.1-26.5 (± 12.2)	3.1-29.1 (± 13.0)	4.7-32.7 (± 14.0)

PRAE = possibly related adverse event.

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

The Safety Analysis Set: will consist of all patients who received at least one dose (partial or in full) of durvalumab. The SAF will be used for analysis of all safety endpoints. In this safety study, the standard full analysis set will be same as SAF, therefore, the SAF will be used for analysis of efficacy endpoints as well.

For analysis of time-to-event endpoints, the SAF will be used with defined censored patients.

2.2 Protocol Deviations

2.2.1 Important Protocol Deviations

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

> "Protocol deviations (PDs) 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 Clinical Study Report (CSR):

- Deviation 1: Patients who received treatment and who deviated from the following key entry criteria in Clinical Study Protocol (CSP):

- Inclusion Criterion 5: Histologically- or cytologically-documented NSCLC with locally-advanced, unresectable Stage III disease (according to the International Association for the Study of Lung Cancer [IASLC] Staging Manual Version 8 [IASLC 2016]).
    (a) Imaging to rule out distant metastasis is required.
    (b) Endobronchial ultrasound with biopsy is encouraged in patients with suspected lymph node involvement.
- Inclusion Criterion 6: Deemed ineligible for chemotherapy per Investigator assessment (eg, comorbidities, poor PS, etc).
- Inclusion Criterion 7: Receipt of radiation therapy that was completed within 42 days prior to first IP dose administration in the study.
- Inclusion Criteria 8: Patients must have received a total dose of radiation of 40 to 66 Gy (standard or hypofractionated BED). Note that patients will be assigned to Cohort A (standard radiation therapy [60 Gy ± 10% or hypofractionated BED]) or Cohort B (palliative radiation therapy [40 to < 54 Gy or hypofractionated BED]) based upon total dose of radiation received. Sites are encouraged to adhere to mean organ radiation dosing as follows:
    a) Mean lung dose < 20 Gy and/or V20 < 35%;
    b) Mean esophagus dose < 34 Gy;
    c) Heart V45 < 35% or V30 < 30%. Heart V45 < 35% or V30 < 30%.
    d) Note: Sites should be aware of the recent RTOG 0617 Study data (Bradley et al 2015) demonstrating that doses higher than 60 Gy may be associated with greater toxicity and worse efficacy. 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 9: Patients must not have progressed following radiation therapy, as per Investigator assessed RECIST 1.1 criteria.
    (a) Patients with measurable disease and/or nonmeasurable and/or no evidence of disease assessed at baseline by computed tomography (CT)/magnetic resonance imaging (MRI) will be eligible for this study.
    (b) Prior irradiated lesions may be considered measurable and selected as target lesions (TLs) providing they fulfil the other criteria for measurability.
- Inclusion Criterion 10: WHO/ECOG PS ≤2.
- Inclusion Criterion 11: No prior exposure to immune-mediated therapy including, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, and antiprogrammed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.
- Exclusion Criterion 1: Patients with locally-advanced NSCLC whose disease has progressed following radiation therapy.
- Exclusion Criterion 2: Mixed small-cell lung cancer and NSCLC histology.

- Exclusion Criterion 5: Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhea, 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 9: Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive hepatitis B virus surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (human immunodeficiency virus [HIV]; positive HIV 1/2 antibodies). Patients with a past or resolved hepatitis B virus infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C antibody are eligible only if polymerase chain reaction is negative for hepatitis C virus ribonucleic acid.
- Exclusion Criterion 14: Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

- 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 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 DBL.

The final classification of IPDs will be made prior to DBL or data cut-off 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 tumor response data will be used to determine each patient's visit response according to RECIST version 1.1. It will also be used to determine, if and when a patient's disease has progressed in accordance with RECIST and their best objective response to study treatment.

The baseline radiological tumor assessment is part of the screening procedure and should be performed within 28 days after the end of radiotherapy, no more than 28 days before the start of durvalumab treatment, and ideally as close as possible to the start of study treatment. Tumor assessments will begin at 8 weeks ± 1 week after durvalumab initiation and continue every 8 weeks ± 1 week through 48 weeks (relative to the date of first dose of durvalumab), and then every 12 weeks ± 1 week thereafter until RECIST 1.1-defined PD, plus an additional regularly scheduled follow-up scan. The on-study schedule of q8w ± 1 week (following the first assessment at 8 weeks ± 1w after the first dose) for first 48 weeks and then q12w ± 1 w thereafter MUST be followed regardless of any delays in dosing. Additional scans can be completed per standard practice post disease progression.

From the investigator's review of the imaging scans, the RECIST tumor 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 tumor 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 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 tumors:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the 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 >1/3 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 tumor 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 tumor.

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

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

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 tumor

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, imAEs), 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 PRAEs (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 PRAEs 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.

3.2.2 Secondary Safety Endpoints

The secondary safety endpoints of this study include:

- Treatment-emergent adverse events (TEAEs) and SAEs

- AESI and AEPI (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) and pulse rate
- Laboratory data including clinical chemistry, haematology and urinalysis
- Physical examination

3.2.3 Adverse Events

AEs and SAEs will be collected throughout the study, from time of the patient signing the informed consent and 90 days after the last dose of durvalumab. A treatment emergent adverse event (TEAE) is an AE with an onset date or a pre-existing AE worsening following the first dose of study treatment through to 90 days after the last dose of durvalumab.

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

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 Possibly-Related Adverse Events

A PRAE is any TEAE with a relatedness to durvalumab of possible, or where the relatedness is missing. When the relatedness of a TEAE is missing on the electronic Case Report Form (eCRF), all efforts will be taken to ensure that the Investigator assigns his/her assessment of relatedness prior to DBL.

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

3.2.3.2 Adverse Events of Special Interest and AEs of Possible Interest

Some clinical concepts (including some selected individual preferred terms and higher-level terms) have been considered “AEs of special interest” (AESI) and “AEs of possible interest” (AEPI) to the durvalumab program.

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

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

These AESIs and AEPIs have been identified as Pneumonitis, Hepatic events, Diarrhea/Colitis, Intestinal perforations, Adrenal Insufficiency, Type 1 diabetes mellitus, Hyperthyroid events, Hypophysitis, Hypothyroid events, Thyroiditis, Renal events, Dermatitis/Rash, Pancreatic events, Myocarditis, Myasthenia gravis, Guillain-Barre syndrome, Myositis, Infusion/hypersensitivity reactions and Other rare/miscellaneous . Other categories may be added or existing terms may be merged as necessary. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which MedDRA preferred terms contribute to each AESI/AEPI. A further review will take place prior to Database lock (DBL) to ensure any further terms not already included are captured within the categories.

3.2.3.3 Immune-Mediated Adverse Event (ImAE)

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/AEPI 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)). No adjudication of the imAEs will be performed for this analysis.

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 respiration rate (breaths/minute), SBP (mmHg), DBP (mmHg), pulse rate (beats/min), weight (kg), height (cm) and body temperature (degrees Celsius).

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 project reference ranges will be used for the primary interpretation of laboratory data.

The following laboratory parameters will be measured at screening, Day 1 of each cycle, and at other times if clinically indicated:

- Clinical Chemistry: albumin, ALP, ALT, amylase and/or lipase, AST, calcium, glucose, LDH, potassium, sodium, total bilirubin, total protein, TSH, urea or BUN (depending on local practice)
- Haematology: haemoglobin, neutrophil count (absolute or percentage), lymphocyte count (absolute or percentage), platelets, total white cell count
- Urinalysis: bilirubin, blood, color and appearance, glucose, ketones, pH, protein, specific gravity

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

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

In addition, the following laboratory parameters will be collected at baseline, Day 1 of Cycle 1, or when clinically indicated:

- Clinical Chemistry: bicarbonate (when available), chloride, creatinine clearance, gamma glutamyltransferase, magnesium, T3 free, T4 free
- Haematology: activated partial prothrombin time (ratio or absolute), INR

3.2.7 Physical Examination

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

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, data 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 maximum[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.

According to the protocol, dose delays are defined as doses administered 4 or more days after the target dosing date and reason for dose delay is collected in the CRF based on this definition.

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 of treatment discontinuation.

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

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

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

Patient 4: RDI = (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 tumor 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 assessment prior to the missed visits.

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.

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 time of analysis will be censored at the last recorded date at which the patient was known to have been alive.

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 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 tumor 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 will be censored at the date at which the patient was last known to have been alive. Patients who died due to reasons other than NSCLC will be censored at the date of death.

3.4 CCI

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3.4.1 CCI

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3.4.1.1 CCI

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3.4.1.2 CCI

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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 (Kg), height (cm), body mass index (BMI kg/m^2).
- 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 tumor 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 radiotherapy: Total dose, Radiotherapy treated location, Time from completion of radiotherapy to study treatment, Dose per fraction, Number of fraction doses, frequency of fraction doses per day, concomitant chemoradiotherapy, treatment setting, radiotherapy technique.
- Previous disease-related cancer therapy: Number of chemotherapy regimens, number of cycles, best response to previous chemoradiotherapy, therapy class, treatment status.
- 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

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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 each cohort (standard radiotherapy and palliative radiotherapy) and overall.
- 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 observations 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 9.4 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 and ECG 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 tumor 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, radiotherapy 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, radiotherapy 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, and 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.
- Patients who failed the screening in the first instance but later rescreened and passed the screening will be part of summary tables along with other patients who passed the screening in the first instance.
- Patients who failed both first screening and rescreening will not be part of summary tables but a listing will be generated for these patients.
- Participants affected by the COVID-19 pandemic will be listed including category for study disruption due to the pandemic and details of disruption. 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 ECG, vital signs, laboratory data, coagulation and urinalysis will not be imputed.
- If triple ECGs are performed, the mean value of any continuous parameters of the ECG will be derived first and it will be used as the value of the ECG at that timepoint/assessment. For abnormalities, the worst case will be used for any summary tables.
- 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 unless year is the same as first dose date then impute first dose date.
- If the year and month are available and the day is missing, impute the day as 01 (the first day of the month) unless month is same as month of first dose of study drug then impute first dose date.

- If the start date is completely missing and end date is present, then take day and month as 01Jan and the year from end date.

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 unless year is the same as last dose date then impute last dose date. If the last dose date is not available then DCO date will be used.
- 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) unless month is same as month of last dose date then impute last dose date. If the last dose date is not available, DCO date will be used.
- If the end date is completely missing, then look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present / medication is still being taken (i.e. do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is 1 day after the last dose date.
- It is not expected to have missing dates for unscheduled laboratory, ECG, diagnostics data. However, if there are missing dates, for any derivations, the dates should be imputed following the rules for stop date of concomitant medications and AEs

4.1.4 Definitions of Visit Windows

Time windows are defined for all summaries of vital signs, ECG, laboratory data, PRO around visits in Section 4.1.4.1 and for tumor 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 halfway 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 Tumor Assessments

The following conventions will apply for tumor assessment data:

- All tumor 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 tumor assessments which are outside the visit windows will be flagged in the data listings.

The above could result in more than one tumor 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 along with issues reported in the Clinical Trial Management System.

4.2.2 Protocol Deviations

Important protocol deviations are defined in Section 2.2 and will be listed and summarized for the SAF.

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 (years), 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 (cm), weight (kg) [prior to start of radiotherapy, and after radiotherapy at screening, and the change], weight groups [<40, ≥40-< 75, ≥ 75-<90, ≥ 90-<120, and ≥ 120 kg], body mass index (BMI kg/m^2) after radiotherapy, and BMI groups [Underweight (<18.5), Normal weight (≥18.5 - <25.0), Overweight (≥25.0 - <30.0), Obese (≥30.0) kg/m^2]
- Nicotine use and consumption
- A summary and a list of patients by site and country will be provided.
- Previous disease-related radiotherapy and cancer therapy.
- Disease characteristics (CCI [redacted], AJCC staging at baseline and diagnosis, histology type at diagnosis, TNM classification at diagnosis, tumor location and time from diagnosis to first dose
- Extent of disease (Radiological assessment, site of locally advanced disease, recurrence of earlier cancer, NSCLC progressing at study entry, time from most recent progression to study entry, reason tumor not amenable for resection
- Medical history in patients with confirmed/suspected COVID-19 infection.

Medical history and relevant surgical history are coded using MedDRA and will be summarized by SOC and PT.

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 and procedures will be summarized by therapeutic subgroup (ATC 2nd level), 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 PRAEs (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 PRAEs 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 PRAEs, 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 standard and palliative radiotherapy cohorts. 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 PRAEs 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, PFS6 (Day 180) and PFS12 (Day 365).

Summaries of the number (%) of patients experiencing a PFS event (overall and also at Month 6 and Month 12) 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 12-month (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).

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 12-monthly 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).

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

4.5 Analysis of Secondary Safety Endpoints

4.5.1 Adverse Events

All TEAEs 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 TEAEs 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, PRAEs, SAEs, AESIs, AEPIs, imAEs, AEs with outcome of death, AEs leading to discontinuation of durvalumab, AEs leading to discontinuation of study. Listings of AESIs, AEPIs 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 PRAE
- At least one AE of CTCAE Grade 3 or Grade 4
- At least one PRAE of CTCAE Grade 3 or Grade 4
- At least one SAE
- At least one Serious PRAE
- At least one AE leading to discontinuation of study treatment

- At least one PRAE leading to discontinuation of study treatment
- At least one AE leading to treatment interruption
- At least one PRAE leading to treatment interruption
- At least one AE with outcome of death
- At least one PRAE with outcome of death
- At least one AESI
- At least one AEPI
- At least one PRAE of special interest (AESI)
- At least one PRAE of possible interest (AEPI)
- At least one imAE
- At least one immune-mediated PRAE

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

- All AEs / PRAEs
- All AEs / PRAEs of CTCAE Grade 3 or Grade 4
- All PRAEs of CTCAE Grade 3 or Grade 4 occurring within the six months of first dosed date
- All PRAEs which start within 90 days of 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 0) 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 / PRAEs with outcome of death
- All SAEs / Serious PRAEs
- All AEs / PRAEs leading to discontinuation from durvalumab (Note: Reason for discontinuation recorded on the patient disposition page)
- All AEs / PRAEs 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 discontinuation 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 Possible Interest

Preferred terms used to identify adverse events of special interest and possible interest (as defined in 3.2.3) will be listed before DBL and documented in the Study Master File. Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI/AEPI grouping. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

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

- Any AESI/AEPI
- Any AESI/AEPI by SOC, PT and maximum CTCAE grade
- Any AESI/AEPI of maximum CTCAE grade 3 or 4
- Any serious AESI/AEPI
- Any AESI/AEPI with outcome of death
- Any AESI/AEPI possibly related to study treatment
- Any AESI/AEPI leading to concomitant medication use (steroids)
- Any AESI/AEPI leading to concomitant medication use (high dose steroids)
- Any AESI/AEPI leading to concomitant medication use (endocrine therapy)
- Any AESI/AEPI leading to concomitant medication use (other immunosuppressants)
- At least one AESI/AEPI leading to discontinuation of study treatment
- Possibly related AESI/AEPI leading to discontinuation of study treatment
- Time to onset of first AESI/AEPI (days)
- Duration (days) of AESI/AEPI

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

4.5.1.2 Immune-mediated Adverse events (imAEs)

The imAEs will be summarized in the similar manner as for the summaries for AESI/AEPI described above.

4.5.1.3 COVID-19 related Adverse events

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

- Any AE in patients with confirmed/suspected COVID-19 infection
- Any AE in patients without confirmed/suspected COVID-19 infection
- Any AE by SOC, PT and maximum CTCAE grade in patients with confirmed/suspected COVID-19 infection.
- Any AE by SOC, PT and maximum CTCAE grade in patients without confirmed/suspected COVID-19 infection
- Any AE associated with COVID-19 infection by SOC and PT
- Any AE excluding AEs associated with COVID-19 infection by SOC and PT
- Any AE with confirmed/suspected COVID-19 infection by SOC and PT
- Any AE excluding confirmed COVID-19 infection by SOC and PT
- Any AE associated with COVID-19 infection and with outcome of death by SOC and PT
- Any AE excluding associated with COVID-19 infection and with outcome of death by SOC and PT
- Any AE associated with COVID-19 infection leading to discontinuation of investigational product by SOC and PT
- Any AE excluding associated with COVID-19 infection leading to discontinuation of investigational product by SOC and PT

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 following discontinuation 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, total protein, Sodium (hypo- and hyper-), Potassium (hypo- and hyper-), Corrected calcium (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 and >20x upper limit of normal (ULN) during the study
  - AST ≥ 3x – ≤ 5x, > 5x – ≤8x, > 8x. >10x 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 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.

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

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

4.5.4.3 Assessment of Renal Function Test Abnormalities

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

- Shift to worse renal impairment category from baseline
- Patients with subsequent CrCl assessment after worsening from baseline
- Worsened renal impairment reversible and transient

The renal impairment categories are defined as:

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

Creatinine clearance rate will be calculated using serum creatinine and the Cockcroft-Gault formula (Cockcroft and Gault 1976).

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

4.6 Analysis of Exploratory Endpoints

CCI

4.6.1 CCI

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CCI

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CCI

CCI

CCI

- CCI
- CCI

4.6.2 CCI

CCI

4.6.3 CCI

CCI

CCI

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4.6.4 CCI

CCI

CCI

4.6.5 CCI

CCI

5. INTERIM ANALYSES

No formal interim analysis is planned for this study.

A data analysis is planned to be performed once all patients had the opportunity to receive treatment for 6 months, ie, the DCO for this primary analysis would be expected 6 months after the last patient has received first dose of durvalumab. The final analysis will be performed at the end of the study when all patients have completed follow-up, or the trial has finished.

6. CHANGES OF ANALYSIS FROM PROTOCOL

No summary output or listings will be produced for ECG parameters as ECG data is only used for safety monitoring and to identify AEs. For vital sign parameters only box plots will be produced.

CCI

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8. APPENDIX

Schedule of activities are presented in Table 1 and Table 2 of the CSP.

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