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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Protocol Amendment No. 1: Final 2.0, 18 August 2023

Clinical Study Protocol	
Drug Substance	Durvalumab
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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)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT / EU CT Number: 2019-004336-31

VERSION HISTORY

Version 2.0, 18 August 2023 (Amendment 1)
Version 1.0, 05 November 2019
Initial creation

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

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP Version 2.0	18-Aug-2023
CSP Version 1.0	05-Nov-2019

CSP Version 2.0 (18-August-2023)

This modification is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13) as it neither significantly impacts the safety or physical/mental integrity of patients nor the scientific value of the study.

Overall Rationale for the Modification

This CSP was amended to clarify initial intent to allow continuation of the treatment with durvalumab for patients who may benefit from it, based on Investigator's opinion, after the individual patient reached end of scheduled visits, but before the study reached last patient last visit/final data cut off date and to update language related to sample size, data analysis, and follow-up of patients after discontinuation of study treatment for clarification. Text was also updated to comply with regulatory requirements.

The updates are summarized below. Other minor editorial updates were made throughout. Administrative changes, such as formatting, updates to abbreviations, and punctuation corrections, are not presented in this summary.

Section Number and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Section 4.1 Overall design; Table 2, footnotes; Section 7.1.1 Follow-up of patients post-discontinuation of study treatment; Section 7.1.2 Follow-up for survival	The minimum expected safety follow-up period of 90 days following the last dose of durvalumab for patients treated with the study treatment has been detailed and clarified, and accordingly new sections (Section 7.1.1 and 7.1.2) were added.	Text related to follow-up of patients after discontinuation of study treatment has been clarified.	Non-substantial
Section 4.4; Section 6.1.3 Duration of treatment and criteria for treatment through progression	A new section as "Continued access to study treatment" was added.	To clarify initial intent to allow continuation of the treatment with durvalumab for patients who may benefit from it, based on investigator's opinion, after the individual patient reached end of scheduled visits, but before the study reached last patient last visit/final DCO date.	Non-substantial
Synopsis; Section 1.3 Schema; Section 9.2 Sample size estimate	Details related to sample size update were included.	To aid patient recruitment, details about the adequate sample size were included.	Non-substantial
Section 9.5 Statistical analysis	Details related to data analysis (DCO for the primary analysis) were added.	To aid patient recruitment, details were included.	Non-substantial
Section 4.4	Clarified definition of the end of study according to European Union and Food and Drug Administration requirements.	For consistency and alignment in terms of posting study results.	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Section 6	Updated the definition for "study treatments" and details of durvalumab in Table 5. Also updated text describing administration of study treatment.	For consistency and alignment with regulatory requirements.	Non-substantial
Section 8.4.1	Updated text pertaining to reporting of SAEs when EDC system is not available/temporarily not accessable. Also specified the reference document for definaiton of expectedness/ listedness.	Updated to comply with regulatory requirements.	Non-substantial
Section 8.4.3	Specified timelins for providing relevant information to the AstraZeneca Patient Safey data entry site.	Updated to comply with regulatory requirements.	Non-substantial
Section 8.4.4	Added Drug Abuse, Medication Error and Drug Misuse definition.	Update required due to CT-3 regulation and corporate safety CAPA.	Non-substantial
Appendix A1	Updated text and added sub-heading "Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP".	Updates required to comply with regulatory requirement (eg, European CTR) and global company requirement.	Non-substantial
Appendix A4	Updated current text for and also added sub-heading "Personal Data Breaches".	Updates required to address European CTR RFI concerns relating to personal data breaches.	Non-substantial
Appendix A6	Updated information about timelines for submission of trial results summaries to European CTIS.	Update required to comply with European CTR.	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Appendix A7	Updated information about retention timelines of records and documents to "25 years after study archiving or as required by local regulations".	Update required to comply with European CTR and global company requirement.	Non-substantial
Appendix B8	Added detailed Drug Abuse and Drug Misuse definition and examples.	Update required due to CT-3 Regulation and corporate safety CAPA.	Non-substantial

Abrreviations: CAPA = corrective and preventive action; CTR = Clinical Trial Regulation; CTIS = Clinical Trial Information System; DCO = data cut off; EDC = electronic data capture; EU = European GCP = Good Clinical Practice; RFI = Request for Information; SAE = serious adverse event.

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1 PROTOCOL SUMMARY

1.1 Schedule of activities

The procedures for the screening and treatment periods in this study are presented in Table 1, and the procedures for the follow-up period are presented in Table 2.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw to occur at the timepoints indicated in the schedule of activities (SoA; Table 1 and Table 2). Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw to occur at the timepoints indicated in the SoAs (Table 1 and Table 2).

- 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), 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 (Response Evaluation Criteria in Solid Tumors [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.

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.

Table 1 Schedule of activities for screening and treatment period

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to C13 or PD (12 months) [a]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ± 3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1 [a]**	**q28d ± 3 days unless dosing needs to be held for toxicity reasons**				
Informed Consent							
Informed consent: study procedures [b]	X						5.1
Consent: genetic sample and analysis (optional)	X						5.1
Study procedures							
Physical exam (full)	X						8.2.2
Targeted physical exam (based on symptoms)		X	X	X	X	X	8.2.2
Assessment of early toxicities (phone call) [c]		X	X	X			8.2.5
Vital signs (temperature, respiration rate, blood pressure, and pulse), body weight, and height) [d]	X	X	X	X	X	X	8.2.3
ECG [e]	X	As clinically indicated					8.2.4
Concomitant medications	< ---------- >						6.4
Demography, including baseline characteristics and tobacco use	X						5.1
Pulmonary function testing (FEV_1) [f]	X						8.2.7
Eligibility criteria	X	X					5.1, 5.2
Laboratory Assessments							
Clinical chemistry [g]	X	X [h]	X	X	X	X	Table 8
Hematology [g]	X	X [h]	X	X	X	X	Table 9
Coagulation		X [i]	As clinically indicated				Table 9
TSH [j], (reflex free T3 or free T4 [k])	X	X	X	X	X	X	Table 8

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to C13 or PD (12 months) [a]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ± 3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1 [a]**	**q28d ± 3 days unless dosing needs to be held for toxicity reasons**				
Urinalysis	X	As clinically indicated					Table 10
Hepatitis B and C, HIV, and tuberculosis [l]	X						8.2.1
Pregnancy test [m]	X	X	X	X	X	X	8.2.1
Monitoring							
WHO/ECOG performance status	X	X	X	X	X	X	8.2.6
AE/SAE assessment [n]	< ---------- >						8.3
Drug accountability		X	All visits				6.3
IP administration							
Durvalumab [o]		X	X	X	X	X	6.1.1.1, 6.1.2.1
Patient-Reported Outcomes							
CCI [redacted]	X	X	PROs should be completed by patients prior to dosing on C1D1. Thereafter, PROs should be completed by the patients at home using a handheld device every 28 days (± 1 day), regardless of delays in dosing				8.1.2.1, 8.1.2.2, 8.1.2.3
Biomarker assessments							
CCI [redacted]	X						8.8.1
CCI [redacted]		X	X			C7, C9, C13 or PD	8.8.1
CCI [redacted]		X [s]					8.8.1
CCI [redacted]		X					8.7.1

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to C13 or PD (12 months) [a]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ± 3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1 [a]**	**q28d ± 3 days unless dosing needs to be held for toxicity reasons**				
Efficacy evaluations							
Tumor assessments (RECIST 1.1) [u]	X	On-study tumor assessments will begin 8 weeks ± 1 w after the first dose, then q8w ± 1 w through 48 weeks (relative to the first dose), and then q12w ± 1 w 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 ± 1 w 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.					8.1, Appendix F

AE = adverse event; C = Cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Event; DNA = Deoxyribonucleic acid; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; CCI [redacted] f CCI [redacted]; FEV_1 = forced expiratory volume in 1 second; CCI [redacted] HIV = Human immunodeficiency virus; ICF = Informed consent form; IP = Investigational product; LFT = Liver function test; MRI = magnetic resonance imaging; PD = Progressive disease; CCI [redacted]; CCI [redacted]; CCI [redacted]; CCI [redacted] q4w = Every 4 weeks; q8w = Every 8 weeks; q12w = Every 12 weeks; q28d = Every 28 days; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = Serious adverse event; SNP = single-nucleotide polymorphism; T_3 = Triiodothyronine; T_4 = Thyroxine; TSH = Thyroid-stimulating hormone; WHO = World Health Organization.

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

[a] These cycles refer to the administration of durvalumab.

[b] Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. All patients will be required to provide consent to supply an archival sample of their tumor. This consent is included in the main patient ICF. Informed consent of study procedures may be obtained prior to the 28-day screening window, if necessary. If laboratory or 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 laboratory results and screening imaging results must have been obtained within 28 days of the first dose.

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

[d] Body weight is recorded at each visit along with vital signs. Height is recorded at screening only. Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws.

[e] Any clinically significant abnormalities detected require triplicate ECG results. Whenever ECGs, vital signs, and blood draws are scheduled for the same

nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws.

[f] Pulmonary function testing includes FEV_1; results for up to 8 weeks prior to study enrollment are permitted.

[g] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[h] If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

[i] Coagulation tests are only performed at baseline on Day 1 (unless performed within 3 days prior to Day 1, in which case they do not need to be repeated) and as clinically indicated.

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

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

[l] Tuberculosis testing is to be performed as needed in line with local practice.

[m] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

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

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

[p] CCI [redacted]

[q] CCI [redacted]

[r] CCI [redacted]

[s] CCI [redacted].

[t] CCI [redacted]

[u] Patients will have baseline scans collected no more than 28 days before the first dose and, ideally, should be performed as close as possible to the first dose. 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 scans must have been obtained within 28 days prior to randomization. RECIST 1.1 assessments will be performed based on local institutional imaging results, using CT/MRI assessments of the chest and abdomen (including the entire liver and both adrenal glands). Additional anatomy

should be imaged based on signs and symptoms of individual patients, including new lesions at follow-up. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of IP treatment initiation). All confirmatory scans should be recorded in the database. For patients who are clinically stable and being treated through radiological progression, the follow-up scan performed after a RECIST 1.1-defined PD should be performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD. For these patients the assessments should continue as indicated here. Special Confirmation of Radiological Progression criteria apply for tumor assessments on the follow-up scan (Appendix F).
Note: If a patient has a delay to an infusion of study drug, the efficacy and CCI should be conducted relative to the date of first dose administration.

Table 2 Schedule of activities for patients who have discontinued study drug or completed treatment with study drug

	Time since last dose of durvalumab								
	Day (± 3)	Months (± 1 week)						12 months and every 3 months (± 2 weeks)	For details, see Section
Evaluation	30	2	3	4	6	8	10		
Physical examination (full)	X								8.2.2
Vital signs	X								8.2.3
Body weight	X	X	X						8.2.3
Pregnancy test [a]	X	As clinically indicated							8.2.1
AE/SAE assessment	X	X	X						8.3
Concomitant medications	X	X	X						6.4
WHO/ECOG PS [b]	At timepoints consistent with tumor assessments; at 30, 60, and 90 days after last dose; and then at initiation of subsequent anticancer therapy								8.2.6
Subsequent anticancer therapy [c,d]	←							→	
Survival status [e]		X	X	X	X	X	X	X	8.1.1
Hematology	X	X	X						8.2.1
Clinical chemistry	X	X	X						8.2.1
Urinalysis	As clinically indicated								8.2.1
TSH (reflex free T3 or free T4) [f]	X	X	X						8.2.1
CCI [redacted]	X	X	X						8.1.2.1, 8.1.2.2, 8.1.2.3, 9.5.2.3
Tumor assessment as per local institutional standard care (RECIST 1.1) [h]	Additional scans to be completed per standard practice post progression. Patients who permanently discontinue IP for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 assessments performed q8w ± 1 week beginning 8 weeks after IP treatment initiation for the first 48 weeks (relative to the first dose) and q12w ± 1 week thereafter until clinical progression/deterioration or RECIST 1.1-defined radiological progression plus one or more additional follow-up scans for confirmation of progression until confirmed radiological progression, the end of study, death, study discontinuation, or Sponsor decision (whichever comes first).								8.1, Appendix F

AE = Adverse event; CT = Computed tomography; eCRF = Electronic case report form; CCI [redacted]

CCI [redacted]; IP = Investigational product; IV = Intravenous; MRI = Magnetic resonance imaging; NSCLC = Non-small cell lung cancer; PD = Progressive disease; CCI [redacted]; CCI [redacted]; q8w, q12w = Every 8, 12 weeks, respectively; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = Serious adverse event; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid-stimulating hormone; WHO/ECOG PS = World Health Organization/Eastern Cooperative Oncology Group Performance Status.

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

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

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

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

[e] Patients who decline to return to the site for evaluations should be contacted by telephone as an alternative. In addition to the regularly scheduled survival follow-up, patients may be contacted or the patient's family, or by contact with the patient's current physician in the week following data cutoff to confirm survival status. Every effort should be made to contact patients by telephone to follow and record survival status.

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

[g] CCI [redacted].

[h] Only for patients yet to progress, RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands). Additional anatomy should be image-based on signs and symptoms of individual patients. For patients who are clinically stable and being treated through radiological progression, the follow-up scan performed after a RECIST 1.1-defined PD should be performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD; special Confirmation of Radiological Progression criteria apply for tumor assessments on the follow-up scan (Appendix F). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. The modality of tumor assessment should be the same throughout the study.

1.2 Synopsis

International Coordinating Investigator

PPD

Fondazione IRCCS Policlinico San Matteo
Viale Camillo Golgi 19
Pavia, Italy

Protocol title:

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)

Rationale:

Durvalumab (MEDI4736) is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of programmed cell death ligand 1 (PD-L1) (but not programmed cell death ligand-2) with programmed cell death receptor (PD-1) on T cells and cluster of differentiation (CD)80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. Results of early studies with durvalumab in advanced cancers are consistent with a class effect of early and sustained tumor control that has been observed previously with other inhibitors of the immune-checkpoint pathway. As radiation therapy is known to upregulate PD-L1, using durvalumab subsequent to radiation therapy could potentially provide better clinical outcomes in this population. 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. The main goal of this study is to evaluate the safety and tolerability of maintenance treatment with durvalumab following radiation therapy in this population.

Objective	Endpoint/variable
Primary objective	
To assess the safety and tolerability profile of durvalumab as defined by Grade 3 and Grade 4 PRAEs within 6 months from the initiation of durvalumab treatment	Grade 3 and Grade 4 PRAEs
Secondary objectives	
To assess the efficacy of durvalumab treatment in terms of PFS and OS	Median PFS according to 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 ORR and DoR	ORR according to RECIST 1.1 as assessed by the Investigator
	DoR according to RECIST 1.1 as assessed by the Investigator
To assess the efficacy of durvalumab treatment in terms of lung cancer mortality	Lung cancer mortality
To further assess the safety and tolerability profile of durvalumab treatment, including all AEs	AEs, SAEs, AESIs, imAEs, physical examinations, vital signs including BP, pulse, ECGs, and laboratory findings including clinical chemistry, hematology, and urinalysis
Exploratory objectives	
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

Objective	Endpoint/variable
CCI	CCI

AE = Adverse event; AESI = Adverse event of special interest; BP = blood pressure; DoR = Duration of response; CTCAE = Common Terminology Criteria for Adverse Event; CCI ECG = Electrocardiogram; CCI CCI d CCI CCI ; imAE = Immune-mediated adverse events; IP = Investigational product; NCI = National Cancer Institute; ORR = Objective response rate; OS = Overall survival; OS12 = Proportion of patients alive at 12 months from first date of treatment; CCI PFS = Progression-free survival; PFS6, PFS12 = Progression-free survival at 6, 12 months, respectively; CCI ; CCI ; PRAE = Possibly related adverse event; CCI ; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = Serious adverse event; TL = Target lesion; CCI .
Note: Toxicities will be classified as per CTCAE grading system NCI CTCAE version 5.0. Analysis of ORR and DoR will be based upon Investigator assessment according to RECIST 1.1. Prior irradiated lesions may be considered measurable and selected as TLs providing they fulfill the other criteria for measurability.
Note: An AESI is an AE of scientific and medical interest specific to understanding of the IP. AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy.

Overall design

This is a Phase II open-label, single-arm, multicenter, international study to evaluate the clinical activity of durvalumab in patients with Stage III unresectable NSCLC who are deemed to be ineligible for chemotherapy per Investigator assessment.

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]). This study will be conducted in Europe and North America.

Study period

Estimated date of first patient enrolled: Q2 2020

Estimated date of last patient completed: Q2 2023

Number of patients

Approximately 102 patients are being treated with durvalumab in this study 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.

Approximately 148 patients are screened to achieve 102 patients treated with durvalumab and 60 evaluable patients.

Note: "Screened" means a patient's or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential patients who are screened for the purpose of determining eligibility for the study, but are not randomized/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Treatments and treatment duration

All patients will receive 1500 mg durvalumab via intravenous (IV) infusion every 4 weeks (q4w) for 12 months (13 doses/cycles). The last administration of durvalumab will be on week 48 unless there is clinical progression, confirmed radiological progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. (Please note: 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 resume the fixed-dosing of durvalumab 1500 mg q4w).

Progression during treatment

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined progressive disease (PD) may continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is to be collected after the initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the Confirmation of Radiological Progression criteria. Patients with confirmed PD who continue to receive durvalumab at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment for the remainder of the 12-month treatment period, and tumor assessments should continue on their regular imaging schedule for the duration of treatment.

Follow-up of patients after discontinuation of study drug

Patients who have discontinued study treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy, will be followed up for adverse events (AEs) and with PRO-questionnaires for 90 days after investigational product (IP) discontinuation, and thereafter followed up with tumor assessments until

RECIST 1.1-defined radiological PD plus an additional follow-up scan or until death (whichever comes first).

Survival

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, as per the SoA.

Steering Committee

If required, a Steering Committee (SC) will be assembled by AstraZeneca for the executive oversight and supervision of the study. The SC will consist of oncology experts and a statistician who serve their role through regular scheduled meetings or teleconferences and, if necessary, additional ad hoc meetings. Details of the SC remit, procedures, processes, and meeting frequency will be outlined in an SC Charter.

Interim analysis

No formal interim analyses are planned for this study.

Statistical methods

The primary objective of this study is to assess the safety and tolerability of durvalumab which is defined as Grade 3 and Grade 4 possibly related adverse events (PRAEs), as assessed by the Investigator, 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).

Safety data will be summarized descriptively overall, by seriousness, by causality and by maximum National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade. The exact 95% confidence intervals (CIs) around the incidence of Grade 3 and Grade 4 PRAEs will be reported for patients overall and separately for each cohort.

The median PFS, median OS, and median time to NSCLC-related death, together with their corresponding 95% CIs, will be calculated using Kaplan-Meier product limit methods. The proportion of patients who are progression-free at 6 and 12 months and the proportion of patients who are alive at 12 months will be presented. In addition, the objective response rate (ORR), based on Investigator assessments, together with the corresponding 95% CIs will be reported.

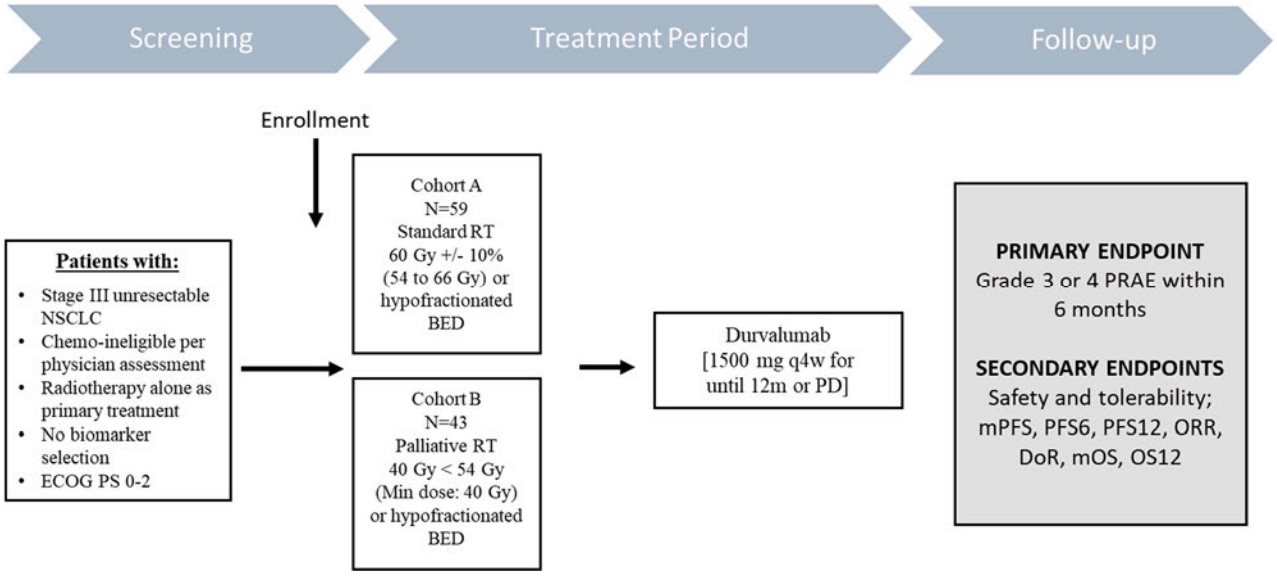
A total of approximately 102 patients are treated with the study drug in 2 cohorts: approximately 59 patients in the Standard Radiotherapy Cohort and approximately 43 patients in the Palliative Radiotherapy Cohort. It is estimated that a sample size of a minimum 60 patients would be required to provide 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, 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.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



BED = bioequivalent dose; DoR = Duration of response; Durva = durvalumab; 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

2 INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades, and by 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total)

(GLOBOCAN 2012). NSCLC represents approximately 80% to 85% of all lung cancers and 30% of patients present with Stage III disease. Standard treatment for patients with a good performance status (PS) and unresectable Stage III NSCLC had been platinum-based doublet chemotherapy and radiotherapy administered concurrently with cCRT. A meta-analysis of concurrent versus sequential CRT demonstrated better outcomes with concurrent therapy, but even with cCRT, 5-year OS ranges between 15% and 32% (Antonia et al 2017, Aupérin et al 2010).

More recently, the PACIFIC Study (D4191C00001) demonstrated that the addition of durvalumab as sequential therapy to platinum-based CRT significantly improves PFS (median PFS 17.2 months with durvalumab compared to 5.6 months with placebo, hazard ratio [HR] of 0.51) and OS (HR of 0.68) (Antonia et al 2018). Given the potential for further clinical benefit, the Sponsor is currently evaluating the efficacy and safety of durvalumab given concurrently with platinum-based CRT in patients with locally-advanced, unresectable NSCLC (Stage III) in PACIFIC2 (D933KC00001).

However, a significant proportion of patients with Stage III unresectable NSCLC are ineligible for chemotherapy for a number of reasons, including comorbidities, poor PS, or elderly age; these patients are therefore faced with fewer treatment options. A common regimen for these patients is radiotherapy alone; however, it is associated with disappointing results in terms of OS (Driessen et al 2016; Miller et al 2018). Using durvalumab subsequent to radiation therapy could potentially provide better clinical outcomes in this population.

2.1 Study rationale

Over the last decade, there has been an increasing interest in studying the therapeutic potential of immune therapy for different types of tumors. In particular, nonclinical and clinical studies have indicated that blockade of immune checkpoints can have a positive effect on antitumor immunity.

Results of early studies with durvalumab in advanced cancers are consistent with a class effect of early and sustained tumor control that has been observed previously with other inhibitors of the immune-checkpoint pathway. A consistent observation across these studies is the long durability of benefits with immune-checkpoint inhibitors. However, not all patients benefit from immune-checkpoint inhibitors as monotherapy. Hence, studies that follow established treatments (such as radiation therapy) with immune-checkpoint inhibitors are needed in order to expand the patient population who might benefit from immune-checkpoint inhibitors.

Radiation has been shown to induce immunogenic cell death. Cell death enhances the ability of the immune system to recognize and respond to the tumor through enhanced antigen release and presentation (tumor specific T-cell activation; Formenti and Demaria 2013, Weichselbaum et al 2017). In addition, ionizing radiation causes upregulation of various proinflammatory

signals and cytokines, which play a key role in immune regulatory pathway, leading to improved antitumor immunity. Twyman-Saint Victor et al also showed that radiation enhanced the diversity of the T-cell receptor repertoire of intratumoral T cells (Twyman-Saint Victor et al 2015). Additionally, radiotherapy has been shown to upregulate the expression of PD-L1 (Butts et al 2014, Deng et al 2014, Zhang et al 2008b), and therefore may confer greater sensitivity to PD-L1-directed therapy.

2.2 Background

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

2.2.1 Immunotherapies

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

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

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pazdur 2008, Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells, leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous antitumor activity.

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

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of nonclinical and clinical studies of mAbs targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Antonia et al 2017, Antonia et al 2018, ASTRO 2017, Aupérin et al 2010, Basch et al 2009, Bergman et al 1994, Herdman et al 2011, Hirano et al 2005, IASLC 2016, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012,Zhang et al 2008a) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Pickard et al 2007, Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition high mutational burden (eg, in bladder carcinoma; Aaronson et al 1993, Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

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

2.2.2 Durvalumab

Durvalumab is a human mAb of the IgG1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (IFN-γ) (Sprangers and Aaronson 1992, Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Sprangers and Aaronson 1992, Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 5000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1 and Section 8.3.12. Refer to the current durvalumab IB for a complete summary of nonclinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

2.3 Benefit/risk assessment

The majority of the safety and efficacy data currently available for durvalumab are based on the first-in-human, single-agent study (Study CD-ON-MEDI4736-1108; hereafter referred to as Study 1108) in patients with advanced solid tumors, the study of durvalumab monotherapy in NSCLC (ATLANTIC Study [NCT02087423]), the study of durvalumab monotherapy in NSCLC following completion of platinum-based chemotherapy concurrent with radiation therapy (PACIFIC Study [NCT02125461]), and the study of durvalumab with or without tremelimumab as first line treatment for patients with advanced or metastatic NSCLC (MYSTIC Study [NCT02453282]). Data from these studies have demonstrated clinical activity of durvalumab therapy in patients with NSCLC. Details pertaining these studies are provided in the current durvalumab IB.

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

2.3.1 Potential benefits

The efficacy of durvalumab was evaluated in the Phase III PACIFIC Study, a multi-center, randomized, double-blind, placebo-controlled study in patients with unresectable Stage III NSCLC who completed at least 2 cycles of concurrent platinum-based chemotherapy and definitive radiation within 42 days prior to initiation of the study drug and had a World Health Organization (WHO) PS 0 or 1 (Antonia et al 2017, Antonia et al 2018). A total of 713 patients were randomized 2:1 to receive durvalumab 10 mg/kg or placebo intravenously every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed RECIST 1.1-defined progression. The prespecified interim PFS analysis based on 81% of total planned events demonstrated a statistically significant improvement in PFS of 16.8 months (95% CI: 13.0, 18.1) with durvalumab versus 5.6 months (95% CI: 4.6, 7.8) with placebo (stratified HR: 0.52; 95% CI: 0.42, 0.65; $p < 0.001$). The PFS benefit in favor of durvalumab was observed irrespective of PD-L1 expression before CRT (PD-L1 expression < 25%, HR: 0.59; 95% CI: 0.43, 0.82; PD-L1 expression ≥ 25%, HR: 0.41; 95% CI: 0.26, 0.65). The response rate was higher with durvalumab than with placebo (28.4% versus 16.0%; $p < 0.001$), and the median duration of response (DoR) was longer (72.8% versus 46.8% of the patients had an ongoing response at 18 months).

As of the time of the PACIFIC OS analysis, the median time to death or distant metastasis was 28.3 months in the durvalumab group and 16.2 months in the placebo group (stratified HR, 0.53;

95% CI, 0.41 to 0.68) (Antonia et al 2018). The 24-month OS rate was 66.3% (95% CI, 61.7 to 70.4) in the durvalumab group, as compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided P 0.005). As of 31 January 2019 (third data cutoff [DCO]), 3-year data demonstrated a durvalumab survival benefit over placebo that was consistent with the OS primary analysis, with a 31% reduction in the risk of death (HR: 0.69; 95% CI, 0.55 to 0.86). The Kaplan-Meier estimate of the median OS was 29.1 months in the placebo group, while it was not yet reached in the durvalumab group. The 12-, 24-, and 36-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively (Gray et al 2019).

2.3.2 Overall risks

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

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

2.3.2.1 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus, and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillian-Barre syndrome, myasthenia gravis).

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

In monotherapy clinical studies, AEs at an incidence of > 20% include events such as fatigue, cough, decreased appetite, dyspnea, and nausea. Approximately 10% of patients discontinued the drug due to an AE. In the PACIFIC Study in patients with Stage III NSCLC following cCRT, AEs (all causality) experienced during the study with an incidence of > 10% (durvalumab vs

placebo) were cough (35.4% vs 25.2%); fatigue (23.8% vs 20.5%); dyspnea (22.3% vs 23.9%); radiation pneumonitis (20.2% vs 15.4%); diarrhea (18.3% vs 18.8%); pyrexia (14.7% vs 9%); decreased appetite (14.3% vs 12.8%); nausea (13.9% vs 13.2%); pneumonia (13.1% vs 7.7%); pneumonitis (12.6% vs 7.7%); arthralgia (12.4% vs 11.1%); pruritus, rash and upper respiratory tract infection (12.2% each vs 4.7%, 7.3% and 9.8%, respectively); constipation (11.8% vs 8.5%); hypothyroidism (11.6% vs 1.7%); headache (10.9% vs 9.0%); asthenia (10.7% vs 13.2%); and back pain (10.5% vs 11.5%). Combined events of pneumonitis or radiation pneumonitis occurred in 33.9% vs 24.8% of patients, including CTCAE Grade 3 pneumonitis or radiation pneumonitis in 3.4% vs 2.6% of patients; no patients in either treatment group reported Grade 4 events of pneumonitis or radiation pneumonitis.

Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and CTCAE Grade 3 to 5 events reported across the durvalumab program.

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

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

2.3.3 Overall benefit/risk

The clinical activity associated with potentiating the proinflammatory effects of radiation therapy suggests that giving durvalumab following radiation therapy may have clinical benefits, including increasing the response rate to radiation therapy.

The safety of durvalumab following radiation therapy is further supported by results from the PACIFIC Study, which showed that durvalumab administered within 42 days of completion of CRT had a well tolerated and manageable safety profile that was consistent with the established safety profile to date. It is therefore reasonable to assume that immunotherapy administered within 42 days of completion of radiation therapy will also be well tolerated.

Therefore, the overall benefit-risk assessment supports the proposed study to evaluate the efficacy and safety of administration of durvalumab following radiation therapy.

3 OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints/variables are listed in Table 3.

Table 3 Study objectives and endpoints

Objective	Endpoint/variable
Primary objective	
To assess the safety and tolerability profile of durvalumab as defined by Grade 3 and Grade 4 PRAEs within 6 months from the initiation of durvalumab treatment	Grade 3 and Grade 4 PRAEs
Secondary objectives	
To assess the efficacy of durvalumab treatment in terms of PFS and OS	Median PFS according to 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 ORR and DoR	ORR according to RECIST 1.1 as assessed by the Investigator
	DoR according to RECIST 1.1 as assessed by the Investigator
To assess the efficacy of durvalumab treatment in terms of lung cancer mortality	Lung cancer mortality
To further assess the safety and tolerability profile of durvalumab treatment, including all AEs	AEs, SAEs, AESIs, imAEs, physical examinations, vital signs including BP, pulse, ECGs, and laboratory findings including clinical chemistry, hematology, and urinalysis
Exploratory objectives	
CCI	CCI CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

AE = Adverse event; AESI = Adverse event of special interest; BP = blood pressure; DoR = Duration of response; CTCAE = Common Terminology Criteria for Adverse Event; CCI ; ECG = Electrocardiogram; CCI
CCI

CCI CCI ;
imAE = Immune-mediated adverse events; IP = Investigational product; NCI = National Cancer Institute; ORR = Objective response rate; OS = Overall survival; OS12 = Proportion of patients alive at 12 months from first date of treatment; CCI ; PFS = Progression-free survival; PFS6, PFS12 = Progression-free survival at 6, 12 months, respectively; CCI ; CCI PRAE = Possibly related adverse event; CCI ; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = Serious adverse event; TL = Target lesion; CCI .

Note: Toxicities will be classified as per CTCAE grading system NCI CTCAE version 5.0. Analysis of ORR and DoR will be based upon Investigator assessment according to RECIST 1.1. Prior irradiated lesions may be considered measurable and selected as TLs providing they fulfill the other criteria for measurability.

Note: An AESI is an AE of scientific and medical interest specific to understanding of the IP. AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. Please refer to Section 8.3.12 for AESI definition.

4 STUDY DESIGN

4.1 Overall 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 Eastern Cooperative Oncology Group (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 the dose of radiotherapy received prior to study entry (Cohort A: Standard Radiotherapy [60 Gy ± 10% or hypofractionated BED]; Cohort B: Palliative Radiotherapy [40 to < 54 Gy or hypofractionated BED]).

Approximately 150 patients will be treated with the study drug in Europe and North America. Patients will be in CR, PR, or have 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 IP dose administration. The last dose of radiation therapy is defined as the day of the last radiation treatment session.

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

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

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

Patients will receive study treatment for 12 months or until RECIST 1.1-defined radiological progression by Investigator unless there is evidence of an unacceptable toxicity, or if the patient requests to stop the study treatment. See Section 6.1.3 for detailed criteria.

Patients who have discontinued study treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy, will be followed up for AEs and with PRO-questionnaires for 90 days after study treatment discontinuation, and thereafter followed up with tumor assessments until RECIST 1.1-defined radiological PD plus an additional follow-up scan or until death (whichever comes first).

4.2 Scientific rationale for study design

4.2.1 Rationale for safety endpoints

This study is designed to evaluate the safety of durvalumab monotherapy, using a fixed-dosing regimen, in unresectable Stage III NSCLC patients who are ineligible for chemotherapy and who have not progressed following radiation therapy. This study is designed to complement and expand the safety database from the ongoing Phase III PACIFIC Study and PACIFIC-5 Study (NCT03706690) and the ongoing Phase II PACIFIC-6 Study (NCT03693300). Given the potential for radiotherapy to increase the likelihood of anti-PD-L1–mediated pneumonitis, a need for additional safety data on the use of durvalumab under this context exists, including in the sub-population of WHO/ECOG PS 2 patients, who have not been representatively included in pivotal studies.

In the PACIFIC Study, the majority of imAEs with durvalumab occurred during the first 6 months of treatment (see the current version of the durvalumab IB). This timing is consistent with published literature using anti-PD-1 or anti-CTLA-4 agents, which indicates that most of the imAEs occur within 3 to 6 months of the initiation of treatment (Topalian et al 2012, Weber et al 2017). This study will assess the safety of durvalumab within the first 6 months of treatment as defined by Grade 3 and Grade 4 PRAEs, including the evaluation of the nature of toxicities (SAEs, AEs, Adverse Events of Special Interest [AESIs], imAEs), interventions and treatment, and outcome of treatment.

4.2.2 Rationale for efficacy endpoints

The secondary aim of this study is to determine the efficacy of durvalumab 1500 mg q4w in terms of ORR, PFS, and OS. PFS has been found to be correlated with OS in previous CRT studies (Mauguen et al 2013). Although the OS benefit has exceeded the PFS benefit in other studies of immune-checkpoint inhibitors in advanced-stage NSCLC (Borghaei et al 2015), there are certain settings in which the utility of survival as an endpoint may potentially be confounded by subsequent therapies. Specifically, there are currently a number of molecules targeting the

PD-1/PD-L1 pathway in late-stage development for the treatment of first-, second-, and/or third-line metastatic NSCLC. It is anticipated that these agents may be approved or become available for use through expanded-access programs or additional clinical studies while this study is ongoing. This poses challenges in being able to fully characterize effects on OS if patients subsequently receive these immunotherapeutic agents.

Antitumor activity will be assessed according to RECIST 1.1 guidelines, with the understanding that in the context of postradiation changes, tumor assessment may be difficult and may need to be repeated over time to reach a clear determination regarding responses and PD (see Section 8.1). The tumor-based efficacy analyses will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria. PFS will be programmatically derived from Investigators' tumor data from all scans based upon RECIST 1.1.

4.2.3 Rationale for other study exploratory endpoints

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.2.4 Rationale for treatment duration

Treatment in this study will continue for 12 months or until RECIST 1.1-defined PD and Investigator determination that the patient is no longer benefiting from treatment with IP, or until another discontinuation criterion is met (see Section 7.1). This guidance is supported by data from the PACIFIC Study, in which patients were treated for up to 12 months with durvalumab, and no new safety signals were observed after 6 months of treatment (Antonia et al 2017). The median duration of treatment in the PACIFIC Study was 40.1 weeks (range, 1 to 54) in the durvalumab group, suggesting that durvalubab treatment was tolerable in this patient population (Antonia et al 2018). Numerous Phase III studies are currently evaluating durvalumab treatment until PD for patients with a variety of malignancies. Although the results of these studies are not yet available, no new safety signals have been identified as a result of the longer duration. In order to balance the patient burden associated with monthly visits until disease progression with the potential for additional clinical benefit with prolonged treatment duration, durvalumab will be administered for 12 months in this study.

4.2.5 Timing of treatment with durvalumab relative to prior radiation therapy

Nonclinical data show that ionizing radiation up-regulates PD-L1 expression (Deng et al 2014, Zhang et al 2008b). In addition, radiotherapy releases new antigens leaving the cancer to act as an in situ vaccine that can elicit tumor-specific T cells. Thus, starting durvalumab as close as possible to the completion of radiation therapy, when antigen release and PD-L1 expression are most likely to be at their maximum, will hopefully result in the most optimal benefit. The timing for durvalumab treatment initiation will be aligned with what has been tested in the PACIFIC Study (ie, 42 days after the end of cCRT).

4.3 Justification for dose

This study will use a fixed dose for durvalumab treatment (1500 mg q4w IV). Based on an average body weight of 75 kg, a fixed dose of 1500 mg of durvalumab q4w is equivalent to a weight-based dose of 20 mg/kg q4w.

4.3.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, nonclinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108) in patients with advanced solid tumors and from a phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

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

A population PK model was developed using the data from Study 1108 (doses = 0.1 to 10 mg/kg q2w or 15 mg/kg q3w; EuroQoL 2013, Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by area under the plasma concentration versus time curve at steady state (4 weeks). Median peak drug concentration at steady state is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median trough drug concentration at steady state is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen

is anticipated to be consistent with 10 mg/kg q2w with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of antidrug antibody impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

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

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg q4w regimen.

4.3.2 Rationale for fixed-dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N = 292; doses = 0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight -based (10 mg/kg q2w) and fixed-dosing (750 mg q2w) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight -based and fixed-dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed-dosing regimen.

Similar findings have been reported by others (Litwin et al 1998, Mauguen et al 2013, Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed-dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed-dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed-dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed-dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to 20 mg/kg q4w) is included in the current study.

4.4 End of study definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under Food and Drug Administration and European regulatory requirements:

- European Union requirements define study completion as the last visit of the last subject for any protocol related activity.
- Food and Drug Administration requirements defines two completion dates:
  - Primary Completion Date – the date that the final patient is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.
  - Study Completion Date – the date the final patient is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (eg, last patient's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

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

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

In the event that a rollover or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The rollover or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new ICF.

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

At the DCO, the clinical study database will close to new data. However, patients will be permitted to continue to receive durvalumab beyond the closure of the database for the remainder of the 12-month treatment period if, in the opinion of the Investigator, they are continuing to receive benefit from durvalumab (refer to Section 6.1.3 for details on patient management following the final DCO as well as following study completion). For patients who do continue to receive durvalumab beyond the time of the DCO, Investigators will continue to report all AEs and SAEs to AstraZeneca Patient Safety until 90 days after durvalumab is discontinued, in accordance with Section 8.4.1. If an Investigator learns of any SAEs, including death, at any time

after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the study drug, the Investigator should notify AstraZeneca Patient Safety. Any SAE or nonserious AE ongoing at the time of this DCO is to be followed up at the discretion of the Investigator and per local practice and in alignment with the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1), unless the event is considered by the Investigator to be unlikely to resolve or the patient is lost to follow-up.

5 STUDY POPULATION

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to receive IP treatment. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who sign informed consent.

For procedures for withdrawal of incorrectly enrolled patients see Section 5.5.

5.1 Inclusion criteria

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

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2 Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses.

3 Provision of signed and dated written genetic ICF prior to collection of sample for genetic analysis (optional).

The ICF process is described in Appendix A 3.

Age

4 Age ≥ 18 years at the time of screening.

Type of patient and disease characteristics

5 Histologically- or cytologically-documented NSCLC with locally-advanced, unresectable Stage III disease (according to the 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.

6 Deemed ineligible for chemotherapy per Investigator assessment (eg, comorbidities, poor PS, etc).

7 Receipt of radiation therapy that was completed within 42 days prior to first IP dose administration in the study.

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%.

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.

(d) Patients with WHO/ECOG PS 2 or chronic lung disease (pulmonary emphysema or chronic obstructive pulmonary disease) must have received a V20 < 25%.

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 fulfill the other criteria for measurability.

10 WHO/ECOG PS of ≤ 2.

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.

12 Adequate organ and marrow function as defined below:

- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count ≥ 1.0×10^9/L
- Platelet count ≥ 75×10^9/L
- Serum bilirubin ≤ 1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
- Measured creatinine clearance (CL) > 30 mL/min or calculated CL > 30 mL/min as determined by Cockcroft-Gault (using actual body weight).

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

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

13 Must have a life expectancy of at least 12 weeks.

Weight

14 Body weight > 30 kg at enrollment and first IP dose administration

Sex

15 Male or female

5.2 Exclusion criteria

Medical conditions

1 Patients with locally-advanced NSCLC whose disease has progressed following radiation therapy.

2 Mixed small cell lung cancer and NSCLC histology.

3 History of allogeneic organ transplantation.

4 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

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

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 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

6 History of another primary malignancy except for

- Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of durvalumab and of low potential risk for recurrence
- Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease

7 History of leptomeningeal carcinomatosis

8 History of active primary immunodeficiency

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** (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 (RNA).

10 Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, lymphopenia, and the laboratory values defined in the inclusion criteria

- Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician
- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician

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

Prior/concomitant therapy

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

13 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of durvalumab. Note: Local surgery of isolated lesions for palliative intent is acceptable.

14 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
   - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
   - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
   - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

Prior/concurrent clinical study experience

15 Participation in another clinical study with an IP administered in the last 4 weeks

16 Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study

17 Prior randomization or treatment in a previous durvalumab clinical study regardless of treatment arm assignment

Other exclusions

18 Patients who refuse chemotherapy by their own decision.

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

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

21 Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements

22 Genetics research study (optional):
   - Exclusion criteria for participation in the optional (DNA) genetics research component of the study include:
     - Previous allogeneic bone marrow transplant
     - Nonleukocyte-depleted whole blood transfusion within 120 days of genetic sample collection

5.3 Lifestyle restrictions

The following restrictions apply while the patient is receiving durvalumab and for the specified times before and after:

1 Female patient of childbearing potential
   - Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least one **highly** effective method of contraception (Table 4) from the time of screening throughout the total

duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use a male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

2 Male patients with a female partner of childbearing potential

- Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 4).

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

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

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

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 4. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills

where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 4 Highly effective methods of contraception (< 1% failure rate)

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

[a] This is also considered a hormonal method

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

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

5.4 Patient enrollment

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

Investigators should keep a record (ie, the patient screening log) of patients who entered screening.

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

- Obtain signed informed consent before any study specific procedures are performed. If laboratory or 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 laboratory and imaging results must have been obtained within 28 days of the first dose, with the exception of PFTs, which must have been obtained within 8 weeks of study enrollment.

- Obtain a unique 7-digit enrollment number (E-code), through the IVRS/IWRS in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
- Determine patient eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional).

Patients will begin treatment on Day 1. Patients must not be treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrollment code cannot be reused. Withdrawn patients will not be replaced.

5.5 Procedures for handling incorrectly enrolled patients

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

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

5.6 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be dosed. These patients should have the reason for study withdrawal recorded as "screen failure" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not dosed patients). Patients may be rescreened a single time, but they may not be re-assigned IP treatment. If a patient who has failed screening is rescreened, a new E-code must be assigned. Patients will reconfirm their consent to participate in the study by re-signing and dating their original consent form(s), next to their initial signature and date.

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

6 STUDY TREATMENTS AND CONCOMITANT THERAPY

Study treatments are all pre-specified, IPs and NIPs, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study patients during the study conduct. Study treatment in this study refers to durvalumab monotherapy.

6.1 Treatments administered

AstraZeneca will supply durvalumab. Details of study treatment are described in Table 5. Dose modifications are described in Section 6.5.

Table 5 Study Treatment

	Durvaluamab
Study treatment name:	Durvalumab
Type:	Biologic
Dosage formulation: [a]	500-mg vial solution for infusion after dilution, 50 mg/mL
Unit dose strength:	500 mg (50 mg/mL)
Route of administration:	IV infusion
Use:	Experimental
IP and NIP:	IP
DosageRegimen: [b]	1500 mg; 20 mg/kg in patients who weigh ≤ 30 kg; q4w [c]
Packaging and labeling:	Study treatment will be provided in 500 mg vials. Each vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirement. [d]
Sourcing:	AstraZeneca

GMP = Good Manufacturing Practice; IP – investigational procuct; IV = Intravenous; NIP = non-investigational product; q4w = Every 4 weeks.

Note: Cycles of durvalumab are 28 days.

[a] Refer to Section 6.1.1.1 for detailed formulation and preparation instructions for durvalumab.

[b] Detailed instructions for durvalumab administration are provided below. Refer to Section 6.1.1.1 for details on duration of treatment.

[c] 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 until the weight improves to > 30 kg, at which point the patient should start receiving the fixed-dosing of durvalumab 1500 mg q4w.

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

6.1.1.1 Durvalumab

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The label-claim volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product should be kept in original packaging until use to prevent prolonged light exposure.

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated durvalumab manager using aseptic technique and following local practices and site requirements. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

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

A dose of 1500 mg (for patients > 30 kg in weight) will be administered using an IV bag containing 0.9% sodium chloride for injection or 5% dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL (ie, 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% sodium chloride for injection or 5% dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

The use of elastometric pumps and use of a pneumatic tube for transport of either a vial or a final prepared product have not been studied; please contact AstraZeneca before using.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered. Infusion time does not include the final flush time.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours otherwise a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded immediately after use.

6.1.2 Dose and treatment regimens

6.1.2.1 Durvalumab monotherapy

All patients will receive 1500 mg durvalumab via IV infusion q4w for 12 months (13 doses/cycles), starting on Week 0. 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. See Figure 2. (Please note, 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 durvalumab infusion time is 1 hour ± 10 minutes; however, if there are interruptions, the total allowed time must not exceed 8 hours with the infusion back maintained at room temperature, otherwise a new dose must be prepared from new vials.

Figure 2 Durvalumab monotherapy dosing schedule

	Durvalumab 1500 mg dose q4w					
	↓	↓	↓	↓	↓	↓
Cycle	1	2	3	4	5 to 13 or PD[a] (12 months)	
Week	0-3	4-7	8-11	12-15	q4w ± 3 days until 48 weeks	

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

[a] Or until discontinuation of study drug due to any of the reasons listed in Section 7.1.

6.1.3 Duration of treatment and criteria for treatment through progression

Treatment will be administered beginning on Day 1 for 12 months for durvalumab monotherapy or until clinical progression or RECIST 1.1-defined radiological progression (refer to Appendix F) unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive study treatment at the discretion of the Investigator and patient as long as they are deemed to be receiving clinical benefit. A follow-up scan is to be collected after the initial RECIST 1.1-defined PD, 4-8 weeks after the prior assessment of PD; this follow-up scan is evaluated using the post-progression evaluation criteria outlined in Appendix F. Patients with confirmed PD who continue to receive durvalumab at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment for the remainder of the 12-month treatment period, and image acquisitions and tumor assessments should continue on their regular imaging schedule for the duration of treatment.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible for continuing durvalumab.

For all patients who are treated through progression, the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient must not have experienced a toxicity that required permanent discontinuation of study treatment.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG PS to > 2.
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.
- The patient still fulfills the eligibility criteria for this study (see Section 5.1 and 5.2) with the exception of inclusion criteria 9, 11, and 14 and exclusion criterion 17.
- Patient agrees to re-consenting to be treated through progression.

Patients will not be permitted to continue treatment with durvalumab if progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) in the TLs (regardless of the appearance of new lesions) (ie, the response and progression events both occurred in the TL while receiving durvalumab).

Patients who AstraZeneca and the Investigator determine may not continue treatment after RECIST 1.1-defined PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up with tumor assessments until RECIST 1.1-defined PD plus an additional follow-up scan or until death (whichever comes first) and followed for survival (refer to Section 7.1.2).

Treatment after final overall survival data cutoff

At the time of the DCO, the analysis portion of the clinical study will have been completed and all patients remaining in the study will be considered to have completed the analysis portion of the study. At the time of DCO, the clinical study database will be closed to new data.

Patients in OS follow-up (progressed and have discontinued treatment) will be considered to have completed the study.

Patients who are receiving treatment at the time of DCO may continue receiving IP until 12 months if the Investigator judges that they are gaining clinical benefit.

All patients will receive efficacy scans and follow-up care in accordance with standard local clinical practice. Data should be recorded on patient charts but will not otherwise be reported for the purposes of this study.

For patients who are continuing to receive treatment with durvalumab following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1).

Following the DCO, SAE reporting applies only to patients who are active on IP and within 90 days after the last dose; in all other cases, only a Statement of Death notification is to be sent to AstraZeneca. No OS data will be recorded in the study database after DCO for the study. Investigators will report SAEs to AstraZeneca Patient Safety via paper case report forms (CRFs) until 90 days after the last dose of study drug, in accordance with Section 8.4.1. Any SAE or nonserious AE ongoing at the time of the DCO is to be followed up at the discretion of the Investigator and per local practice and in alignment with the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1), unless the event is considered by the Investigator to be unlikely to resolve, or the patient is lost to follow-up. Data will not be captured for the purposes of this study outside of being recorded in the patients' source documents.

Different drug supply options will be available depending on the country, and these will be proposed to the patient when the most appropriate alternatives for continued treatment have been agreed between AZ and the Investigator. Options may include the participation in a new rollover study or, if the study drug has been locally approved for use in this disease indication, patients may be discontinued and switched to the marketed product, in accordance with local laws. In the event that a rollover or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The rollover or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new ICF.

Continued Access to Study treatment

As described in Section 4.4, the study will remain open until all patients have discontinued study treatment and completed their last expected visit/contact.

Before the study reaches the final DCO, AstraZeneca will continue to supply durvalumab to patients who were enrolled to receive durvalumab until completion of a patient's current 12-month treatment period or until meeting any other discontinuation criteria, as defined in Section 7.1. Patients should be followed according to the institution's standard of care

assessments. No further data collection is required, except for reporting of AEs and SAEs, however drug dispensation data may be collected in electronic data capture (EDC).

AstraZeneca can continue to supply durvalumab in the continued access phase of this study and after completion of the 12-month treatment period while, in the opinion of the Investigator, the patient is benefiting from durvalumab therapy.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the patient(s) to alternative supply, where possible.

6.1.4 Storage

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

6.2 Measures to minimize bias: randomization and blinding

Not applicable.

6.3 Treatment compliance

The administration of durvalumab should be recorded in the appropriate sections of the eCRF.

Any change from the dosing schedule, dose interruptions, and dose discontinuations should be recorded in the eCRF.

Treatment compliance will be ensured by reconciliation of site drug accountability logs.

The IP Storage Manager is responsible for managing the durvalumab from receipt by the study site until the destruction or return of all unused durvalumab.

6.4 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including the follow-up period following the last dose of study drug.

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

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

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

Restricted, prohibited, and permitted concomitant medications are described in Table 6 and Table 7. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1).

Table 6 Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on-study treatment.
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on-study treatment.
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on-study treatment. (Concurrent use of hormones for noncancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding TLs, for palliative intent is acceptable [eg, by local surgery or radiotherapy]).
Live attenuated vaccines	Should not be given through 30 days after the last dose of durvalumab.

Prohibited medication/class of drug:	**Usage:**
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	• Should not be given concomitantly, or used for premedication prior to the I-O infusions The following are allowed exceptions: • Use of immunosuppressive medications for the management of durvalumab-related AEs • Use in patients with contrast allergies In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of nonimmunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
EGFR TKIs	• Should not be given concomitantly • Should be used with caution in the 90 days post-last dose of durvalumab Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor.

AE = adverse event; CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4; EGFR = epidermal growth factor receptor; mAB = monoclonal antibody; PD-1 = programmed cell death receptor ; PD-L1 = programmed cell death ligand 1; TKI = tyrosine kinase inhibitor; TL = target lesion.

Table 7 Supportive medications

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

NTL = nontarget lesion.

6.4.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

6.4.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either nonclinically or in patients. As durvalumab is a monoclonal antibody and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions. The MOA of durvalumab involves binding to PD-L1, and therefore significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

6.4.3 Rescue medication

As a result of imAEs that could potentially be experienced by patients on durvalumab, steroids, and other immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if countries cannot source rescue medications locally or if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy related

toxicities. These rescue medications must be receipted, controlled, and administered by the pharmacist and stored according to the labeled storage conditions, with temperature excursions reported accordingly by the pharmacist.

6.5 Dose modification

Dose delays are permitted for durvalumab (see Dosing Modification and Toxicity Management Guidelines in Section 8.4.5.1). However, dose reduction is not permitted.

6.6 Treatment after the end of the study

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving durvalumab up to completion of a patient's 12-month treatment period (see Section 6.1.3).

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

An individual patient will not receive any further treatment (durvalumab) if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1)
- Pregnancy or intent to become pregnant
- Noncompliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Clinical progression or confirmed radiological progression (refer to Appendix F) and Investigator determination that the patient is no longer benefiting from treatment with IP.

7.1.1 Follow-up of patients post discontinuation of study treatment

All patients who discontinue the study treatment will be followed up for safety assessments (AEs) and with CCI [redacted] 90 days after their last dose of study treatment and for

survival follow-up. Additional assessments to be performed at the time of the 90-day safety follow-up are detailed in the SoA (Table 2).

Patients who have discontinued study treatment prior to objective RECIST 1.1-defined radiological progression will be followed up with tumor assessments according to the SoA (Table 2) until RECIST 1.1-defined PD or death, regardless of whether or not the patient started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

Subsequent anticancer therapy (including radiation therapy) will be assessed and recorded from the end of treatment with study treatment through the safety and survival follow-up period or until death for patients who have discontinued study treatment, including at PD.

7.1.2 Follow-up for survival

Patients will be followed up for survival status as indicated in the SoA (Table 2) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. Additional assessments, including subsequent anticancer therapy, are to be recorded at the time of survival follow-up and are detailed in the SoA (Table 2).

7.1.3 Procedures for discontinuation of study treatment

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

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see the SoAs in Table 1 and Table 2).

Patients who permanently discontinue drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed every 8 weeks (q8w) ± 1 w for the first 48 weeks (relative to the date of the first dose), and then every 12 weeks ± 1 w thereafter until RECIST 1.1-defined radiological PD plus an additional follow-up scan or death (whichever comes first) as defined the SoAs (Table 1 and Table 2).

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

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

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the SoAs (Table 1 and Table 2) as an alternative.

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

7.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow-up."

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

7.3 Withdrawal from the study

Patients are free to withdraw from the study at any time (treatment and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further durvalumab or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to

survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1 and Table 2).

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

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

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

Adherence to the study design requirements, including those specified in the SoA (Table 1 and Table 2), is essential and required for study conduct.

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

Procedures conducted as part of the patient's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1 and Table 2).

8.1 Efficacy assessments

The key efficacy endpoints are: median PFS; proportion of patients progression-free at 6 and 12 months (PFS6 and PFS12, respectively); median OS; proportion of patients alive at

12 months (OS12); and median time to NSCLC-related death, from first IP dose administration; ORR and DoR. Efficacy assessments of PFS, ORR, and DoR will be derived (by AstraZeneca) using Investigator assessments according to RECIST 1.1.

Tumor assessments utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands) collected during screening/baseline and at regular (follow-up) intervals during study treatment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. It is important to follow the tumor assessment schedule as closely as possible (refer to Table 1 and Table 2). If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Treatment continues for 12 months or until disease progression (clinical progression/deterioration ± radiological progression by RECIST 1.1), and scanning/tumor assessments continue throughout treatment. An additional follow-up scan is requested following progression if clinically feasible.

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

For all patients who are treated through progression, a follow-up scan is to be collected after the initial RECIST 1.1-defined PD, 4-8 weeks after the prior assessment of PD; this follow-up scan is evaluated using the post-progression criteria outlined in Appendix F. If the subsequent scan confirms the immediate prior radiological PD, no additional scans are required unless the patient is allowed to continue study treatment; however, if the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST 1.1-defined PD which in turn will require a subsequent scan evaluated using the post-progression criteria outlined in Appendix F.

8.1.1 Survival assessments

Assessments for survival must be made as shown in Table 2. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

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

8.1.2 Clinical outcome assessments

A Clinical Outcome Assessment (COA) is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. COAs can be reported by patients (PRO), clinicians (ClinRo), or observers (ObsRo).

CCI

The following PROs will be collected as detailed in SoA (Table 1, Table 2): CCI

CCI

8.1.2.1 CCI

CCI

CCI

8.1.2.2 CCI

CCI

CCI

8.1.2.3 CCI

CCI

CCI

8.1.2.4 CCI

CCI

CCI

CCI

- CCI
- CCI
- CCI
- CCI

- CCI
- CCI
- CCI
- CCI
- CCI

CCI

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 and Table 2).

8.2.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs in Table 1 and Table 2).

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

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

The laboratory variables to be measured are presented in Table 8 (clinical chemistry), Table 9 (hematology), and Table 10 (urinalysis).

Other safety tests to be performed at screening include assessment for HBsAg, hepatitis C antibodies, HIV antibodies. Tuberculosis testing is to be performed at screening in line with local practice.

The following laboratory variables will be measured:

Table 8 Clinical chemistry

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥ 2 × upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only one of these parameters is routinely measured, either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.

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

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

Table 9 Hematology

Absolute neutrophil count [a]	Absolute lymphocyte count[a]
Hemoglobin	Platelet count
Total white cell count	Coagulation

Note: For coagulation parameters, activated partial thromboplastin time (either as a ratio or as an absolute value in seconds) and international normalized ratio are to be assessed at baseline on Cycle 1 Day 1 and as clinically indicated.

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by Statistical Programming if entered as percentage. Total white cell count therefore has to be provided.

Table 10 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis should be done at baseline (screening) and then as clinically indicated.

Note: Microscopy is preferred to investigate white blood cells and the high power field should be used for red and white blood cells; dipstick can be used as well.

If a patient shows an AST or ALT ≥ 3 × ULN together with total bilirubin (TBL) ≥ 2 × ULN, refer to Appendix E for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

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

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

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

8.2.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at 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.

8.2.3 Vital signs

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

First infusion

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

BP, pulse, temperature, and respiration rate will be collected from patients before, during, and after the first infusion at the following times (based on a 60-minute infusion):

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

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

Subsequent infusions

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

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

8.2.4 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study (see the SoAs). 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.

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

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

8.2.5 Early patient review for safety

Patients should be contacted 2 weeks (± 1 day) after receiving the first 3 cycles of durvalumab monotherapy (Cycle 1 Day 14 ± 1, Cycle 2 Day 14 ± 1, and Cycle 3 Day 14 ± 1) of study drug(s) to ensure early identification and management of toxicities.

8.2.6 World Health Organization/Eastern Cooperative Oncology Group performance status

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

0 Fully active; able to carry out all usual activities without restrictions

1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)

2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5 Dead

Any significant change from baseline or screening must be reported as an AE.

8.2.7 Other safety assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (interstitial lung disease) investigation

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

- Physical examination

  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc) including auscultation for lung field will be assessed
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    (ii) Tumor markers: Particular tumor markers which are related to disease progression.
    (iii) Additional clinical chemistry: C-reactive protein (CRP), lactate dehydrogenase (LDH)

Pulmonary function testing

At screening, pulmonary function will be assessed by measurement of forced expiratory volume.

8.3 Collection of adverse events

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

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

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

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

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

AEs and SAEs will be collected from the time of the patient signing the ICF until 90 days after the last dose of durvalumab. If an event that starts after the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study drug, then it should be reported as an AE or SAE as applicable.

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

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

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs, SAEs, and AESIs (as defined in Section 8.3.12) will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 90 days after the last dose of durvalumab), but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

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

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

- Date the AE met criteria for SAE

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would be an SAE if it satisfies the criteria shown in Appendix B 2.

8.3.5 Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol (CSP).

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: “Have you had any health problems since the previous visit/you were last asked?”, or revealed by observation will be collected and recorded in the CRF. When collecting

AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory tests and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

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

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

8.3.8 Hy's Law

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

8.3.9 Disease progression

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

8.3.10 New malignancies

AEs for malignant tumors reported during a study should generally be assessed as serious AEs. If no other seriousness criteria apply, the "important medical event" criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a nonserious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as nonserious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is not the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

8.3.11 Deaths

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

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the coinvolvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow-up period and the event

is considered to be due to a late onset toxicity to study drug then it should also be reported as an SAE.

8.3.12 Adverse events of special interest

An AESI is one of scientific and medical interest specific to understanding of the IP and may require close monitoring. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

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

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

AESI/imAEs observed with anti-PD-L/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye and skin, hematological, and rheumatological events, vasculitis, noninfectious meningitis, and noninfectious encephalitis. It is possible that events with an inflammatory or immune-related mechanism could occur in nearly all organs.

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 8.4.5.1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of

his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

8.3.13 Safety data to be collected following the final DCO of the study

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5.1). All data after the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

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

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Prompt notification by the Investigator to AstraZeneca of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent IECs, and Investigators.

For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.All SAEs must be reported, whether or not considered causally related to the IP. All SAEs will be recorded in the CRF.

If any SAE occurs during the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the Investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

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

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca unless the pregnancy is discovered before the study patient has received any study drug.

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

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

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

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

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

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

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

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

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of durvalumab monotherapy should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees/IRB prior to use.

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

8.4.3 Reporting of Overdose

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

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

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

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

8.4.4 Medication Error, Drug Abuse, and Drug Misuse

8.4.4.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **one** (Initial Fatal/Life-Threatening or Follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.3.2) and **within 30 days** for all other events.

8.4.4.2 Medication Error

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

The definition of a medication error can be found in Appendix B 8.

8.4.4.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 8.

8.4.4.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study patient) of IP or AstraZeneca NIP for medicinal purposes outside of the authorised product information, or for unauthorised IPs or AstraZeneca NIPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 8.

8.4.5 Management of IP-related toxicities

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

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

All toxicities will be graded according to NCI CTCAE, Version 5.0.

8.4.5.1 Specific toxicity management and dose modification information – durvalumab

Comprehensive toxicity management guidelines (TMGs) have been developed to assist Investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitor, durvalumab (PD-L1 inhibitor). Given the similar underlying mechanisms of toxicities observed with these 2 compounds, these guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when durvalumab is used alone or in combination and is administered concurrently or sequentially with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents) as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and nonimmune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or in combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised, however, to use local practice guidelines and consult local references for the management of toxicities observed with other anticancer treatment.

The most current version of the TMGs entitled, “Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune-Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy),” and is provided to the investigative site as an Annex document and is maintained within the Site Master File. In addition, a current version of TMGs is available

through the following link: https://tmg.azirae.com. Please contact the clinical study associate for information on how to gain access to this website.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune-related. In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 of this protocol and the TMGs). Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and TMGs. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy by the reporting Investigator.

8.5 Pharmacokinetics

Not applicable.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

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9 STATISTICAL CONSIDERATIONS

9.1 Statistical considerations

All statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be prepared and finalized within 3 months of the first enrolled patient and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data. The aim of the study is to assess the safety and tolerability of durvalumab after radiotherapy with standard radiation therapy [60 Gy ± 10%] or hypofractionated BED or palliative radiation therapy [40 to < 54◦Gy]) or hypofractionated BED.

9.2 Sample size estimate

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 11.

Table 11 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)

AE = adverse event; CI = confidence interval; n = number of patients; PRAE = possibly related adverse event; RT = radiation therapy.

9.3 Definitions of analysis sets

All analyses will be performed on the safety analysis set.

9.3.1 Safety analysis set

The safety analysis set will consist of all patients who received at least one dose of study treatment. Safety and efficacy data will be summarized using the safety analysis set.

9.4 Outcome measures for analyses

1 **AE:** Number and proportion of patients with AEs in total and by causality and severity

2 **AE:** Number and proportion of patients with Grade 3 and Grade 4 AEs in total and by causality

3 **SAE:** Number and proportion of patients with SAEs in total and by causality and severity

4 **AEs leading to death:** Number and proportion of patients with AEs leading to death

5 **AEs leading to treatment interruption or discontinuation:** Number and proportion of patients with AEs leading to treatment interruption and/or discontinuation

6 **AESI:** Defined as an AE of scientific and medical interest specific to understanding of the IP. AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. In order to further characterize safety objectives related to AESIs, outcome measures will be assessed, which may include (and are not necessarily limited to) the following:

   (a) Number and proportion of patients with AESIs, by predefined type (or newly defined by this study) in total and by seriousness, severity and causality, including immune-relatedness;

(b) Number and proportion of patients who received steroids, immunosuppressants, and/or hormone replacement therapy to manage AESIs;

(c) Time from start of durvalumab to the onset of an AESI predefined type, all interventions of AESIs by type of intervention (including intervention with steroids, immunosuppressants, and/or hormone replacement therapy), and time from onset of an AESI type to resolution;

(d) Duration of the intervention with steroids, immunosuppressants, and/or hormone replacement therapy until the resolution of AESI;

(e) The imAEs will be assessed as a subset of AESIs. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA and where there is no clear alternate etiology.

(f) Laboratory findings, vital signs, and other safety parameters associated with AESIs will be summarized as part of the AESI outcome measures.

7 **PFS:** Defined as the time from the first date of treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from IP or receives another anticancer therapy prior to progression.

8 PFS (days) = Date of event or Censor date – treatment start date + 1

9 Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable assessment prior to the 2 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.

10 **OS:** Defined as the time from the first date of treatment until death due to any cause.

11 **OS (days) =** Death date or Censor date - treatment start date + 1

12 Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

13 Lung cancer mortality (NSCLC-related death): Defined as the time from the date of treatment start until death due to lung cancer.

Time to NSCLC-related deaths (days) = NSCLC-related death date or Censor date - treatment start date + 1

Any patient not known to have died due to lung cancer will be censored based on the last recorded date on which the patient was known to be alive or died due to reason other than lung cancer.

14 **ORR**: Based on Investigator−assessed response to treatment of CR and PR, per RECIST1.1.

15 **DoR**: Defined as the time from the date of first documented response per RECIST1.1 until the first date of documented progression per RECIST1.1 or death in the absence of disease progression.

16 DoR (days) = Date of PFS event or censoring – Date of first response + 1

17 The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a patient does not progress following a response, then the patients' DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have a documented response.

18 CCI

19 CCI

20 **Treatment duration:** Defined as Treatment end date - Treatment start date + 1; will be summarized.

In addition, demographics, medical history, comorbidities, diagnosis (eg, stage and histology), and prior therapeutic management of NSCLC will be reported. Specific details of planned analyses will be described in the SAP.

9.5 Statistical analyses

Descriptive statistics will be used for all variables. Continuous variables will be summarized by the number of observations (n), mean, standard deviation, median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.

For all summaries of AEs, only treatment-emergent AEs will be included. Treatment-emergent AEs are defined as events present at baseline that worsen in intensity after administration of IP or events absent at baseline that emerge after administration of IP, for the period extending to 90 days after the last dose of IP. Baseline will be the last assessment of the variable under consideration prior to the first IP dose administration.

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 data from this analysis would be published to support the real-world use of durvalumab.

9.5.1 Analysis of the primary variable

Safety data will be summarized descriptively overall, by seriousness, by causality, and by maximum NCI CTCAE Grade. The exact 95% CIs around the incidence of Grade 3 and Grade 4 PRAEs will be reported for patients overall and separately for each cohort.

9.5.2 Analysis of the secondary variables

9.5.2.1 Safety variables

Adverse events

Total SAEs, AESIs, AEs leading to death, and AEs leading to study drug interruption or discontinuation will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term, causality, and maximum NCI CTCAE Grade. Deaths from all causes will be also summarized.

Data from all cycles of will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred term and CTCAE Grade) will be listed individually by patient. Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of IP may be included in the AE summaries, but the majority of the AE summaries will omit the AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any AE that occurs after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

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

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the first IP dose administration.

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

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

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

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

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

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a predose and at least one postdose value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable, the patient need only have one postdose value recorded.

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

9.5.2.2 Efficacy variables

Efficacy data will be reported for patients overall and separately for the cohorts of Standard Radiotherapy and Palliative Radiotherapy whenever possible.

Progression-free survival

The median PFS together with the corresponding 95% CIs will be reported using Kaplan-Meier product limit methods. In addition, the proportion of patients who are progression-free at 6 and 12 months will be presented.

Overall survival

The median OS together with the corresponding 95% CIs will be reported using the Kaplan-Meier product limit methods. In addition, the proportion of patients who are alive at 12 months will be reported.

Lung cancer mortality (NSCLC-related deaths)

The median time to NSCLC-related death together with the corresponding 95% CIs will be reported using the Kaplan-Meier product limit methods.

Objective response rate

The ORR, based on Investigator assessments (following RECIST 1.1 criteria; see Appendix F), together with the corresponding 95% CIs will be reported.

Duration of response

The average DoR will also be calculated for responders. If appropriate, CIs will be used to characterize the precision of the estimate.

9.5.2.3 Patient-reported outcomes

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Table 13 CCI

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SUBGROUP ANALYSIS

Summaries for endpoints of interest by subgroup will be detailed in the SAP.

9.6 Interim analysis

No formal interim analysis is planned for this study.

9.6.1 Steering committee

If required, a SC will be assembled by AstraZeneca for the executive oversight and supervision of the study. The SC will consist of oncology experts and a statistician who serve their role through regular scheduled meetings or teleconferences and, if necessary, additional ad hoc meetings. Details of the SC remit, procedures, processes, and meeting frequency will be outlined in an SC Charter.

9.7 Data management by AstraZeneca or delegate

Data management will be performed by a Contract Research Organization according to the Data Management Plan.

Any data collected through third party sources will be obtained and reconciled against study data. Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process. When all data have been coded, validated, signed, and locked, clean file will be declared, and the final database will be locked.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical, and study oversight considerations

A 1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal obligations and ethical obligations are met.

- A “serious breach” means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical trial.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority , IRB/IEC, and Investigators.

- Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

The investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient's partner becomes pregnant during or within 90 days after the last dose of durvalumab, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Patients will be assigned a unique identifier by AstraZeneca. Any patient records or datasets that are transferred to AstraZeneca will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

- The patient must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.
- The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The patient must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities

and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

- The patient must be informed that in some cases their data may be pseudonymised. The General data Protection Regultaion defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and
- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).

- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to patients:

- Notification to patients is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the patients. The site and/or Principal Investigator shall conduct the notification by contacting the patients using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to patients. If the personal data breach needs to be notified to the patients, the notification to patients is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the patients.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the patients. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the patients. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the patients. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and patients, where applicable.

A 5 Committee structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on *http://astrazenecaclinicaltrials.com* and *http://www.clinicaltrials.gov* as will the summary of the *main* study results when they are available. The clinical study and/or summary of *main* study results may also be available on other websites according to the regulations of the countries in which the *main* study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval

of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event (AE) is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of serious adverse events

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical treatment to prevent one of the outcomes listed above

AEs for malignant tumors reported during a study should generally be assessed as serious. If no other seriousness criteria apply, the ‘important medical event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a nonserious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as nonserious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is not the tumor for which entry into the study is a criterion and that is

being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

B 3 Life-threatening

"Life-threatening" means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 CTCAE Grade

The grading scales found in the revised National Cancer Institute CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the criteria recommended in the CTCAE manual that converts severity levels into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A guide to interpreting the causality question

When making an assessment of causality consider the following factors when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related."

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication error, Drug Abuse, and Drug Misuse

Medication Error

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

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong patient received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to patient (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IP or AstraZeneca NIP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the data entry site using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study patient or if the drug abuse involves a person not enrolled in the study (such as a relative of the study patient).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study patient or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of IP or AstraZeneca NIP for medicinal purposes outside of the authorised product information, or for unauthorised IPs or AstraZeneca NIPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the data entry site using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study patient or if the drug misuse regards a person not enrolled in the study (such as a relative of the study patient).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person

- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study patient feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

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Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1).

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's law criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol (CSP).

E 4.2 Potential Hy's law criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Appendix E 6).
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL (meeting serious criteria for "important medical event") with causality assessment "yes/related" according to CSP process for SAE reporting
- For patients that met PHL criteria prior to starting study treatment, the Investigator is not required to submit a PHL SAE unless there is a significant change# in the patient's condition
- The Study Physician will contact the Investigator to provide guidance, discuss, and agree on an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
  - Complete the follow-up SAE Form as required
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
  - Complete the 3 Liver eCRF Modules as information becomes available

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and assessment of potential Hy's law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the Study Physician will contact the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study treatment, and to ensure timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria was met. The AZ Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an SAE: update the previously submitted PHL SAE eCRF accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study treatment:

- Send updated SAE (report term 'Hy's Law') according to AZ standard processes.
  - The "important medical event" serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. In this case, the Investigator will follow the instructions below:

- Provide any further update to the previously submitted SAE of PHL (report term now 'Hy's Law case'), ensuring causality assessment is related to study treatment and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required when potential Hy's law criteria are met before and after starting study treatment

This section is applicable to patients with liver metastases who meet PHL criteria on-study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a **significant change** in the patient's condition[#] compared with the last visit where PHL criteria were met[#].

- If there is no significant change, no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix E 4.2.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 7 Actions required for repeat episodes of potential Hy's law

This section is applicable when a patient meets PHL criteria on-study treatment, and has already met PHL criteria at a previous on-study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease), or did the patient meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix E 6?

If **No**: Follow the process described in Appendix E 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met.

- If there is no significant change, no action is required
- If there is a significant change, follow the process described in Appendix E 4.2 for reporting PHL as an SAE.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

Appendix F Guidelines for evaluation of objective tumor response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for this study with regard to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for determination of Confirmation of Radiological Progression.

Definitions of measurable, nonmeasurable, target, and nontarget lesions

Measurable:

A lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have a short axis[2]diameter of ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

Nonmeasurable:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis diameter at baseline[3])
- Truly nonmeasurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination (manual palpation) that is not measurable by CT or MRI
- Brain metastasis

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered nonmeasurable.

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[2] The short axis is defined as the longest axis perpendicular to long axis

[3] Lymph nodes with < 10 mm short axis diameter are considered nonpathological and should not be recorded or followed as NTLs.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if noncystic lesions are present in the same patient, these should be selected over cystic lesions as TLs.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline. Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

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

Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least ~2 weeks after biopsy, allowing time for healing.

Nontarget lesions (NTLs):

Additional measurable lesions not recorded as TLs and nonmeasurable lesions (or sites of disease) should be identified as NTLs at baseline.

Imaging modalities

A summary of the imaging modalities to be used for RECIST 1.1 assessment of TL, NTL, and new lesions is provided in Table 14.

Table 14 Summary of imaging modalities for tumor assessment

Target Lesions	Nontarget Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan
		FDG-PET/CT

CT = Computed tomography; FDG-PET/CT = ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI = Magnetic resonance imaging.

CT and MRI
CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible anatomical images for measurement of TL, assessment of NTL, and identification of any new lesions.

It is recommended that IV contrast-enhanced CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement (eg, pelvis, brain) should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to intravenous CT contrast, a noncontrast CT examination of the chest and an MRI with intravenous MRI contrast of the abdomen is appropriate. In patients with severely compromised renal function, a noncontrast CT examination of the chest and abdomen is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, and scanner across all imaging time points per patient.

Clinical examination
Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Chest X-ray
Chest X-ray assessment will not be used for assessment of TL. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray
Plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound
Ultrasound examination will not be used for RECIST assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Endoscopy and laparoscopy
Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers
Tumor markers on cytological or histological (biopsy) samples will not be used for tumor response assessments as per RECIST 1.1.

Histology and cytology
Histology on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to new lesions or progression of NTLs, respectively.

Isotopic bone scan
Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan which cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that timepoint.

FDG-PET/CT
^{18}F-Fluoro-deoxyglucose positron emission tomography/CT (FDG-PET/CT) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive FDG uptake[4] not present on baseline or prior FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline or prior FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to verify new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically-based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor

[4] A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed.

measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with intravenous contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

Tumor response evaluation
Schedule of evaluation

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including the entire liver and both adrenal glands) must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient, eg, new lesions at follow-up.

Baseline assessments should be performed no more than 28 days before the first dose, and ideally should be performed as close as possible to the first dose. Efficacy by RECIST 1.1 for all patients will be assessed according to the schedules of activities. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled imaging visits.

Target lesions
Documentation of TLs

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. 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 that can be measured reproducibly should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.

- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, definitive radiotherapy, embolization, surgery, etc during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST case report form. If a TL has been completely removed (surgery), the longest diameter should be recorded as 0 mm.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 15).

Table 15 Evaluation of target lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter 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.
Stable disease (SD)	Neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) – this includes the baseline sum if that is the smallest on-study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg missing anatomy) or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

CR = Complete response; NE = Not Evaluable; PR = Partial response; PD = Progression of disease; SD = Stable disease; TL = Target lesion.

Nontarget lesions
Evaluation of NTLs

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. 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 (see Table 16).

Table 16 Evaluation of nontarget lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be nonpathological in size (< 10 mm short axis).
NonCR/nonPD	Persistence of one or more NTL.
Progression of disease (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.

CR = Complete response; NE = Not Evaluable; NTL = Nontarget lesion; PR = Partial response; PD = Progression of disease; TL = Target lesion.

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

New lesions

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. 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. If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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.

Symptomatic deterioration

Symptomatic (clinical) deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with "symptomatic deterioration" requiring discontinuation of treatment without objective radiologic evidence of disease progression at that time should continue to undergo tumor assessments where clinically feasible.

Evaluation of overall visit response
The overall visit response will be derived using the algorithm shown in Table 17.

Table 17 Overall visit response

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	NonCR/NonPD	No	PR
CR	NE	No	PR
PR	NonPD or NE	No	PR
SD	NonPD or NE	No	SD
NE	NonPD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete response; NA = Not applicable (only relevant if there were no target and/or NTLs at baseline); NE = Not Evaluable; NTL = Nontarget lesion; PD = Progression of disease; PR = Partial response; SD = Stable disease.

Confirmation of Radiological Progression
A follow-up scan is collected after the initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD, and the Confirmation of Radiological Progression criteria described below are applied for tumor assessments of this follow-up scan. Patients with confirmed radiological PD who continue to receive study treatment at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit, and will continue to have tumor assessments on their regular imaging schedule for the duration of treatment.

Confirmation of Radiological Progression guidelines are set for the following reasons:

- For patient management and treatment decisions
- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of PD in order to distinguish pseudoprogression from true radiologic progression.

Confirmation of Radiological Progression criteria:
An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if any of the following criteria are met in the subsequent follow-up scan (acquired preferably at the next regularly scheduled imaging visit but no sooner than 4 weeks after the RECIST 1.1-defined PD scan):

- $\geq$ 20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits, each with an absolute increase of at least 5 mm in sum of diameters compared to nadir (as per RECIST 1.1 definition)
- *and/or* significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint (as per RECIST 1.1 definition)
- *and/or* significant progression (worsening) of pre-existing new lesions at the follow-up scan timepoint compared with the immediate prior timepoint (unique definition)
- *and/or* additional (brand) new unequivocal lesions at the follow-up scan timepoint (as per RECIST 1.1 definition)

NOTE: In order to have confirmed radiological progression, there should be 2 consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the Confirmation of Radiological Progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, in the absence of significant clinical deterioration, then the patient may continue with assessments until the next PD by RECIST 1.1, which will also require a follow-up scan evaluated using the Confirmation of Radiological Progression criteria. **If the first PD (by RECIST 1.1) is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

Specifications for anatomical imaging
These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT scan
CT scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest, abdomen, and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on

signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether noncontrast CT or MRI (enhanced or nonenhanced) should be performed should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of nontarget disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed then CT without IV contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a maximum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

MRI scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies [eg, neck]) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

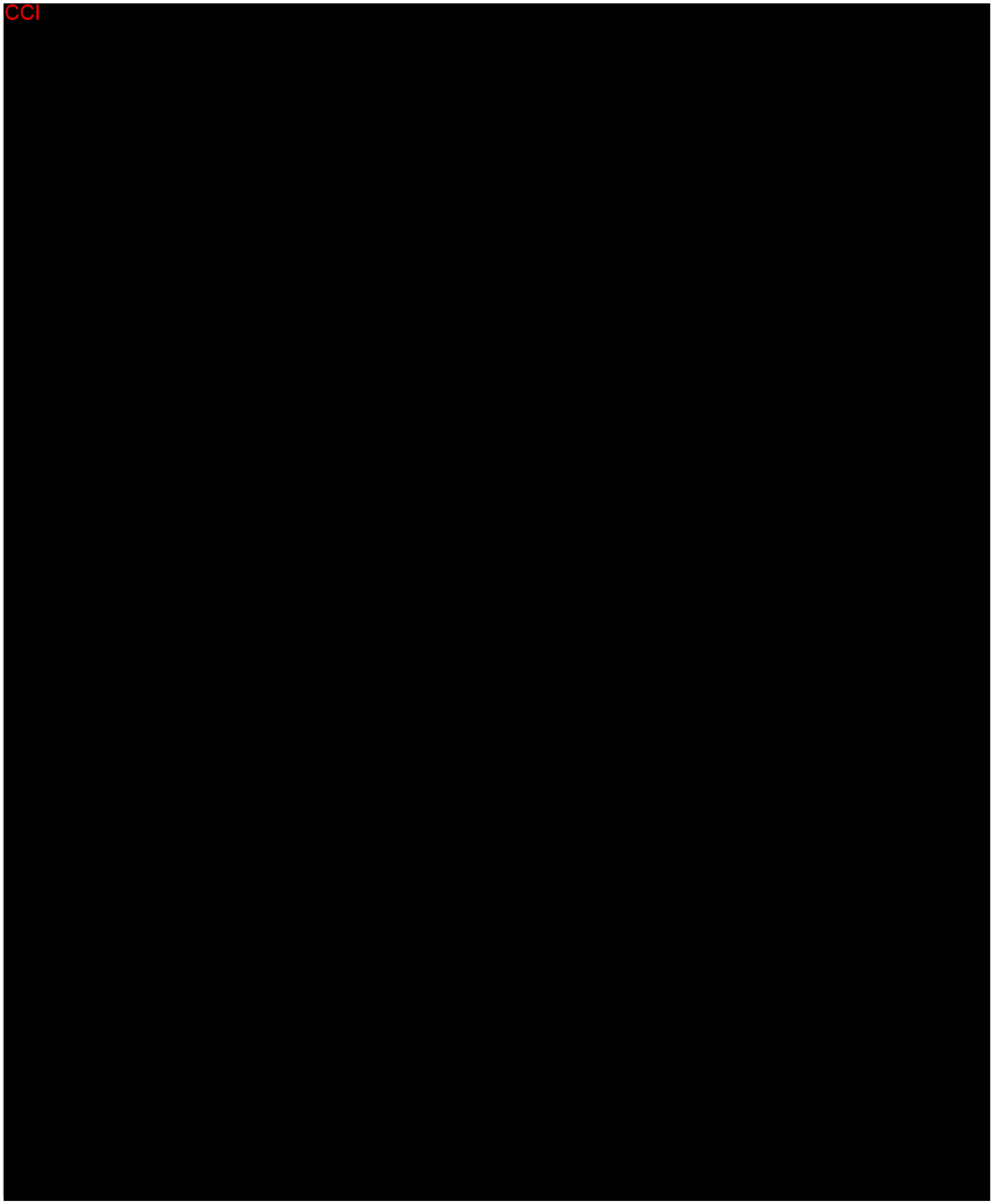
For these reasons, CT is the imaging modality of choice.

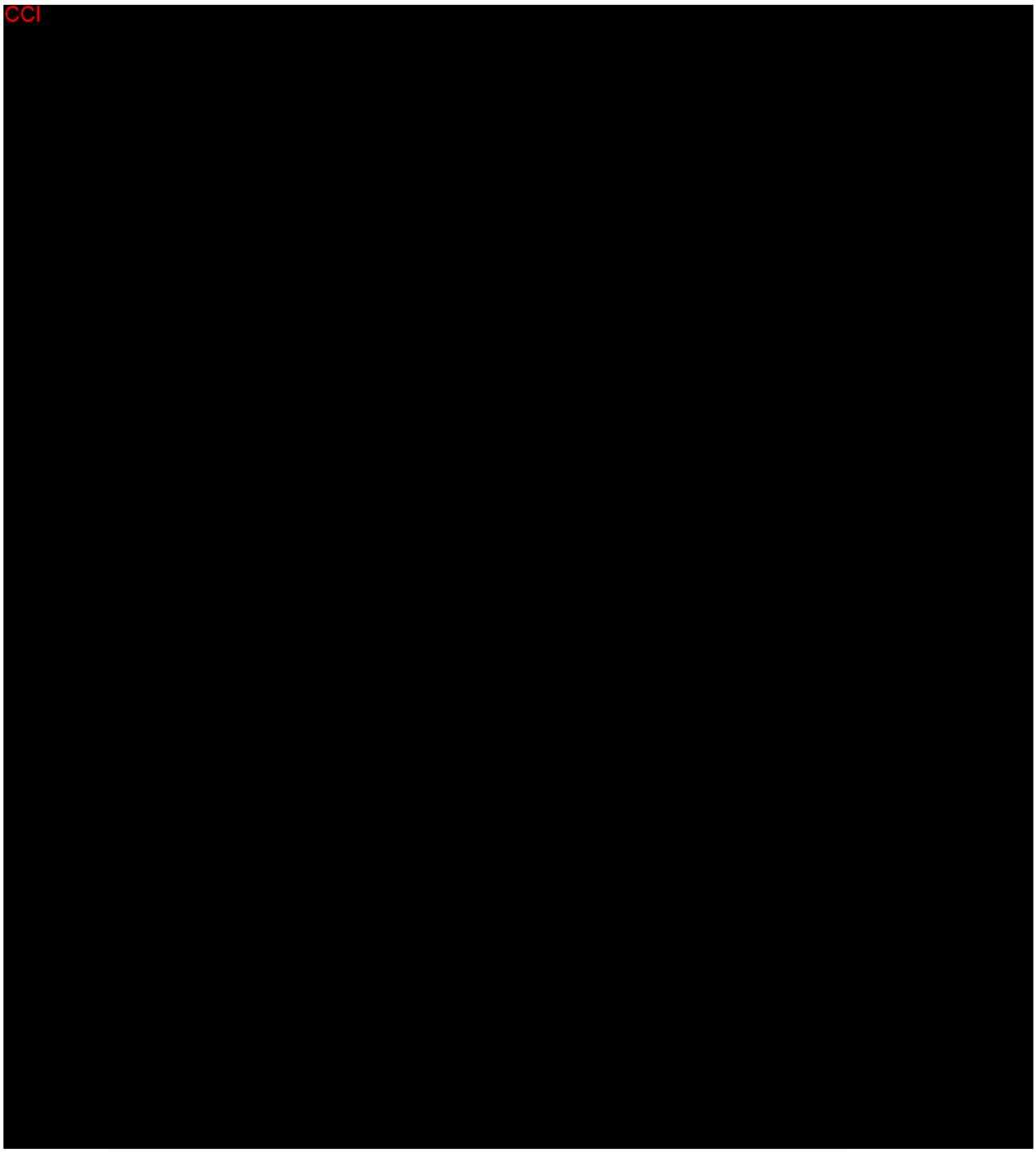
References

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix G CCI

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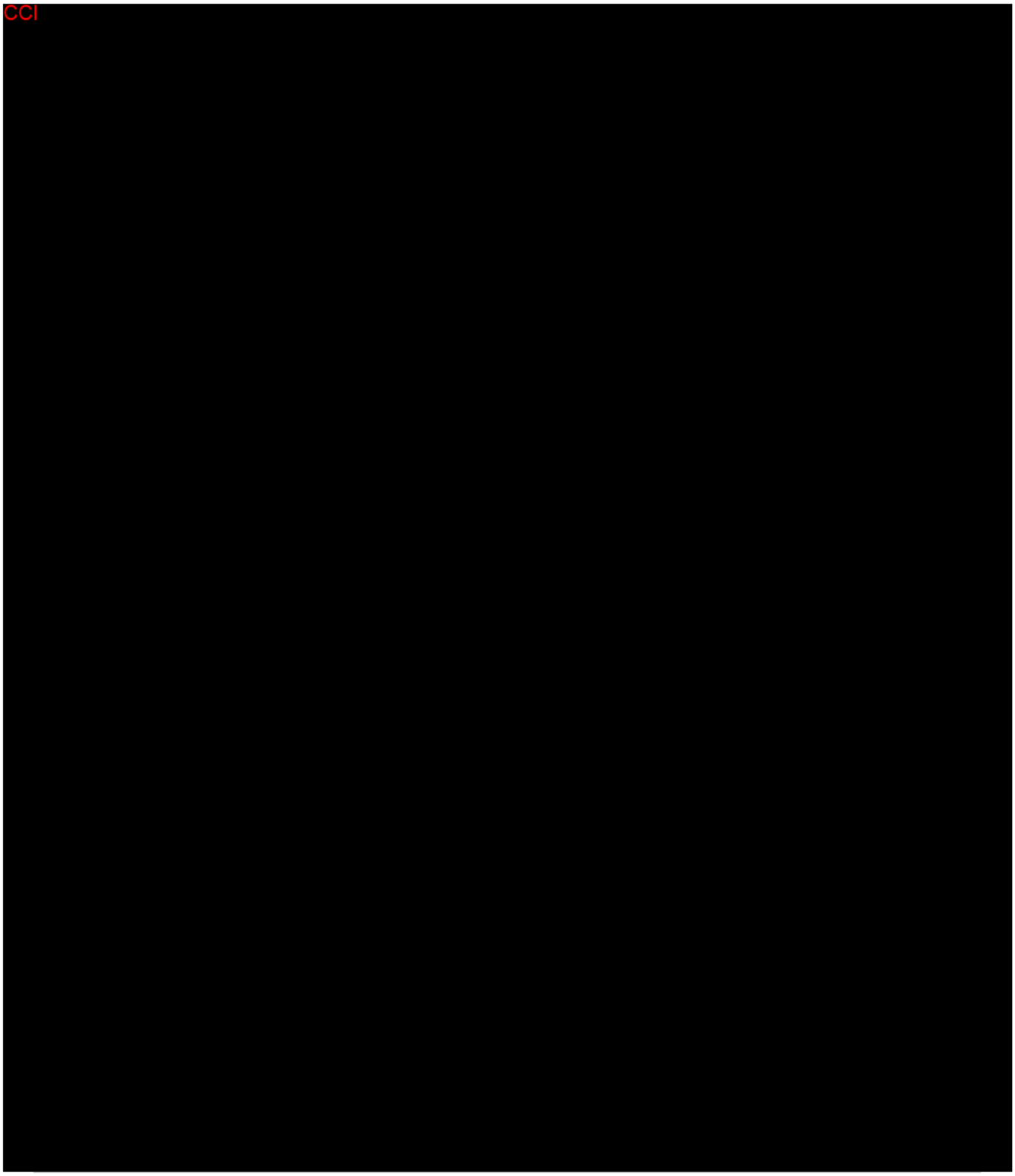
CCI


CCI


CCI

CCI

CCI

Appendix H Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BED	bioequivalent dose
BP	blood pressure
C	cycle
cCRT	concurrent chemotherapy and radiotherapy
CD	cluster of differentiation
CI	confidence interval
CL	clearance
COA	Clinical Outcome Assessment
CR	complete response
CRF	case report form (electronic/paper)
CRP	C-reactive protein
CRT	chemotherapy and radiotherapy
CSP	Clinical Study Protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
CTIS	Clinical Trial Information System
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DCO	data cutoff
DILI	drug induced liver injury
DoR	duration of response
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

eCRF	electronic case report form
EDC	electronic data capture
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
FDG-PET/CT	^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography
GCP	Good Clinical Practice
Gy	gray
CCI	CCI
HBsAg	hepatitus B virus surface antigen
HIV	human immunodeficiency virus
HL	Hy's Law
HR	hazard ratio
HRCT	high-resolution computed tomography
CCI	CCI
IASLC	International Association for the Study of Lung Cancer
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IEC	independent ethics committee, synonymous to IRB
IFN-γ	interferon gamma
IgG	immunoglobulin G
IHC	immunohistochemistry
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IP	Investigational Product
IRB	institutional review board, synonymous to ethics committee (EC) and independent ethics committee (IEC)
IRT	Interactive Response Technology
IV	intravenous
LDH	lactate dehydrogenase
mAb	monoclonal antibody

MOA	mechanism of action
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
NIP	non-investigational product
NSCLC	non-small cell lung cancer
NTL	nontarget lesion
ORR	objective response rate
OS	overall survival
OS12	proportion of patients alive at 12 months from first date of treatment
PD	progressive disease
PD-1	programmed cell death receptor
PD-L1, PD-L2	programmed cell death ligand 1, programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFS6	progression-free survival at 6 months
PFS12	progression-free survival at 12 months
CCI	CCI
CCI	CCI
PHL	potential Hy's law
PK	pharmacokinetics
PR	partial response
PRAE	possibly related adverse event
PRO	patient-reported outcomes
CCI	CCI
PS	performance status
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q8w	every 8 weeks
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid

RT-QPCR	reverse transcription quantitative polymerase chain reaction
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SC	Steering Committee
SD	stable disease
SoA	schedule of activities
sPD-L1	soluble programmed death ligand 1
SPO2	saturation of peripheral oxygen
T4	thyroxine
TBL	total bilirubin
TL	target lesion
TMG	toxicity management guidelines
ULN	upper limit of normal
WHO	World Health Organization

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