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

Clinicaltrials.gov Identifier: NCT03693300

Clinical Study Protocol

Version: 4.0

Date: 06 July 2021

Clinical Study Protocol	
Drug Substance	Durvalumab (MEDI4736)
Study Code	D4194C00006
Version	4.0
Date	06 July 2021

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden
Regulatory Agency Identifying Number(s):
EudraCT Number: 2018-002220-16

VERSION HISTORY

Version 4.0, 06 July 2021
Section 1.1 (Synopsis): Name and contact information of the International Co-ordinating Investigator, PPD PPD, removed (investigator left the study as active investigator).
Section 1.1 (Synopsis), Section 3 (Study objectives), Table 3 footnote: It was clarified that TRAEs and PRAEs are used interchangeably and PRAEs will be reported in the SAP, Tables, Figures, and Listings, and CSR.
Section 1.1 (Synopsis, Study period): The estimated date of first patient enrolled was replaced by the actual date.
Section 1.1 (Synopsis, Treatments and treatment duration), Section 4.1 (Overall design, Figure 2), and Section 6.1.2 (Dose and treatment regimens): It was clarified that treatment for up to a maximum of 24 months is referring to a maximum of 24 months from Cycle 1 Day 1.
Section 1.2 (Schedule of assessments), Table 2, Section 7.1.1: It was clarified that additional scans to be completed per standard practice post progression are not mandatory to be recorded in eCRF.
Section 2 (Introduction): It was added that the PACIFIC Study data also led to the approval of durvalumab (MEDI4736) by the EMA.
Section 2.3.2.1 (Durvalumab [MEDI4736]) risks): The risk language was updated based on the latest AstraZeneca durvalumab protocol template.
Section 4.1 (Overall design, Investigational product, dosage and mode of administration): It was clarified that treatment is for a maximum of 24 months from Cycle 1 Day 1.
Section 4.1.1 (Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis), Appendix H (Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID 19 Outbreak): New Section 4.1.1 and new Appendix H were added based on latest AstraZeneca durvalumab protocol template.
Section 4.3.2 (Rationale for fixed dosing): Reference to US FDA approval for use of durvalumab in urothelial cancer was deleted following the voluntary withdrawal of this conditionally approved indication by AstraZeneca, in consultation and with guidance provided by the FDA.
Section 4.4 (End of study definition): The definition of study completion for a patient and the planned time of the final DCO were added.
Section 4.4 (End of study definition) and Section 6.1.3 (Treatment after the end of the study, Treatment after final overall survival data cut-off): Based on the latest AstraZeneca durvalumab protocol template, it was added that patients may be transitioned to a rollover or safety extension study if such a study is available at the time of end of study treatment, the final DCO / database closure.
Section 6.1.1 (Investigational product, Preparation of durvalumab (MEDI4736) doses for administration with an IV bag) and Section 8.2.3 (Vital signs): A time window of ±10 minutes for the durvalumab infusion time was added based on latest AstraZeneca durvalumab protocol template.
Section 6.1.3 (Treatment after the end of the study, Treatment after final overall survival data cut-off): The misleading sentence that no OS data will be recorded in the study database after DCO was deleted and it was clarified that in this section the DCO is referring to the final DCO.
Section 6.5 (Dose modification): A reference to the Dosing Modification and Toxicity Management Guidelines in the Annex document was added.
Section 8.1.1 (Survival assessments): It was added that patients on treatment or in survival follow-up will be contacted following the DCO to provide complete survival data.

Section 8.1.2.4 (Administration of patient-reported outcome questionnaires): It was added that an appropriate back-up option for the ePRO device used to complete the PRO questionnaires may be considered if technical or other issues prohibit completion on the device. A reference to new Section 4.1.1 (Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis) was added to the general rule that site staff should not read or complete the PRO questionnaires on behalf of the patient.

Section 8.3.13 (Safety data to be collected following the final data cut-off of the study): It was clarified that in this section the DCO is referring to the final DCO.

Section 8.4.1 (Reporting of serious adverse events): The guidance on how to proceed if the WBDC system is unavailable was updated to match the safety handling plan.

Section 8.4.5.1 (Specific toxicity management and dose modification information – Durvalumab and durvalumab + tremelimumab): The reference to the website containing the current Dosing Modification and Toxicity Management Guidelines was removed.

Appendix G (Patient-reported outcomes): It was clarified in a footnote to the CCI questionnaire that initials and full Date of Birth will not be asked from the patient.

Version 3.0, 20 April 2020
Section 1.1 (Synopsis), Section 1.2, Table 1 (SoA), Section 1.3 (Figure 1), Section 4.1 (Overall Design), Section 4.1 (Overall Design) Figure 2, Section 4.2.5 (Timing of treatment with durvalumab (MEDI4736) relative to sequential chemoradiation therapy), Section 5.1 (Inclusion Criteria), Section 9.2 (Sample Size Determination) Table 13: The time window from end of sCRT to first dose of IP was extended from 28 to 42 days.
Section 1.2, Table 1, Footnote d (SoA): A ± 3 days visit window was added for the early toxicity assessment (phone call), due now on C1D14± 3, C2D14± 3, and C3D14± 3, to facilitate site logistics.
Section 1.2, Table 1, Footnote l (SoA): The frequency of on study pregnancy testing was changed from "every 4 weeks" to "prior to every dosing visit (within 3 calendar days prior to dosing in line with other laboratory tests)".
Section 2.3.2.1 (Durvalumab Risks): The risk language was updated based on latest AstraZeneca durvalumab protocol template.
Section 5.1 (Inclusion Criterion 7): Inclusion criterion 7 was amended to supplement guidance on acceptable baseline imaging. It was added that assessment of tumour response should be performed based on the latest scan performed per physician assessment/criteria). If the patient has an intermediate scan between chemotherapy and radiotherapy, this scan should be used as baseline scan provided it fulfils the RECIST-defined CT imaging acquisition parameters.
Section 5.2 (Exclusion Criterion 11, option (a)): It was added to exclusion criterion 11 that patients with ≥Grade 2 lymphopenia will be evaluated on a case-by-case basis after consultation with the Study Physician.
Section 6.1.3 (Duration of Treatment and Criteria for Treatment through Progression and for Retreatment): The language was updated based on the latest AstraZeneca durvalumab protocol template.
Section 8.2.1 (Clinical Safety Laboratory Assessments): The request to collect reference ranges for additional safety samples (collected as clinically indicated) was removed as AstraZeneca standard reference ranges will be used by default.
Section 8.2.2 (Physical Examination): Clarification was made that targeted physical examinations during the treatment cycles are not expected in asymptomatic patients.
Section 8.2.3 (Vital Signs): Clarification that respiratory rate and temperature measurements are part of the vital signs assessments.
Section 8.3.13 (Adverse Events of Special Interest): The language was updated based on latest AstraZeneca durvalumab protocol template.
Section 9.2 (Sample Size Determination): The sample size per cohort was changed: WHO/ECOG PS 0 to 1 cohort from 120 to 100-120 patients and WHO/ECOG PS 2 cohort from 30 to **up to** 30, depending on recruitment.
Section 9.6 (Interim Analysis): It was added that an additional early assessment of study data may be conducted when minimum 50 patients in the WHO/ECOG PS 0 to 1 cohort or WHO/ECOG PS 2 cohort have had the opportunity to receive durvalumab (MEDI4736) for a minimum of 6 months, for publication purposes. The early safety evaluation to be conducted once 10 patients in the WHO/ECOG PS 2 cohort have been treated for a minimum of 6 months or discontinued due to an AE or disease progression remains part of the protocol.
Appendix B2: New language on malignancies/definition of serious adverse events (SAE) was based on latest AstraZeneca durvalumab protocol template.

Version 2.0, 17 July 2019
Section 5.1 (Inclusion criteria): Reference to hepatic metastasis alanine aminotransferase and aspartate aminotransferase limits for patients with hepatic metastases has been removed as patients are required to have non-metastatic disease. **Section 5.1 and 5.2 (Eligibility criteria):** Eligibility criteria have been updated to allow gemcitabine in combination with cisplatin or carboplatin as a prior sCRT treatment, provided there is no overlap between chemotherapy and radiation. **Section 8.1.2.4 (Administration of patient-reported outcome [PRO] questionnaires):** Clarification that PROs should take approximately 15 minutes to be completed and should be completed prior to study procedures. Additional change that patients unable to read PROs are exempt from completing the PROs rather than have the PROs read to them. **Section 8.1.2.5 (Calculation or derivation of patient-reported outcome variables):** Clarification that CCI [redacted] time to symptom/QoL/function deterioration is from the start of study drug until the date of the first clinically meaningful deterioration that is confirmed at the consecutive visit which is at least 14 days apart. **Section 8.2.1 (Haematology safety laboratory assessments):** Clarification of language related to coagulation testing at baseline on Day 1. **Section 8.4.5.1 (Toxicity management related to durvalumab) and Appendix G:** Section has been updated to reflect that Toxicity Management Guidelines (TMGs) are now provided as an Annex to the Protocol. Appendix G has been removed. **Appendix H (now Appendix G; PROs):** The Patient Global Impression of Severity for Cancer Symptoms PRO has been removed as this is not used in this study.

Version 1.0, 16 July 2018
Initial creation

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Rationale:

This study is being conducted to provide safety, efficacy, and quality of life (QoL) data to complement the results of the PACIFIC Study, which assessed treatment with durvalumab (MEDI4736) in patients with unresectable Stage III non-small cell lung cancer (NSCLC) who had not progressed after concurrent chemoradiation therapy (cCRT). Durvalumab (MEDI4736) was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of unresectable Stage III NSCLC in February 2018. This study will expand on the data currently available from the PACIFIC Study by assessing the clinical profile of durvalumab (MEDI4736) in patients who have not progressed after sequential chemoradiation therapy (sCRT), and in patients of World Health Organisation/Eastern Cooperative Oncology Group Performance Status 0 to 1 and 2 (WHO/ECOG PS 0 to 1 and 2).

OBJECTIVE	ENDPOINT/VARIABLE
PRIMARY OBJECTIVE	
To assess the safety and tolerability profile of durvalumab (MEDI4736) as defined by Grade 3 and Grade 4 TRAEs[a] within 6 months from the initiation of durvalumab (MEDI4736) treatment	Grade 3 or Grade 4 TRAEs[a]
SECONDARY OBJECTIVES	
Efficacy objectives	
To assess the efficacy of durvalumab (MEDI4736) treatment in terms of PFS and OS	Median PFS according to RECIST 1.1 as assessed by the Investigator
	Median PFS12 and PFS24 according to RECIST 1.1 as assessed by the Investigator
	Median OS, OS12, OS24, and OS36
To further assess the efficacy of durvalumab (MEDI4736) 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 (MEDI4736) treatment in terms of lung cancer mortality	Lung cancer mortality
Secondary safety objective	

OBJECTIVE	ENDPOINT/VARIABLE
To further assess the safety and tolerability profile of durvalumab (MEDI4736) treatment, including all AEs	AEs, SAEs, AESIs, imAEs, physical examinations, vital signs including BP, pulse, respiratory rate, temperature, ECGs, and laboratory findings including clinical chemistry, haematology and urinalysis
EXPLORATORY OBJECTIVES	
CCI	CCI CCI CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

a. TRAEs and PRAEs are used interchangeably and PRAEs will be reported in the SAP, Tables, Figures, and Listings, and CSR.

Note: Toxicities will be classified as per CTCAE grading system NCI CTCAE version 4.03. Analysis of ORR and DoR will be based upon Investigator assessment according to RECIST 1.1. Prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

Note: An AESI is an AE of scientific and medical interest specific to understanding of the IP. AESIs for durvalumab (MEDI4736) include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy.

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

AE: Adverse event; AESI: Adverse event of special interest; BP: Blood pressure; CCI ; DoR: Duration of response; CSR: Clinical study report; CTCAE: Common Terminology Criteria for Adverse Event; ECG: Electrocardiogram; CCI ; imAE: Immune-mediated adverse event; IP: Investigational product; NCI: National Cancer Institute; ORR: Objective response rate; OS: Overall survival; OS12, OS24, OS36: Proportion of patients alive at 12 months, 24 months, 36 months, respectively, from first date of treatment; PD-L1: Programmed death ligand 1; PFS: Progression-free survival; CCI ; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; PFS: Progression-free survival; PFS12, PFS24: Proportion of patients progression-free at 12 months and 24 months, respectively, from first date of treatment; PRAE: Possibly related adverse event; SAE: Serious adverse event; SAP: Statistical analysis plan; CCI ; TRAE: Treatment-related adverse event; CCI

Overall design:

This is a Phase II, open-label, multi-centre, study to determine the safety of a fixed dose of durvalumab (MEDI4736) (1500 mg) every 4 weeks [q4w] in patients with unresectable Stage III NSCLC, who have not progressed following platinum-based sCRT. This study will be conducted in Europe and North America.

Study period:

Actual date of first patient enrolled quarter Q2 2019.

Estimated date of last patient completed Q2 2023.

Number of patients and patient population:

Up to 150 patients with unresectable Stage III NSCLC will be treated with the study drug. Patients whose disease has not progressed following treatment with platinum-based sCRT will be eligible for this study. Patients must have completed their last dose of radiation therapy within 42 days prior to the first investigational product (IP) dose administration. The last dose of radiation therapy is defined as the day of the last radiation treatment session.

Treatments and treatment duration:

Patients will receive durvalumab (MEDI4736) 1500 mg via intravenous (IV) infusion q4w for a maximum of 24 months from Cycle 1 Day 1. Study drug should be discontinued prior to 24 months if there is confirmed progression of disease (PD) as defined by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) (unless the Investigator considers the patient continues to receive benefit from the study drug and the patient meets the eligibility criteria for treatment beyond progression), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue IP occur.

Tumour assessments

Tumour assessments will be performed as per RECIST 1.1 criteria, using computed tomography (CT)/magnetic resonance imaging (MRI). The baseline assessment is part of the screening procedures and should be performed within 28 days after the end of sCRT and before the start of study drug. Imaging assessment performed according to local standard of care (SoC) within 28 days before the first dose of study drug, but prior to signing the informed consent form (ICF), can be used for screening purposes if the patient consents to the use of those results. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks (q8w) for the first 12 months and every 12 weeks (q12w) thereafter, until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping study drug and/or initiation of subsequent therapy). 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 visits. The schedule of imaging radiological assessments must be followed regardless of any dose delays with durvalumab (MEDI4736).

Progression during treatment

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study drug at the discretion of the Investigator and patient, after re-consenting for treatment through progression. A follow-up scan is to be performed after the initial RECIST 1.1-defined radiological PD, no less than 4 weeks after the prior assessment of PD and no later than the next regularly scheduled imaging visit, and this scan is evaluated using the Confirmation of Radiological Progression Criteria. If the subsequent scan does not confirm the immediate prior radiological PD, then the patient may continue on study drug at the discretion of the Investigator and after the patient has consented to do so; imaging assessments should continue until the next RECIST 1.1-defined PD, which in turn will require a subsequent scan evaluated using the Confirmation of Radiological Progression Criteria.

Follow-up of patients post discontinuation of study drug

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, withdrawal from treatment, or patients who have started a subsequent anticancer therapy, will be followed up for adverse events (AEs) and with patient-reported outcomes (PRO) questionnaires for 90 days after the last dose of IP, and thereafter followed up with tumour assessments until RECIST 1.1-defined radiological PD plus an additional follow-up scan or until death (whichever comes first).

Overall survival

All patients in the study should be followed up for survival every 12 weeks until death, withdrawal of consent, or the end of the study.

Steering Committee

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.

Interim analysis

No formal interim analysis is planned for this study. However, the SC will conduct an early safety evaluation when 10 patients in the WHO/ECOG PS 2 cohort have been treated for a minimum of 6 months or discontinued due to an AE or disease progression, whichever occurs first. At the time of the early safety evaluation, safety data for patients in the WHO/ECOG PS 0 to 1 cohort will also be provided to the SC for completeness in the overall risk/benefit assessment. If needed for publication purposes, an additional early assessment of study data may be conducted when minimum 50 patients in the WHO/ECOG PS 0 to 1 cohort or WHO/ECOG PS 2 cohort have had the opportunity to receive durvalumab (MEDI4736) for a minimum of 6 months.

Statistical methods

The primary objective of this study is to assess the safety and tolerability of durvalumab (MEDI4736), defined as Grade 3 and Grade 4 treatment-related adverse events (TRAEs) observed during the initial 6 months of durvalumab (MEDI4736) treatment. In addition, safety and tolerability of durvalumab (MEDI4736) will be characterized for the cohorts of WHO/ECOG PS 0 to 1 and 2 patients.

Safety data will be summarized descriptively overall, by seriousness, by causality and by maximum National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) Grade based on the safety analysis set (ie, all patients who received at least 1 dose of study drug). The exact 95% confidence intervals (CIs) around the incidence of Grade 3 and Grade 4 TRAEs will be reported for patients overall and separately for the cohorts of WHO/ECOG PS 0 to 1 and 2 patients.

The median progression-free survival (PFS) and median overall survival (OS), as well as the median time to NSCLC-related death, together with their corresponding 95% CIs will be calculated using Kaplan-Meier product limit methods and will be reported for patients overall and separately for the cohorts of WHO/ECOG PS 0 to 1 and 2 patients. In addition, the objective response rate (ORR) (based on Investigator assessment by RECIST 1.1 criteria), together with the corresponding 95% CI, will be reported for patients overall and separately for the cohorts of WHO/ECOG PS 0 to 1 and 2 patients.

This is a safety study and no formal sample size calculation will be done. Between 100 and 120 patients will be enrolled in the WHO/ECOG PS 0 to 1 Cohort and up to 30 patients in the

WHO/ECOG PS 2 Cohort depending on recruitment. CCI
CCI

1.2 Schedule of assessments

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 (Schedule of assessments [SoA]).

Whenever vital sign assessments and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. Whenever electrocardiograms (ECGs), vital signs assessments, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital sign assessments, and then blood draws.

Patients may delay dosing due to immune-mediated adverse events (imAEs) or non-imAEs or for reasons other than TRAE.

- In case of imAEs or non-imAEs, dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (Section 8.4.5).
- If dosing must be delayed for reasons other than TRAEs, dosing will resume as soon as feasible.

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

Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumour efficacy (RECIST) and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-life of durvalumab (MEDI4736) (see current Investigator Brochure [IB]).

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 of first IP dose administration.

PROs and tumour efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of first IP administration (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 assessments for screening and treatment period

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD (max. 24 months)[a,b]	Final visit	For details see Section
Week	**-4 to -1**	**1**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**					
Informed consent								
Informed consent: Study procedures	X							5.1
CCI	X							5.1
Study procedures								
Physical examination (full)	X							8.2.2
Targeted physical examinations (symptomatic patients only)		X	X	X	X	X	X	8.2.2
Assessment of early toxicities (phone call)[d]		X	X	X				8.2.5
Vital signs (temperature, respiratory rate, blood pressure, and pulse), body weight, and height[e]	X	X	X	X	X	X	X	8.2.3
ECG[f]	X	As clinically indicated						8.2.4
Concomitant medications	←	———	———	———	———	———	→	6.4
Medical history	X							
Demography, including baseline characteristics and tobacco use	X							
Eligibility criteria	X	X						5.1, 5.2
Laboratory assessments								
Clinical chemistry	X	X[g]	X[h]	X[h]	X[h]	X[h]	X	8.2.1
Haematology	X	X[g]	X[h]	X[h]	X[h]	X[h]	X	8.2.1
Coagulation		X[i]	As clinically indicated					8.2.1
TSH (reflex free T3 or free T4)[g,j,k]	X	X[k]	X	X	X	X	X	8.2.1
Urinalysis	X	As clinically indicated						8.2.1
Hepatitis B and C, HIV, and tuberculosis	X							8.2.1

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD (max. 24 months)[a,b]	Final visit	For details see Section
Week	**-4 to -1**	**1**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**					
Pregnancy test[l]	X	X	X	X	X	X	X	8.2.1
Monitoring								
CCI	X	X	X	X	X	X	X	8.2.6
AE/SAE assessment[m]	←						→	8.3
Drug accountability		X	All visits					6.3
IP administration								
Durvalumab (MEDI4736)[n]		X	X	X	X	X	X	6.1
QoL assessments								
CCI	X	X	X	X	X	X	X	8.1.2.1, 8.1.2.2
CCI	X	X	X	X	X	X	X	8.1.2.3
Biomarker assessments								
CCI	X							8.8.1.1
CCI	X							8.8.1.1
CCI	X	X	X	X				8.8.1.2
CCI		X						8.7.1

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD (max. 24 months)[a,b]	Final visit	For details see Section
Week	**-4 to -1**	**1**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**					
Efficacy evaluations								
Tumour evaluation as per local institutional standard care (CT or MRI) (RECIST 1.1)[b,s]	X	The allowed window for the tumour assessment is ±7 days. On-study tumour assessments begin 8 weeks ±1 week after IP treatment initiation and continue q8w ±1 week through 52 weeks (relative to the date of IP treatment initiation) and q12w ±1 week thereafter (relative to the date of IP treatment initiation) until disease progression, plus an additional follow-up scan is performed if clinically feasible. The on-study imaging schedule of 8 weeks ±1 week through 52 weeks and then q12w ±1 week thereafter MUST be followed regardless of any delays in dosing. Additional scans can be completed per standard practice post disease progression.						8.1

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

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

c CCI [redacted]

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

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

f Any clinically significant abnormalities detected require triplicate ECG results.

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

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

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

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

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

l For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of IP and then prior to every dosing visit (within 3 calendar days prior to dosing). Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

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

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

[o] Will be administered using a site-based electronic device. At screening, ePRO should be done after informed consent but before any other screening procedures. At C1D1, and following visits, ePRO should be done prior to any other assessments and before dosing that day. PRO questionnaires should be completed as long as the patient continues with the study drug, until confirmed PD. Patients with confirmed PD who continue to receive the study drug at the discretion of the Investigator will follow the PRO assessments in Table 1 until the study drug is stopped.

[p] CCI

[q] CCI

[r] CCI

[s] RECIST 1.1 assessments will be performed based on local institutional imaging results, using CT/MRI assessments of the chest and abdomen (including the entire liver and both adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients, including new lesions at follow-up. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of IP treatment initiation). All confirmatory scans should be recorded in the database. For patients who are clinically stable and being treated through radiological progression, the follow-up scan performed after a RECIST 1.1-defined PD should be performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD. For these patients the assessments should continue as indicated here. Special Confirmation of Radiological Progression Criteria apply for tumour assessments on the follow-up scan (Appendix F).

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

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

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

Table 2 Schedule of assessments for patients who have discontinued study drug

	Time since last dose of IP						
	Day (±3)	Months (±1 week)				12 months and every 3 months (±2 weeks)	For details, see Section
Evaluation	30	2	3	6	9		
Physical examination (full)	X						8.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	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
CCI [redacted]	CCI [redacted]						8.2.6
Subsequent anticancer therapy[c,d]	←					→	
Survival status[e]		X	X	X	X	X	8.1.1
Haematology	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
CCI [redacted]	X	X	X				8.1.2.3
Tumour assessment as per local institutional standard care (CT or MRI) (RECIST 1.1)[h]	Additional scans to be completed per standard practice post progression (not mandatory to be recorded in eCRF). Patients who permanently discontinue IP for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 assessments performed q8w ±1 week beginning 8 weeks after IP treatment initiation for the first 52 weeks and q12w ±1 week thereafter until clinical progression/deterioration or RECIST 1.1-defined radiological progression plus 1 or more additional follow-up scans for confirmation of progression until confirmed radiological progression, the end of study, death, study discontinuation, or Sponsor decision (whichever comes first).						8.1

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

[b] CCI [redacted]

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

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

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

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

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

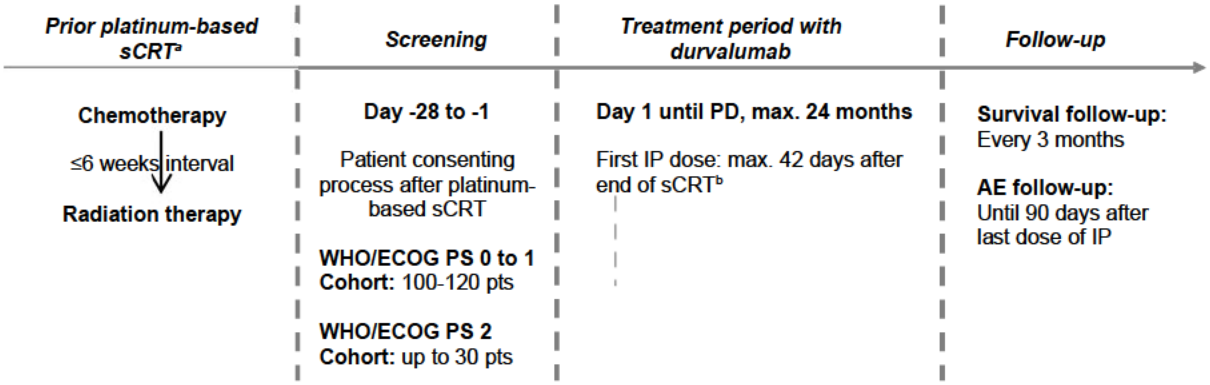
[h] Only for patients yet to progress, RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands). Additional anatomy should be image-based on signs and symptoms of individual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

AE: Adverse event; CT: Computed tomography; DCO: Data cut-off; eCRF: Electronic case report form; CCI [redacted] IP: Investigational product; IV: Intravenous; MRI: Magnetic resonance imaging; NSCLC: Non-small cell lung cancer; PD: Progression of disease; CCI [redacted] q8w, q12w: Every 8, 12 weeks, respectively; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SAE: Serious adverse event; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-stimulating hormone; CCI [redacted]

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design schema



[a] Patients must have received at least 2 cycles of platinum-based chemotherapy before radiation therapy. The interval between administration of the last dose of chemotherapy regimen and start of radiation therapy must be no more than 6 weeks. Consolidation chemotherapy after radiation is not permitted. If the patient's platinum-based chemotherapy contained gemcitabine, no overlap between chemotherapy and radiation therapy is permitted. If the patient's platinum-based chemotherapy contained cisplatin or carboplatin and etoposide, vinblastine, vinorelbine, a taxane (paclitaxel or docetaxel), or pemetrexed (ie, an agent other than gemcitabine), an overlap of 1 cycle of chemotherapy and radiation therapy is acceptable.

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

AE: Adverse event; IP: Investigational product; max.: maximum; PD: Progression of disease; sCRT: Sequential chemoradiation therapy; WHO/ECOG PS: World Health Organisation/Eastern Cooperative Oncology Group Performance Status.

2 INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades (WHO 2012). In 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 worldwide, with 1.59 million deaths (19.4% of the total). NSCLC represents approximately 80% to 85% of all lung cancers (American Cancer Society 2016) and approximately 30% of patients present with Stage III disease (Cancer Treatment Centers of America 2017).

Standard treatment for patients with a good performance status (PS) and unresectable Stage III NSCLC has been platinum-based doublet chemotherapy concurrent with radiotherapy (chemoradiation therapy [CRT]) administered with curative intent (Yoon et al 2017). However, the median PFS among patients who have received CRT is poor (approximately 8 months) (Ahn et al 2015). A meta-analysis of cCRT versus sCRT showed better outcomes with cCRT, but even with cCRT, the 5-year OS is only approximately 15% (Aupérin et al 2010).

More recently, the PACIFIC Study (D4191C00001) demonstrated that the addition of durvalumab (MEDI4736) following platinum-based cCRT significantly improves PFS (Antonia et al 2017). The median PFS with durvalumab (MEDI4736) was 16.8 months (95% CI 13.0, 18.1) versus 5.6 months with placebo (95% CI: 4.6, 7.8), and with a stratified hazard ratio (HR) for disease progression or death of 0.52 (95% CI: 0.42, 0.65; $p<0.001$). The response rate was higher with durvalumab (MEDI4736) versus placebo (28.4% versus 16.0%; $p<0.001$) and the median time to death or distant metastasis was longer with durvalumab (MEDI4736) than with placebo (23.2 versus 14.6 months; $p<0.001$). Grade 3 or 4 AEs were similar in both groups, occurring in 29.9% of the patients who received durvalumab (MEDI4736) and 26.1% of those who received placebo.

The PACIFIC Study data led to the approval of durvalumab (MEDI4736) by the US FDA in February 2018, Health Canada in May 2018, and EMA in September 2018 for the treatment of unresectable Stage III NSCLC following CRT. Additional regulatory applications are currently under review globally. The standard of care for patients with unresectable Stage III NSCLC is now anticipated to be cCRT followed by durvalumab (MEDI4736).

A significant proportion of patients are unable to receive cCRT for a number of reasons, including lack of immediate access to radiation therapy facilities or poor PS. As such, many patients receive sCRT and this study aims to assess the clinical profile of durvalumab (MEDI4736) therapy following sCRT in patients with WHO/ECOG PS 0 to 1 and WHO/ECOG PS 2.

2.1 Study rationale

Prior to the PACIFIC Study, minimal advances had been made for the treatment of patients with unresectable Stage III NSCLC. The treatment of choice in patients with unresectable stage IIIA and IIIB NSCLC has been cCRT (Postmus et al 2017, NCCN 2018). If cCRT is not feasible, including in frail patients who are unable to tolerate cCRT, sequential chemotherapy followed by definitive radiation therapy (sCRT) represents an alternative (NCCN 2018). Overall, around 15% of the patients with unresectable Stage IIIA or Stage IIIB disease receive sCRT in the US and these numbers might be higher in Europe. Compared to sCRT, cCRT leads to better survival by optimising local control, but cCRT does not reduce the risk of distant relapse (Aupérin et al 2010). A pooled analysis of 41 Phase II/III studies confirmed that consolidation chemotherapy after cCRT does not improve survival for patients with Stage III locally-advanced NSCLC (Tsujino et al 2013).

CRT induces initial tumour shrinkage as a result of tumour cell death and may enhance antigen release and presentation, which in turn may aid in the priming of immune cells to recognise and eliminate tumour cells.

Chemotherapy and radiotherapy can also up-regulate the expression of programmed cell death ligand 1 (PD-L1) (Zhang et al 2008, Deng et al 2014, Dovedi et al 2014) due to the release of cytokines and other inflammatory molecules. These factors may confer greater sensitivity to PD-1/L1 pathway blockade. The results of the PACIFIC Study demonstrate that durvalumab added after definitive CRT provides clinical benefit by potentiating the pro-inflammatory effects of the definitive therapy.

The PACIFIC Study only evaluated patients who had not progressed after completing cCRT. A significant unmet medical need still exists in patients who are not eligible for cCRT.

Collection of safety, efficacy, and QoL data for durvalumab (MEDI4736) as consolidation therapy after sCRT is warranted.

2.2 Background

2.2.1 Unmet need and potential role of immunotherapies in NSCLC

The addition of systemic therapy to radiation therapy has been reported to improve survival of patients with NSCLC in studies that have used cisplatin-based systemic therapy regimens (Aupérin et al 2006, Non-small Cell Lung Cancer Collaborative Group 1995). cCRT has been found to be more beneficial than sCRT (Fournel et al 2005, Curran et al 2011, Aupérin et al 2010). In the Stage III unresectable setting, a combination of systemic therapy and radiotherapy is usually administered. CALGB 8433 showed an improvement of survival of CRT over radiotherapy alone for these patients (Dillman et al 1996). Additionally, the West Japan Lung Cancer Group has shown that concurrent cisplatin-based chemotherapy was superior to sCRT in Stage III patients (Furuse et al 1999). In the Radiation Therapy Oncology

Group (RTOG) 9410 study, 2 cCRT regimens and 1 sCRT regimen were compared in Stage II and III NSCLC patients (Curran et al 2011), showing that concurrent delivery of cisplatin-based chemotherapy with thoracic radiotherapy confers a long-term survival benefit compared with the sequential delivery of these therapies. Two important meta-analyses have demonstrated that adding sequential or concomitant chemotherapy to radical radiotherapy improved survival in locally-advanced NSCLC. The HR for survival with the addition of sequential chemotherapy to radiotherapy was 0.88 (95% CI: 0.81, 0.96) (Non-small Cell Lung Cancer Collaborative Group 1995) and the HR with the addition of platinum-based concomitant chemotherapy to radiotherapy was 0.89 (95% CI: 0.81, 0.98) (Aupérin et al 2006); however, these data should be interpreted with caution since there was some heterogeneity between the studies as well as in different sensitivity analyses. The NSCLC Collaborative Group performed a meta-analysis of 6 randomised studies, which further confirmed the benefit in OS of cCRT compared to sequential therapy (Aupérin et al 2010) (HR: 0.84, 95% CI: 0.74, 0.95; p=0.004), mainly due to a better locoregional control, but at the cost of an increased acute oesophageal toxicity. No differences were observed between cCRT and sCRT for PFS (HR: 0.90, 95% CI: 0.79, 1.01; p=0.07). Despite the benefit to OS with cCRT, OS remains low with a 5-year OS of only approximately 15% (Aupérin et al 2010). These studies indicate that cisplatin-based systemic therapy with concurrent radiotherapy is an effective means of treatment, although relapses are still frequent.

While advances have been made in improving survival from Stage III NSCLC by optimising local control, evidence suggests that cCRT or sCRT do not reduce the risk of distant relapse (Aupérin et al 2010). With fewer cycles and, in some cases, lower doses of chemotherapy delivered in the concurrent setting, several studies have assessed whether delivering induction or consolidation treatment will improve survival, with discordant results. A Phase II study by the Southwest Oncology Group suggests a possible median survival benefit in patients treated with cCRT followed by consolidation docetaxel (median survival was 26 months) (Gandara et al 2006). Similarly, a retrospective study found that consolidation therapy after cCRT resulted in approximately 11 months longer median OS than cCRT alone (Liu et al 2015). These findings were not corroborated by a Phase III study conducted by the Hoosier Oncology Group and US Oncology that evaluated the role of consolidation docetaxel in patients with inoperable Stage III NSCLC (Hanna et al 2008). The study terminated earlier than planned after an interim analysis showed no significant differences in survival between the 2 arms; median survival time for patients in the docetaxel arm versus the observation arm was 21.2 versus 23.2 months. There was a significant increase in severe toxicities in the docetaxel arm. More recently, a pooled analysis of 41 Phase II/III studies confirmed that there remains no evidence to suggest that consolidation chemotherapy after cCRT improves survival for patients with Stage III NSCLC and current guidelines continue to recommend cCRT alone for the treatment of inoperable Stage III NSCLC (Bayman et al 2014; Tsujino et al 2013).

The sequential/consolidation setting post cCRT or sCRT seems to be ideal to evaluate the efficacy of immunotherapy, which is aimed at boosting the ability of the patient's immune system to eliminate cancer cells. CRT often induces initial tumour shrinkage followed by eventual PD as the tumours find mechanisms to bypass the CRT-induced growth inhibition. The initial tumour shrinkage observed in some patients following CRT is the result of cell death and tumour damage. CRT-induced cell death can enhance the ability of the immune system to recognise and respond to the tumour through enhanced antigen release and presentation which, in turn, aids in the priming of immune cells to recognise and eliminate tumour cells (Zhang et al 2008; Deng et al 2014; Dovedi et al 2014). Therefore, triggering or augmenting an antigenic anti-tumour response with CRT and combining or following this treatment with anti-PD-L1 therapy, which acts to preserve ongoing immune responses by blocking an immunosuppressive signal theoretically may result in enhanced anti-tumour activity by improving local control and decreasing systemic spread.

Tumours that are poorly immunogenic or that have become immunosuppressive can potentially be made immunogenic through administration of pro-immunogenic therapies designed to increase antigen release from the cancer cell. Potential priming agents for immunotherapy agents include chemotherapy and radiotherapy. Some cytotoxic therapies, such as anthracyclines or ionising radiation, promote 'immunogenic cell death', which includes the release of 'danger' molecules from tumour cells such as calreticulin, high mobility group protein B1 and adenosine triphosphate. These danger molecules polarize dendritic cells toward a pro-inflammatory phenotype and increase priming toward T helper 1 anti-tumour T cells and away from regulatory T cells (Vanneman and Dranoff 2012). Additionally, a recent Phase II study in patients with Stage IIIB/IV NSCLC or extensive-disease small-cell lung cancer investigated whether the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) agent ipilimumab could be given safely in combination with standard chemotherapy (carboplatin–paclitaxel) as well as whether it would be optimal to initiate ipilimumab at the same time as chemotherapy, or after 2 cycles of treatment. The results from this Phase II study showed that the combination was reasonably well-tolerated, and that a 'phased regimen' in which immunotherapy began after chemotherapy resulted in substantially improved PFS compared with carboplatin–paclitaxel alone. While this study did not actively investigate dosing effects, the data show that the clinical effects of administering immunotherapy in combination with chemotherapy are strongly dependent on the sequencing of treatment (Dunn et al 2004).

Recently, the results of a landmark Phase III PACIFIC Study (Antonia et al 2017) were reported. The PACIFIC Study evaluated the role of immune checkpoint blockade in unresectable Stage III NSCLC. Eligible patients had disease that had not yet progressed after at least 2 cycles of platinum-based cCRT at a dose of 54 to 66 Gy. A total of 713 patients (PS 0 to 1) were randomly assigned to receive an anti-PD-L1 antibody, durvalumab (MEDI4736), at a dose of 10 mg/kg of body weight or placebo Q2W for up to 12 months.

Pre-planned interim analysis showed that the co-primary endpoint of median PFS was 16.8 months (95% CI: 13.0, 18.1) with durvalumab (MEDI4736) versus 5.6 months (95% CI: 4.6, 7.8) with placebo (stratified HR for disease progression or death: 0.52; 95% CI: 0.42, 0.65; p<0.001). The response rate was higher with durvalumab (MEDI4736) 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). The median time to death or distant metastasis was longer with durvalumab (MEDI4736) than with placebo (23.2 months versus 14.6 months; p <0.001). Grade 3 or 4 AEs occurred in 29.9% of the patients who received durvalumab (MEDI4736) and 26.1% of those who received placebo. Treatment-related (as assessed by the reporting Investigator) CTCAE AEs of Grade 3 or 4 were reported in 57 (12.0%) patients receiving durvalumab and 11 (4.7%) patients receiving placebo (PACIFIC Study, data on file).

The PACIFIC Study only evaluated patients who had not progressed after completing cCRT, and therefore a significant unmet medical need still exists in patients who are not eligible for cCRT. Collection of safety, efficacy, and QoL data for durvalumab as consolidation therapy after sCRT is warranted.

2.2.2 Immunotherapies

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

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T cell activation. The PD-1 receptor (cluster of differentiation [CD] 279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7 homolog 1 [B7-H1]; CD274) and programmed cell death 1 ligand 2 (PD-L2) (B7-DC; CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to a family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T cell proliferation. Tumour cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

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

The inhibitory mechanism described above is co-opted by tumours that express PD-L1 as a way of evading immune detection and elimination (Qin et al 2016). 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 (Stewart et al 2015). This activity overcomes PD-L1-mediated inhibition of anti-tumour immunity. While functional blockade of PD-L1 results in T cell reactivation, this mechanism of action (MOA) is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumour immune responses in patients with cancer. Results of pre-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance anti-tumour immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012,Zhang et al 2008) with responses that tend to be more pronounced in patients with tumours that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). This hypothesis has been proven correct in a number of Phase II and III clinical studies of NSCLC, including PACIFIC (Antonia et al 2017), KN024 (Reck et al 2016), KN042 (Mok et al 2016), KN189 (Gandhi et al 2018), IMPower150 (Socinski et al 2018), IMPower130 (Papadimitrakopoulou et al 2016), CM227(Hellmann et al 2018) and others.

In contrast, CTLA-4 is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (Fife and Bluestone 2008). Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T cell activation and anti-tumour activity in animal models, including killing of established murine solid tumours and induction of protective anti-tumour immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing anti-tumour activity in patients with solid tumours.

Interestingly, high mutation burden (Hellmann et al 2018) may contribute to the responses seen with immune therapy and is becoming a biomarker of increasing interest for potential prediction of efficacy with immunotherapies.

A wealth of clinical data exists to demonstrate that blockade of negative regulatory signals to T cells such as CTLA-4 and PD-L1 results in promising clinical activity. Ipilimumab was first granted US FDA approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and durvalumab and atezolizumab, 2 anti-PD-L1 agents, have been granted

approvals by agencies for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell NSCLC, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumour types.

2.2.3 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) is a human mAb of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune is referred to as AstraZeneca throughout this document). The proposed MOA for durvalumab (MEDI4736) is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumour elimination. In vitro studies demonstrate that durvalumab (MEDI4736) antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (IFN-γ) (Stewart et al 2015). In vivo studies have shown that durvalumab (MEDI4736) inhibits tumour growth in xenograft models via a T cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab (MEDI4736) is expected to stimulate the patient's anti-tumour immune response by binding to PD-L1 and shifting the balance toward an anti-tumour response. Durvalumab (MEDI4736) has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab (MEDI4736) has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab (MEDI4736) monotherapy are summarized in Section 4.3.1 and Section 8.3.12. Refer to the current durvalumab (MEDI4736) IB for a complete summary of pre-clinical 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 (MEDI4736) are based on the first-in-human, single-agent study (Study 1108) in patients with advanced solid tumours, the study of durvalumab (MEDI4736) monotherapy in NSCLC (Study D4191C00003 [ATLANTIC]), and the study of durvalumab (MEDI4736) monotherapy in NSCLC following completion of platinum-based chemotherapy concurrent with radiation therapy (PACIFIC Study). Data from these studies have demonstrated clinical activity of durvalumab (MEDI4736) therapy in patients with NSCLC. Details pertaining to Study 1108 and ATLANTIC are provided in the current durvalumab (MEDI4736) IB.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of durvalumab (MEDI4736) may be found in the durvalumab (MEDI4736) IB.

2.3.1 Potential benefits

The efficacy of durvalumab (MEDI4736) was evaluated in the PACIFIC Study, a multi-centre, randomised, 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 WHO PS 0 or 1 (Antonia et al 2017). A total of 713 patients were randomised 2:1 to receive durvalumab (MEDI4736) 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 pre-specified 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 (MEDI4736) 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 favour 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 (MEDI4736) than with placebo (28.4% versus 16.0%; p<0.001), and the median DoR was longer (72.8% versus 46.8% of the patients had an ongoing response at 18 months). The median time to death or distant metastasis was longer with durvalumab (MEDI4736) than with placebo (23.2 months versus 14.6 months; HR: 0.52; 95% CI, 0.39, 0.69; p <0.001). The OS data were immature at the time of the interim analysis of the PFS, as the number of events required for the planned first OS interim analysis had not been reached at the time of this PFS analysis.

2.3.2 Overall risks

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

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

2.3.2.1 Durvalumab (MEDI4736) risks

Risks with durvalumab (MEDI4736) include, but are not limited to, diarrhoea/colitis, pneumonitis/ILD, endocrinopathies (i.e., events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus [DM] and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barre syndrome, myasthenia gravis).

For information on all identified and potential risks with durvalumab (MEDI4736), please always refer to the current version of the durvalumab (MEDI4736) IB.

In the PACIFIC Study (Antonia et al 2017), treatment-emergent adverse events (TEAEs) occurred in 67.8% of patients in the durvalumab (MEDI4736) group compared to 53.4% in the placebo group. Grade 3 or 4 AEs occurred in 29.9% of patients who received durvalumab (MEDI4736) and 26.1% of those who received placebo. The most common Grade 3 or 4 AE was pneumonia, which occurred in 4.4% of patients who received durvalumab (MEDI4736) and in 3.8% of patients in the placebo group. Pneumonitis or radiation pneumonitis of any grade occurred in 33.9% and 24.8% of patients who received durvalumab (MEDI4736) and placebo, respectively; pneumonitis or radiation pneumonitis of Grade 3 or 4 occurred in 3.4% and 2.6% of patients, respectively. The most frequent AEs leading to discontinuation of durvalumab (MEDI4736) and placebo were pneumonitis or radiation pneumonitis (in 6.3% and 4.3% of patients, respectively) and pneumonia (in 1.1% and 1.3% of patients, respectively). Adverse events of special interest (AESIs) of any grade were reported in 66.1% of patients in the durvalumab (MEDI4736) group and in 48.7% of patients in the placebo group; events of Grade 3 or higher were less than 10% in both groups. The most frequent AESIs of any grade with durvalumab (MEDI4736) versus placebo were diarrhoea (18.3% and 18.8%), pneumonitis (12.6% and 7.7%), rash (12.2% and 7.3%), and pruritus (12.2% and 4.7%). Finally, the rate of imAEs was 24.2% with durvalumab (MEDI4736) and 8.1% with placebo. The rates of severe imAEs, and of pneumonitis in particular, were not significantly different (any Grade 3 or 4 immune-mediated event 3.4% and 2.6%, and Grade 3 or 4 pneumonitis 1.7% and 2.6%, for durvalumab and placebo, respectively). Overall, the safety profile of durvalumab (MEDI4736) in this population was consistent with that of other immunotherapies and with its known safety profile as monotherapy with NSCLC.

In monotherapy clinical studies, AEs at an incidence of $\geq$20% include events such as fatigue and decreased appetite. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Toxicity Criteria (CTC) Grades 3 to 5 events reported across the durvalumab (MEDI4736) program.

The majority of TRAEs 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 (MEDI4736) monotherapy AE data can be found in the current version of the durvalumab (MEDI4736) IB.

2.3.3 Overall benefit/risk

In summary, the potential for clinical benefit associated with inhibition of the PD-1/PD-L1 pathway, supported by the clinical benefit in terms of PFS and ORR observed in earlier studies in patients with NSCLC, including the pivotal Phase III PACIFIC Study, outweighs the known and potential risks based on the AEs reported in patients treated with durvalumab (MEDI4736) and other PD-1/PD-L1 inhibitors. Thus, the benefit/risk assessment, favours the conduct of this proposed study.

3 OBJECTIVES AND ENDPOINTS

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

Table 3 Study objectives

OBJECTIVE	ENDPOINT/VARIABLE
PRIMARY OBJECTIVE	
To assess the safety and tolerability profile of durvalumab (MEDI4736) as defined by Grade 3 and Grade 4 TRAEs[a] within 6 months from the initiation of durvalumab (MEDI4736) treatment	Grade 3 or Grade 4 TRAEs[a]
SECONDARY OBJECTIVES	
Efficacy objectives	
To assess the efficacy of durvalumab (MEDI4736) treatment in terms of PFS and OS	Median PFS according to RECIST 1.1 as assessed by the Investigator
	Median PFS12 and PFS24 according to RECIST 1.1 as assessed by the Investigator
	Median OS, OS12, OS24, and OS36
To further assess the efficacy of durvalumab (MEDI4736) 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 (MEDI4736) treatment in terms of lung cancer mortality	Lung cancer mortality

OBJECTIVE	ENDPOINT/VARIABLE
Secondary safety objective	
To further assess the safety and tolerability profile of durvalumab (MEDI4736) treatment, including all AEs	AEs, SAEs, AESIs, imAEs, physical examinations, vital signs including BP, pulse, temperature, and respiratory rate; ECGs, and laboratory findings including clinical chemistry, haematology and urinalysis
EXPLORATORY OBJECTIVES	
CCI	CCI CCI CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

a. TRAEs and PRAEs are used interchangeably and PRAEs will be reported in the SAP, Tables, Figures, and Listings, and CSR.

Note: Toxicities will be classified as per CTCAE grading system NCI CTCAE version 4.03. 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 fulfil 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 (MEDI4736) 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.

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

AE: Adverse event; AESI: Adverse event of special interest; BP: Blood pressure; CSR: Clinical study report; CCI DoR: Duration of response; CTCAE: Common Terminology Criteria for Adverse Event; ECG: Electrocardiogram; CCI imAE: Immune-mediated adverse event; IP: Investigational product; NCI: National Cancer Institute; ORR: Objective response rate; OS: Overall survival; OS12, OS24, OS36: Proportion of patients alive at 12 months, 24 months, 36 months, respectively, from first date of treatment; CCI PFS: Progression-free survival; CCI ; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; PFS: Progression-free survival; PFS12, PFS24: Proportion of patients progression-free at 12 months and 24 months, respectively, from first date of treatment; PRAE: Possibly related adverse event; SAE: Serious adverse event; SAP: Statistical analysis plan; TL: Target lesion; CCI ; TRAE: Treatment-related adverse event; CCI

Data of the following exploratory endpoints will be reported in the clinical study report (CSR): CCI

4 STUDY DESIGN

4.1 Overall design

This is a Phase II, open-label, multi-centre study to determine safety of a fixed dose of durvalumab (MEDI4736) (1500 mg) monotherapy in patients with unresectable Stage III NSCLC who have not progressed following definitive, platinum-based sCRT.

An overview of the study design and the study flow chart are presented in Figure 1 and Figure 2, respectively. Details on study objectives and efficacy and safety endpoints are provided in Table 3.

Number of patients and patient population

Up to 150 patients will be treated with the study drug in Europe and North America. Patients will be in complete response (CR), partial response (PR), or have stable disease (SD) following definitive, platinum-based sCRT, as assessed by the Investigator and further supported by the screening imaging radiological assessment. Patients must not have progressed following definitive, platinum-based sCRT; radiation therapy must be completed within 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 will be treated with the study drug in 2 cohorts: approximately 100-120 patients in the WHO/ECOG PS 0 to 1 Cohort and up to 30 patients in the WHO/ECOG PS 2 Cohort.

Investigational product, dosage and mode of administration

Durvalumab (MEDI4736) 1500 mg via IV infusion q4w, starting on Week 1 after confirmation of eligibility, for a maximum of 24 months from Cycle 1 Day 1, or until PD (unless the Investigator considers the patient continues to receive benefit from the IP), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Treatment initiation within the first 14 days after sCRT therapy is, however, highly encouraged. For patients who are recovering from toxicities associated with prior treatment, administration of the first IP dose may be delayed by up to 42 days from the end of the sCRT.

For details on treatments given during the study, see Section 6.1.

Tumour response assessments

Tumour assessments using CT/MRI will be performed at the times specified in Table 1 and Table 2. RECIST 1.1 measurements as assessed by the Investigator will be used to derive the secondary variables of PFS, ORR, and DoR. Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD.

Overall survival assessments

Once a patient has had objective progression recorded and has discontinued study drug, the patient will be followed up for survival status q12w until death, withdrawal of consent or the end of the study.

Schedule of assessments

The SoA at screening and during the treatment period is presented in Table 1. The SoA during follow-up for patients who have discontinued the study drug due to confirmed PD, toxicity, or any other reason, is presented in Table 2.

Guidelines for the management of toxicities are described in Section 8.4.5.

Details of the PGx component of the study (relating to deoxyribonucleic acid [DNA]) are provided in Appendix D.

Interim analysis

No formal interim analysis is planned for this study. However, the SC will conduct an early safety evaluation when 10 patients in the WHO/ECOG PS 2 cohort have been treated for a minimum of 6 months or discontinued due to an AE or disease progression, whichever occurs first. At the time of the early safety evaluation, safety data for patients in the WHO/ECOG PS 0 to 1 cohort will also be provided to the SC for completeness in the overall risk/benefit assessment. If needed for publication purposes, an additional early assessment of study data

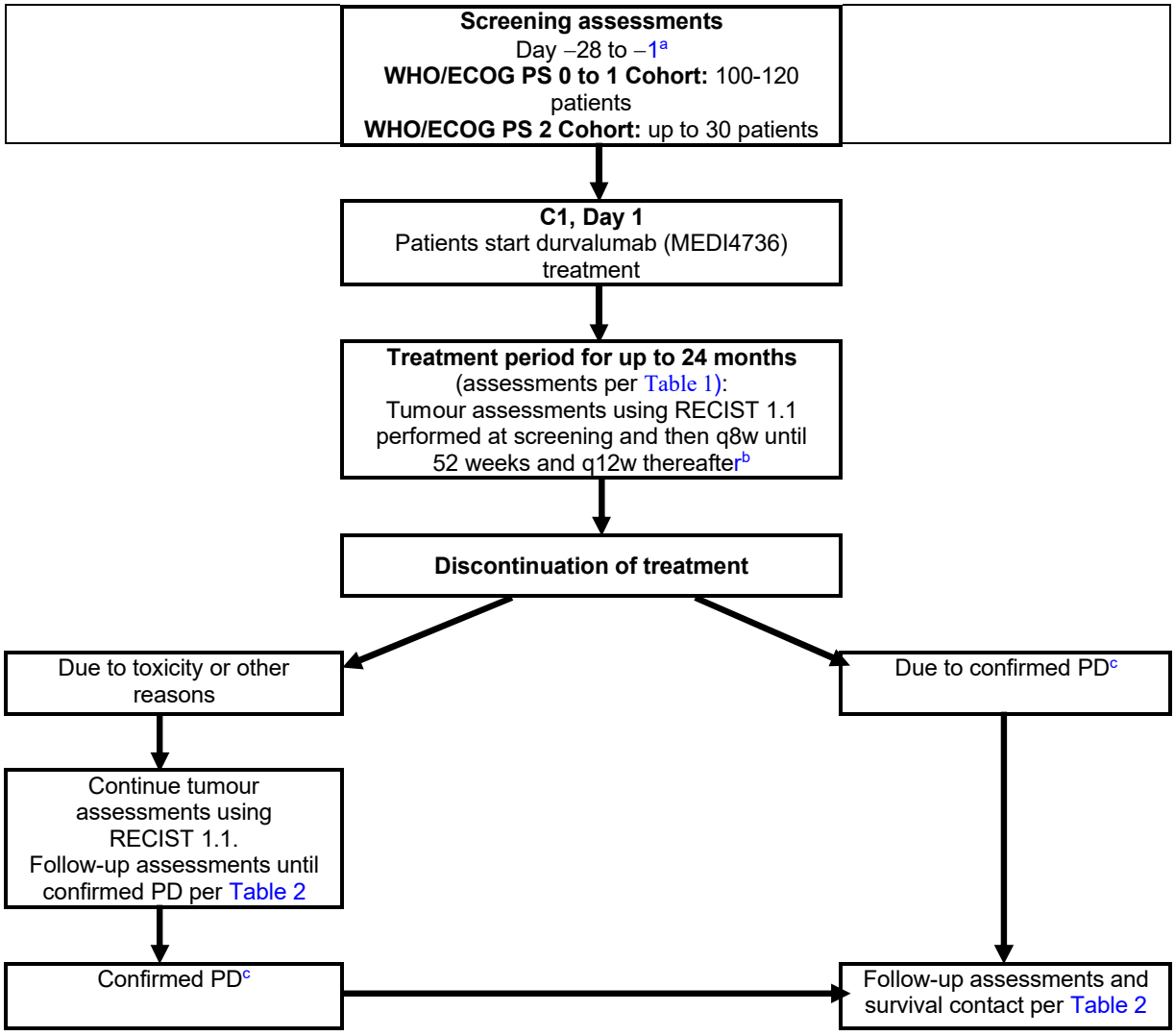
may be conducted when minimum 50 patients in the WHO/ECOG PS 0 to 1 cohort or WHO/ECOG PS 2 cohort have had the opportunity to receive durvalumab (MEDI4736) for a minimum of 6 months.

End of analysis portion of study

Once the planned statistical analyses have been performed, the analysis portion of the clinical study will have been completed. Patients in OS follow-up (progressed and have completed treatment) will be considered to have completed the study.

For patients who continue to receive IP after the time of the data cut-off (DCO), Investigators will report all SAEs to AstraZeneca Patient Safety until 90 days after last IP dose. Following the DCO for the study, SAE reporting applies only to patients who are receiving IP or who are within the 90-day follow-up period post the last dose of IP (for more details see Section 4.4).

Figure 2 Study flow chart



[a] Screening assessments can be performed in a step-wise process. The baseline tumour assessment is part of the screening procedures and should be performed within 42 days after the end of sCRT and 28 days before the start of study drug. For patients who are recovering from toxicities associated with prior treatment, IP treatment initiation may be delayed by up to 42 days from the end of the sCRT.

[b] During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study drug at the discretion of the Investigator and patient. A follow-up scan is to be performed after the initial RECIST 1.1-defined radiological PD, no less than 4 weeks after the prior assessment of PD and no later than the next regularly scheduled imaging visit, and this scan is evaluated using the Confirmation of Radiological Progression Criteria outlined in Appendix F. If the subsequent scan does not confirm the immediate prior radiological PD, then the patient may continue on study drug at the discretion of the Investigator and if the patient has consented to do so; imaging assessments should continue until the next RECIST 1.1-defined radiological PD, which in turn will require a subsequent scan evaluated using the Confirmation of Radiological Progression Criteria outlined in Appendix F. For all patients who are treated through progression, the Investigator should ensure patients do not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 6.1.3. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug.

[c] Patients with confirmed PD who continue to receive the study drug at the discretion of the Investigator (following consultation with AstraZeneca) can receive the study drug for a maximum of 24 months from Cycle 1 Day 1. For all patients who are treated through progression, the Investigator should ensure patients do not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient must continue to meet those inclusion and exclusion criteria that are relevant to treatment through disease progression as specified in Section 6.1.3. The same exceptions as noted in footnote [b] apply. Patients will follow the assessments in Table 1 including tumour assessments q8w (relative to the date of IP treatment initiation) until the study drug is stopped. Patients who continue to receive treatment after the DCO should receive tumour assessment scans and other assessments as per local clinical practice. It is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory assessments prior to and periodically during the treatment with durvalumab (MEDI4736) in order to manage AEs in accordance with the durvalumab (MEDI4736) toxicity management guidelines (Section 8.4.5). The study drug should be discontinued if there is confirmed PD in TLs following a previous response (PR or CR) to the study drug in those lesions.

Note: At DCO for the study, patients who are receiving IP can either choose to discontinue from the study or, where the Investigator judges that patients are gaining clinical benefit, patients may continue to receive IP. For patients who do continue to receive IP beyond the time of the DCO, Investigators must continue to report all SAEs to AstraZeneca Patient Safety until 90 days after last IP dose. Any SAE or non-serious 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 (Section 8.4.5), unless the event is considered by the Investigator to be unlikely to resolve or the patient is lost to follow-up.

AE: Adverse event; C: Cycle; CR: Complete response; DCO: Data cut-off; IP: Investigational product; PD: Progression of disease; PR: Partial response; SAE: Serious adverse event; q8w, q12w: Every 8, 12 weeks, respectively; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; sCRT: Sequential chemoradiation therapy; WHO/ECOG PS: World Health Organisation/Eastern Cooperative Oncology Group Performance Status; TL: Target lesion.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

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

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice (GCP), and minimize risks to study integrity. Where allowable by local health authorities, ethics committees, health care provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent (note, in the case of verbal consent/reconsent, the ICF should be signed at the patient's next contact with the study site).
- Home or Remote visit: Performed by a site qualified health care professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

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

4.2 Scientific rationale for study design

4.2.1 Rationale for study safety endpoints

This study is designed to further evaluate the safety of durvalumab (MEDI4736) monotherapy, using a fixed-dosing regimen, in unresectable Stage III NSCLC patients who have not progressed following definitive, platinum-based sCRT. This study is designed to complement and expand the safety database from the ongoing Phase III PACIFIC Study. As the PACIFIC Study evaluated a weight-based dosing regimen (mg/kg) for durvalumab (MEDI4736), expanding data on the safety profile of the fixed-dose combination is warranted, particularly for more severe AEs, and in the context of the very recent concept of immune checkpoint blockade as consolidation therapy in unresectable Stage III NSCLC patients who have undergone sCRT. 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 (MEDI4736) under this context exists, including in the sub-populations of WHO/ECOG PS 0 to 1 and 2 patients, who have not been representatively included in pivotal studies.

In the PACIFIC Study, the majority of imAEs with durvalumab (MEDI4736) occurred during the first 6 months of treatment (see the current version of the durvalumab [MEDI4736] 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 2014, Weber et al 2017). The PACIFIC 6 Study will assess the safety of durvalumab (MEDI4736) within the first 6 months of treatment as defined by Grade 3 and Grade 4 TRAEs, including the evaluation of the nature of toxicities (SAEs, AEs, AESIs, imAEs), interventions and treatment, and outcome of treatment.

4.2.2 Rationale for study efficacy endpoints

The secondary aim of this study is to determine the efficacy of durvalumab (MEDI4736) 1500 mg q4w in terms of 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 mechanisms or additional clinical studies while the PACIFIC 6 Study is ongoing. This poses challenges in being able to fully characterize effects on OS if patients subsequently receive these immunotherapeutic agents.

Anti-tumour activity will be assessed according to RECIST 1.1 guidelines, with the understanding that in the context of post-radiation changes, tumour assessment may be difficult and may need to be repeated over time to reach a clear determination regarding responses and PD (see Section 8.1). The tumour-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' tumour data from all scans based upon RECIST 1.1.

4.2.3 Rationale for other study exploratory endpoints

CCI [redacted]

CCI [redacted]

CCI

CCI

4.2.4 Rationale for treatment duration

Treatment in this study will continue up to 24 months or until RECIST 1.1-defined PD and Investigator determination that the patient is no longer benefitting from treatment with IP, or until another discontinuation criterion is met (see Section 7.1). This guidance is supported by data from the CheckMate-153 Study that indicated that patients treated with nivolumab (an anti-PD-1 agent) until PD showed superior PFS when compared to treatment with nivolumab with a 1-year fixed duration (HR: 0.43; 95% CI: 0.25, 0.76), a trend toward improved OS, and no new safety signals after 1 year of treatment (Spigel et al 2017). In the PACIFIC Study, although patients were treated for up to 12 months with durvalumab (MEDI4736), no new safety signals were observed after 6 months of treatment. Numerous Phase 3 studies are currently evaluating durvalumab (MEDI4736) treatment until PD for patients with a variety of malignancies; while the results of these studies are not yet available, no new safety signals have been identified as a result of the longer duration. The 12-month and 18-month PFS rates following durvalumab (MEDI4736) treatment in Stage III NSCLC patients in the PACIFIC Study were 55.9% (95% CI: 51.0, 60.4) and 44.2% (95% CI: 37.7, 50.5), respectively, suggesting that a significant number of patients had to discontinue therapy prior to disease progression based on the 12-month treatment regimen. Based on these observations, no new safety signals are expected beyond 1 year of treatment with durvalumab, but there exists the potential for additional clinical and survival benefit beyond 1 year of treatment. 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 (MEDI4736) will be administered for a maximum of 24 months in this study.

4.2.5 Timing of treatment with durvalumab (MEDI4736) relative to sequential chemoradiation therapy

Non-clinical data show that both chemotherapy and ionising radiation up-regulate PD-L1 expression (Deng et al 2014, Zhang et al 2008). In addition, chemotherapy and radiotherapy both release new antigens leaving the cancer to act as an in situ vaccine that can elicit tumour-specific T cells. Thus, starting durvalumab (MEDI4736) as close as possible to the completion of the sCRT, 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 (MEDI4736) treatment initiation will be consistent with the PACIFIC Study, i.e., 42 days after the end of CRT.

4.3 Justification for dose

This study will utilise a fixed dose for durvalumab (MEDI4736) treatment (1500 mg q4w IV). Based on an average body weight of 75 kg, a fixed dose of 1500 mg of durvalumab (MEDI4736) q4w is equivalent to a weight-based dose of 20 mg/kg q4w.

4.3.1 Durvalumab (MEDI4736) monotherapy dose rationale

A durvalumab (MEDI4736) dose of 20 mg/kg q4w is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics (PDx), biomarkers, and activity data from Study 1108 in patients with advanced solid tumours and from a Phase I study performed in Japanese patients with advanced solid tumour (D4190C00002).

Pharmacokinetics/pharmacodynamics data

Based on available PK/PDx data from the ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg q2w or 15 mg/kg q3w, durvalumab (MEDI4736) exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab (MEDI4736) 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 (MEDI4736) with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (MEDI4736). (For further information on immunogenicity, please see the current durvalumab [MEDI4736] IB.)

Data from Study D4190C00006 (hereafter referred to as Study 006), a Phase I study in NSCLC patients using the combination of durvalumab (MEDI4736) and tremelimumab also show an approximately dose-proportional increase in PK exposure for durvalumab (MEDI4736) over the dose range of 3 to 20 mg/kg durvalumab (MEDI4736) q4w or q2w. (For further information on PK observations in Study 006, please see the current durvalumab [MEDI4736] IB.) The observed durvalumab (MEDI4736) PK data from the combination Study 006 were well in line with the predicted monotherapy PK data (5^{th} median and 95^{th} percentiles) for a q4w regimen.

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

($C_{trough,ss}$) 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, PDx, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of anti-drug antibody impact; and (d) achieve PK exposure that yielded maximal anti-tumour activity in animal models.

Given the similar area under the plasma concentration versus 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 based on 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 (MEDI4736) 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 (MEDI4736) using monotherapy data from Study 1108 and the PACIFIC Study (n=1310, doses including 10 mg/kg q2w or 15 mg/kg q3w or 20 mg/kg q4w; solid tumours). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (MEDI4736) (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg q2w or 20 mg/kg q4w) and fixed dosing (750 mg q2w or 1500 mg q4w) of durvalumab (MEDI4736) was evaluated by comparing predicted steady state PK exposure ($AUC_{ss,0\text{-}28days}$, $C_{max,ss}$, and $C_{min,ss}$) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg and a fixed dose of 1500 mg q4w was selected to approximate 20 mg/kg q4w (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 (10 mg/kg q2w) and fixed dosing (750 mg q2w) regimens yield similar median steady state PK exposures and associated variability, supporting the potential switch of durvalumab (MEDI4736) from weight-based to fixed dose. Similar considerations hold for the q4w dosing regimens (20 mg/kg q4w versus 1500 mg q4w).

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 mAbs 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/PDx 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, it was considered feasible to switch to fixed-dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg q4w durvalumab (MEDI4736) (equivalent to 20 mg/kg q4w) is included in the PACIFIC 6 Study.

4.3.3 Predictive biomarkers and rationale for an unselected population in the PACIFIC 6 Study

For this study, enrolment is not restricted to any biomarker-defined sub-population, but where possible, these patient characteristics are assessed in an exploratory manner and in the context of this study and other studies.

In the PACIFIC Study, benefit was also observed irrespective of PD-L1 status. Indeed, no significant between-group differences were noted in PD-L1 expression. Importantly, half the patients enrolled in this study had squamous cell lung cancer, in which the correlation between the PD-L1 biomarker and benefit in advanced-stage NSCLC is weak.

Tumour biopsies and viable tissue may be difficult to obtain post sCRT. Tumours evolve with time and in response to treatment and PD-L1 expression is likely to be different post cCRT. In addition, non-clinical data shows that both chemotherapy and ionising radiation up-regulate PD-L1 expression (Deng et al 2014, Zhang et al 2008). Therefore, PD-L1 expression from a biopsy sample prior to sCRT may not accurately reflect the state of disease at the time the patient enrols in this study. In addition, tumours that are poorly immunogenic or that have become immunosuppressive can likely be made immunogenic through administration of pro-immunogenic therapies designed to increase antigen release from the cancer cell. Therefore, as stated, inclusion in this study is not restricted based on PD-L1 expression from any available tissue samples. If it is feasible, biopsies will be taken post CRT. If possible based on the number and viability of the samples collected, it will be retrospectively assessed whether there is any correlation between PD-L1 expression and response to treatment.

Current experience with single-agent immunotherapy studies suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich the patient population by selecting patients likely to respond to therapy. At the time of the initial writing of this protocol, no assay has been established/validated and no single approach has proven accurate for Stage III NSCLC patient enrichment for immune-mediated therapies. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumour cells and or tumour-infiltrating cells may be associated with greater clinical benefit. For example, data presented by Roche for MPDL3280A suggest that PD-L1 expression on infiltrating lymphocytes in NSCLC, melanoma, and renal cell carcinoma patient cohorts is associated with greater clinical benefit from anti-PD-L1 treatment (Powderly et al 2013). Using a proprietary assay for PD-L1

immunohistochemistry, the authors found a 36% ORR in PD-L1-positive patients with 50% of patients who were PD-L1-positive having SD and 33% having a PR. In contrast, in PD-L1 negative patients, they found only a 13% ORR with 28% of patients having SD and 13% having a PR. Importantly, a significant portion of patients (17%) that were negative for PD-L1 were able to respond to MPDL3280A treatment.

Similarly, in data presented by Bristol-Myers Squibb, PD-L1 staining assessed using a different method and scoring algorithm appeared to be associated with greater clinical benefit in patients treated with nivolumab (anti-PD-1) (Grosso et al 2013). The authors found a 44% ORR in PD-L1-positive patients versus a 17% ORR in PD-L1-negative patients. Additionally, in their studies, PD-L1-positive patients had a higher PFS (9.1 months versus 2.0 months) and OS (21 months versus 12 months) than PD-L1-negative patients.

Therefore, while it appears that PD-L1 expression may improve the probability and/or quality of response to PD-1 pathway targeting agents and, therefore, may have merit as an enrichment tool, it is important to note that the published findings are from single-arm studies and may not permit to distinguish between prognostic factors or predictive markers for response to PD-L1 and PD-L1 therapies.

In summary, the Phase III PACIFIC Study demonstrated clinical benefit in patients irrespective of PD-L1 status; furthermore, it will be difficult to obtain post-sCRT biopsies immediately prior to enrolment in the PACIFIC 6 Study. Therefore, in the PACIFIC 6 Study, enrolment will not be restricted to any biomarker-defined sub-population.

4.4 End of study definition

The end of the study is defined as the last visit of the last patient undergoing the study. A patient is considered to have completed the study when he/she has completed his/her last study visit per protocol.

The final DCO is planned to occur when the last patient had the opportunity to receive durvalumab (MEDI4736) for a maximum of 24 months, followed by a 90-day safety follow-up period post the last dose of IP.

At the final DCO, the clinical study database will close to new data. However, patients will be permitted to continue to receive IP beyond the closure of the database if a rollover or safety extension study is available at the time of the final DCO and, in the opinion of the Investigator, they are continuing to receive benefit from IP. For patients who do continue to receive IP beyond the time of the final DCO, Investigators will continue to report all SAEs to AstraZeneca Patient Safety until 90 days after last IP dose, 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 non-serious AE ongoing at the time of this final 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 (Section 8.4.5), unless the event is considered by the Investigator to be unlikely to resolve or the patient is lost to follow-up.

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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 considered to be screen failures (refer to Section 5.6).

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

For inclusion in the study, patients should fulfil the following criteria:

Informed consent

1 Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the 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 informed consent prior to collection of sample for genetic analysis (optional).

The ICF process is described in Appendix A, A 3.

Age

4 18 years or older at the time of signing the ICF.

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]). Positron emission tomography (PET)/CT, MRI of the brain, and endobronchial ultrasound with biopsy are highly encouraged at diagnosis.

6 Receipt of sCRT which must have been completed within 42 days prior to first IP dose administration in the study.

(a) The platinum-based chemotherapy regimen must contain cisplatin or carboplatin and 1 of the following agents: etoposide, vinblastine, vinorelbine, a taxane (paclitaxel or docetaxel), or pemetrexed, according to the local SoC regimens. Platinum-based chemotherapy containing cisplatin or carboplatin and gemcitabine is permitted under certain conditions – refer to bullet point 6(b).

(b) Patients must have received at least 2 cycles of platinum-based chemotherapy before radiation therapy. The interval between administration of the last dose of chemotherapy regimen and start of radiation therapy must be no more than 6 weeks. Consolidation chemotherapy after radiation is not permitted.

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

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

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

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

(ii) Mean oesophagus <34 Gy;

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

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

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

7 Patients must not have progressed following platinum-based sCRT, as per Investigator-assessed RECIST 1.1 criteria. In order to assess disease progression, the baseline imaging (CT/MRI) used for Screening purposes should be compared against the most recently performed scan that allows physician assessment as per RECIST 1.1 criteria (i.e. fulfils the RECIST 1.1 defined imaging acquisition parameters). If an intermediate scan taken between chemotherapy and radiotherapy is available and that scan is suitable for physician assessment as per RECIST 1.1 criteria, then this scan should be used.

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

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

8 Must have a life expectancy of at least 12 weeks at enrolment.

9 WHO/ECOG PS ≤2.

10 Adequate organ and marrow function at enrolment as defined below. These parameters should be achieved without augmentation by growth factors, transfusions, or infusions within 14 days of screening unless required for SoC:

(a) Haemoglobin ≥9.0 g/dL;

(b) Absolute neutrophil count $>1.0 \times 10^9$/L;

(c) Platelet count >75 × 10^9/L;

(d) Serum bilirubin ≤1.5 × 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.

(e) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN.

(f) Measured creatinine clearance >40 mL/min or calculated creatinine clearance >40 mL/min as determined by Cockcroft-Gault (using actual body weight) (Cockcroft and Gault 1976).

Males:

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

Females:

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

Weight

11 Body weight >30 kg at enrolment and first IP dose administration.

Sex

12 Male or female.

Reproduction

13 Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. 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:

(a) 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 post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

(b) Women ≥50 years of age would be considered post-menopausal 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, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

5.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

Medical conditions

1 Patients with locally-advanced NSCLC whose disease has progressed following platinum-based sCRT.

2 Patients who have disease considered for surgical treatment as part of their care plan, such as Pancoast or superior sulcus tumours.

3 Mixed small-cell lung cancer and NSCLC histology.

4 History of allogeneic organ transplantation.

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

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

7 History of another primary malignancy except for:
   (a) Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
   (b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   (c) Adequately treated carcinoma in situ without evidence of disease.

8 History of leptomeningeal carcinomatosis.

9 History of active primary immunodeficiency.

10 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 surface antigen [HbsAg] result), **hepatitis C virus** (HCV), or **human immunodeficiency virus (HIV)** (positive HIV 1/2 antibodies). Patients with a past or resolved hepatitis B virus (HBV) 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 HCV ribonucleic acid (RNA).

11 Any unresolved toxicity of NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
   (a) Patients with Grade ≥2 neuropathy or Grade ≥2 lymphopenia will be evaluated on a case-by-case basis after consultation with the Study Physician.
   (b) Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab (MEDI4736) may be included only after consultation with the Study Physician.
12 Known allergy or hypersensitivity to durvalumab (MEDI4736) or any of the IP excipients.

Prior/concomitant therapy

13 Patients who have received cCRT for locally-advanced NSCLC, or who received sCRT with at least 2 concomitant CRT cycles. Prior surgical resection (ie, Stage I or II) is permitted.

   Note: Patients whose platinum-based chemotherapy contained gemcitabine and who received sCRT with at least 1 concomitant CRT cycle are excluded from this study.
14 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP.

   Note: Patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.
15 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP.

   Note: Local surgery of isolated lesions for palliative intent is acceptable.
16 Prior exposure to immune-mediated therapy, including but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.
17 Current or prior use of immunosuppressive medication within 14 days before the first dose of IP. The following are exceptions to this criterion:
   (a) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection);
   (b) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent;
   (c) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

Prior/concurrent clinical study experience

18 Previous IP assignment in the present study.
19 Concurrent enrolment in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up period of an interventional study.

20 Participation in another clinical study with an IP during the 4 weeks prior to the first IP dose administration.

21 Prior randomisation or treatment in a previous durvalumab (MEDI4736) ± tremelimumab clinical study regardless of treatment arm assignment.

Other exclusions

22 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 IP.

23 Judgment by the Investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions, and requirements.

24 Genetic research study (optional):

Exclusion criteria for participation in the optional (DNA) genetic research component of the study include:

(a) Previous allogeneic bone marrow transplant.

(b) Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection.

Procedures for withdrawal of incorrectly enrolled patients are provided in Section 7.3.

5.3 Lifestyle restrictions

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

1 Female patients of childbearing potential

(a) 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 1 **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 [MEDI4736] 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

(a) 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 [MEDI4736] 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.

(b) 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 post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal 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 MOA [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 IP or until alternate anticancer therapy is started.
4 Restrictions relating to concomitant medications are described in Section 6.4.

5.4 Patient enrolment

All patients will be centrally assigned to study drug using an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

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

1 Obtain signed informed consent from the potential patient before any study specific procedures are performed that are not part of routine medical care.
2 Obtain a unique 7-digit enrolment number (E-code), through the IVRS/IWRS. This number is the patient's unique identifier and will be maintained throughout the study.
3 Determine patient eligibility (see Section 5.1 and 5.2).
4 Obtain signed informed consent for genetic research study (optional and where applicable).

Patients will begin treatment on Day 1. If a patient does not meet eligibility criteria or withdraws from participation in the study after enrolment, then his/her E- number cannot be

reused. Investigator(s) should keep a record/screening log of patients who entered pre-study screening.

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 the study drug. 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 study drug, 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 the study drug. 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 fulfil 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". This reason for study withdrawal is only valid for screen failures (ie, not for patients who are assigned IP treatment). Patients may be re-screened a single time, but they may not be re-assigned IP treatment. If a patient who has failed screening is re-screened, 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6 STUDY TREATMENTS

Study treatment is defined as any IPs (including marketed product comparator and placebo) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to durvalumab (MEDI4736).

6.1 Treatments administered

6.1.1 Investigational product

AstraZeneca will supply durvalumab (MEDI4736) (described in Table 5).

Table 5 Study treatment

Study treatment name	Durvalumab (MEDI4736)
Dosage formulation	500-mg vial solution for infusion after dilution, 50 mg/mL
Route of administration	IV
Dosing instructions[a]	1500 mg IV q4w[b]
Packaging and labelling	Provided in 500-mg vials, labelled in accordance with GMP Annex 13 and per country regulatory requirement[c]
Provider	AstraZeneca

[a] Refer to Section 6.1.3 for details on duration of treatment and criteria for treatment through progression.

[b] If a patient's weight decreases to ≤30 kg, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab (MEDI4736) q4w until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab (MEDI4736) 1500 mg q4w.

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

Note: Cycles of durvalumab (MEDI4736) administration are 28 days.

GMP: Good Manufacturing Practice; IP: Investigational product; IV: Intravenous; q4w: Every 4 weeks.

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), CCI [redacted] CCI [redacted] The label claim fill volume is 10.0 mL.

Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

IP 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 (MEDI4736) doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the pharmacist using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

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

If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736)

concentration ranging from 1 to 20 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 (MEDI4736) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. The bag should be mixed by gently inverting to ensure homogeneity of the dose in the bag.

If participant weight falls to ≤30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag size selected such that the final concentration is within 1 to 20 mg/mL.

Standard infusion time is 1 hour ± 10 minutes, however if there are interruptions, the total allowed time should not exceed 8 hours at room temperature.

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

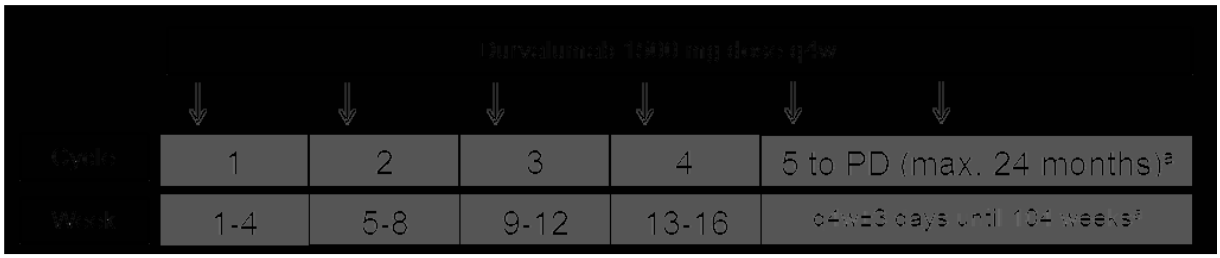
The IV line will be flushed according to local practices to ensure the full dose was administered. Infusion time does not include the final flush time.

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

6.1.2 Dose and treatment regimens

Patients will receive 1500 mg durvalumab (MEDI4736) monotherapy via IV infusion q4w for up to a maximum of 24 months from Cycle 1 Day 1 (up to 26 doses/cycles) with the last administration at Week 104 (Figure 3). The study drug should be discontinued prior to 24 months if there is clinical progression or confirmed radiological progression or if there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Please note, if a patient's weight decreases to ≤30 kg, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab (MEDI4736) q4w after consultation between the Investigator and Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab (MEDI4736) 1500 mg q4w.

Figure 3 Durvalumab (MEDI4736) monotherapy dosing schedule



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

Max.: Maximum; PD: Progression of disease; q4w: Every 4 weeks.

6.1.3 Duration of treatment and criteria for treatment through progression and discontinuation

Patients with CR, PR, or SD (based on Investigator assessment) following completion of sCRT will receive durvalumab (MEDI4736) treatment for a maximum of 24 months or until RECIST 1.1-defined PD (unless the Investigator considers the patient continues to receive benefit from the IP), initiation of alternative cancer therapy, 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 the study drug at the discretion of the Investigator and patient, as long as they are deemed to be receiving clinical benefit, after re-consenting for treatment through progression. 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.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG PS to >1 for the Cohort of PS 0 to 1 patients, and to >2 for the Cohort of PS 2 patients.
- 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 tumour compression, or spinal cord compression) requiring urgent alternative medical intervention. (Concurrent radiation treatment is not permitted. If patients require palliative radiation or prophylactic radiation [eg, of brain], consult AstraZeneca for exception to this rule; protocol therapy will need to be held prior to and during the radiation.)
- The patient still fulfils the eligibility criteria for this study (see Sections 5.1 and 5.2) with the exception of inclusion criterion 11 and exclusion criteria 13, 16, 17, 18, and 21.
- The patient agrees to re-consenting to be treated through progression.

An individual patient will not receive any further IP if any of the discontinuation criteria listed in Section 7.1 apply.

Treatment after final overall survival data cut-off

At the time of the final 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 final 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 final DCO may continue receiving IP if the Investigator judges that they are gaining clinical benefit.

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

For patients who do continue to receive IP beyond the time of the final DCO, 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 non-serious 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 (Section 8.4.5), 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.

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.

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 end of 24 months of study treatment, or at the time of the final DCO / 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.

6.1.4 Storage

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

6.2 Measures to minimise bias: randomisation and blinding

Not applicable.

6.3 Treatment compliance

All administrations of the IP should be recorded in the appropriate sections of the electronic case report form (eCRF).

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

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

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

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 (ie, until 90 days after last dose of IP), including the follow-up period following the last dose of IP.

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 enrolment or receives during the study must be recorded along with:

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

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 in 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 drug
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 drug
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 drug. (Concurrent use of hormones for non-cancer-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 IP
Immunosuppressive medications, including but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the immuno-oncology infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-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 non-immunotherapy 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 (MEDI4736). Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab (MEDI4736) has been given concomitantly

Prohibited medication/class of drug	Usage
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

AE: Adverse event; CRT: Chemoradiation therapy; CTLA-4: Cytotoxic T-lymphocyte antigen 4; EGFR: Epidermal growth factor receptor; IP: Investigational product; mAb: Monoclonal antibody; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; SoC: Standard of care; TKI: Tyrosine kinase inhibitor; TL: Target lesion; TNF-α: tumour necrosis factor alpha.

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 in Table 6	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management)	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.4.1 Other concomitant treatment

Medication, other than the supportive medication listed in Table 7, that 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 eCRF.

6.4.2 Durvalumab (MEDI4736) drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab (MEDI4736) either pre-clinically or in patients. As durvalumab (MEDI4736) is an mAb 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 (MEDI4736) will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected PK drug-drug interactions. The MOA of durvalumab (MEDI4736) involves binding to PD-L1, and therefore significant PDx 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 (MEDI4736), steroids and other immunosuppressant rescue medication have 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 supplying these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy related toxicities. These rescue medications must be receipted, controlled, and administered by the pharmacist and stored according to the labelled storage conditions, with temperature excursions reported accordingly by the pharmacist.

6.5 Dose modification

Dose delays are permitted for the management of certain IP-related toxicities as described in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1 and Dosing Modification and Toxicity Management Guidelines in the Annex document to this CSP). Dose reductions are not permitted.

6.6 Treatment after the end of the study

After the final analysis, AstraZeneca will continue to supply the IP to patients up to the time that they discontinue the treatment for whatever reason (see Section 6.1.3).

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study drug

An individual patient will not receive any further IP 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. Patient who discontinue treatment are normally expected to continue to participate in the study unless they specifically withdraw their consent to 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 (Section 8.4.5).
- Pregnancy or intent to become pregnant.

- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy including another IP.
- Clinical progression or confirmed radiological progression (refer to Appendix F) and Investigator determination that the patient is no longer benefitting from treatment with the IP.

7.1.1 Procedures for discontinuation of study drug

Discontinuation of study drug, 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 who 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 assessments with schedule relative to the date of administration of the last dose of IP (see Table 2).

Patients who permanently discontinue IP for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 assessments performed q8w ±1 week beginning 8 weeks after IP treatment initiation for the first 52 weeks and q12w ±1 week thereafter until clinical progression/deterioration or RECIST 1.1-defined radiological progression plus 1 or more additional follow-up scans for confirmation of progression until confirmed radiological progression, the end of study, death, study discontinuation, or Sponsor decision (whichever comes first). Additional scans are to be completed per standard practice post progression (not mandatory to be recorded in eCRF).

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 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 survival 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 potentially lost to follow-up, and evaluations should resume according to the protocol.

In order to support the analysis of the secondary endpoints of PFS and OS, the survival status of all enrolled patients should be re-checked; this includes those patients who withdrew consent or are classified as "potentially lost to follow-up."

- Potentially 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 eCRF 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 eCRF modules will be updated.)

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by, for example, repeat telephone calls, certified letter to the patient's last known mailing address, or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study, the patient should be considered to be lost to

follow-up with unknown vital status at the end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

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

Patients who withdraw consent for further participation in the study will not receive any further IP 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)
- The use of any samples (see Appendix C).

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Table 1 and Table 2.

A Web-Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

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 drug.

Adherence to the study design requirements, including those specified in 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 obtained before signing of the ICF may be utilised for screening or baseline purposes, provided that the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 1 and Table 2 and the patient consents to the use of these results.

8.1 Efficacy assessments

The key efficacy endpoints are: median PFS; proportion of patients progression-free at 12 months (PFS12) and 24 months (PFS24); median OS; proportion of patients alive at 12 months (OS12), 24 months (OS24), and 36 months (OS36), respectively; 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.

Tumour assessments utilise images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands), collected during 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 tumour 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 a maximum of 24 months or until disease progression (clinical progression/deterioration ± radiological progression by RECIST 1.1), and scanning/tumour assessments continue throughout treatment. An additional follow-up scan is requested following progression if clinically feasible.

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

8.1.1 Survival assessments

Assessments for survival must be made q12w (±2 weeks) following treatment discontinuation. 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. Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If participants are confirmed to be alive or if the death date is after the DCO date, then these participants will be censored at the date of DCO.

8.1.2 Patient-reported outcome assessments

'Patient-reported outcomes' is an umbrella term referring to any report of the status of a patient's health condition that comes directly from the patient, without interpretation of anyone else. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical studies. The following PRO questionnaires will be administered in this study: CCI

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8.1.2.1 CCI

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8.1.2.2 CCI

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8.1.2.3 CCI

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8.1.2.4 Administration of patient-reported outcome questionnaires

Patients will perform the PRO assessments using an electronic tablet (ePRO) during clinic visits and will take approximately 15 minutes to complete.

Each centre must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be administered and completed at the clinic as per Table 1 and Table 2.

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

- PRO questionnaires must be completed prior to treatment administration. As feasible, site staff should ensure PRO questionnaires are completed prior to discussion of disease progression and other study procedures, such as laboratory samples to further avoid biasing the patient's response to the questions.
- The research nurse or appointed site staff should stress that the information is confidential. Therefore, if the patient has any medical problems, he or she should discuss them with the doctor or research nurse separately from the PRO assessment. The PRO questionnaires must be completed in private by the patient.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items. The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. The patients should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided in the ePRO device.
- All PRO questionnaires are to be completed using an ePRO device. If technical or other issues prohibit completion on the device, an appropriate back-up option may be considered for the study with prior approval and instruction from the Sponsor.

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

As a general rule, site staff should not read or complete the PRO questionnaires on behalf of the patient (see Section 4.1.1 for study conduct mitigation during study disruptions). If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient should be exempted from completing PRO questionnaires but may still participate in the study.

Patients exempted in this regard should be flagged appropriately by the site staff in the source documents.

8.1.2.5 Calculation or derivation of patient-reported outcome variables

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Table 8 CCI

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Table 9 CCI

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8.2 Safety assessments

Planned timepoints for all safety assessments are provided in Table 1 and Table 2.

8.2.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see 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. Urine 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 soon as possible (preferably within 24 to 48 hours).

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

The laboratory variables to be measured are presented in Table 10 (clinical chemistry), Table 11 (haematology), and Table 12 (urinalysis).

Other safety assessments to be performed at screening include HbsAg, hepatitis C antibodies, and HIV antibodies.

The following laboratory variables will be measured.

Table 10 Clinical chemistry

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

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × ULN (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 1 of these parameters is routinely measured, then either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, 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 IP dose administration), 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.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IP: Investigational product; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-stimulating hormone; ULN: Upper limit of normal.

Table 11 Haematology

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

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

[b] For coagulation parameters, activated partial thromboplastin time (either as ratio or as an absolute value in seconds) and international normalised ratio are to be assessed at baseline on Day 1 and as clinically indicated.

Table 12 Urinalysis

Bilirubin	Ketones
Blood	pH
Colour and appearance	Protein
Glucose	Specific gravity

Note: Microscopy is preferred to investigate white blood cells and use the high-power field for red blood cells, dipstick can be used as well.
Note: Urinalysis should be done at baseline (screening) and then as clinically indicated.

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

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 Table 1 and Table 2). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, haematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilised by the Investigator on the basis of clinical observations and symptomatology. Targeted physical examinations during the treatment cycles (C1 onwards) are not required for asymptomatic patients. 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 respiratory rate) will be evaluated according to the assessment schedules (see Table 1 and Table 2). Body weight is also recorded at each visit along with vital signs. The following timepoints for vital signs assessments apply to infusions of durvalumab (MEDI4736).

First IP dose administration

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

BP and pulse, and other vital signs (including temperature and respiratory rate) will be collected before, during, and after IP infusion at the following times (based on a 60-minute ± 10 minutes infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minute [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±10 minutes)
- A 1-hour observation period is recommended after the first infusion of IP. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each IP infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. Additional monitoring with assessment of vital signs will be at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Subsequent IP dose administrations

BP, pulse, and other vital signs (including temperature and respiratory rate) should be measured and collected/recorded in the eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered in an unscheduled vital signs eCRF 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, please enter the vital signs values into the eCRF.

8.2.4 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study (see Table 1). 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 QT interval corrected for heart rate using Fridericia's formula (QTcF) value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

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

8.2.5 Early patient review for safety

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

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8.2.7 Other safety assessments

If new or worsening pulmonary symptoms (eg, dyspnoea) 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, haematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to

exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis /ILD should be considered and the Dosing Modification and Toxicity Management Guidelines (Section 8.4.5) 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 (including images) will be collected.

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

8.3 Collection of adverse events

The 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 and SAE can be found in Appendix B.

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

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

8.3.1 Method of detecting adverse events and serious adverse events

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

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

AEs and SAEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (90 days after the last dose of IP). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late-onset toxicity to study drug then it should be reported as an AE or SAE, as applicable.

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

Investigators are not obligated to actively seek AE or SAE 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 drug or study participation, the Investigator may notify the Sponsor.

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

8.3.3 Follow-up of adverse events and serious adverse events

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation or study completion.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 90 days after the last dose of IP), but without further recording in the eCRF. Any SAE or non-serious 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 (Section 8.4.5), unless the event is considered by the Investigator to be unlikely to resolve or the patient is lost to follow-up. 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 the 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 fulfilled
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8.3.5
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 4.03 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 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, B 2. An AE of severe intensity need not necessarily 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, 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, 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 investigational product?"

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

A guide to the interpretation of the causality question is found in Appendix B, B 7.

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

8.3.7 Adverse events based on examinations and tests

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

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Sections 8.3.9 and 8.3.10.

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 total bilirubin ≥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 HL.

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 that are unequivocally due to disease progression should not be reported as an AE during the study.

8.3.10 New cancers

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

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 IP must be reported as follows:

- Death clearly the result of 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 co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca 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 IP 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 the IP 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 and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. 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 (MEDI4736) 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 (MEDI4736) 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 aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions with regard to an event being an imAE, the Investigator should promptly contact the Study Physician. AESIs may have additional clinical information collected in the eCRF.

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, skin, hematological, rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab (MEDI4736) IB. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (Section 8.4.5). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the IP/study regimen by the reporting Investigator.

8.3.13 Safety data to be collected following the final data cut-off of the study

For patients continuing to receive IP 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 IP in order to manage AEs in accordance with the durvalumab (MEDI4736) Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5). All data post 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 IP treatment (or within the 90 days following the last dose of IP treatment) post the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he/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 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

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

If the WBDC system is unavailable, the Investigator will contact the Study Representative immediately. The Study Representative will give guidance on how to send the SAE report, eg, using a paper back-up SAE report, recognizing that the same reporting time frames still apply.

As soon as the WBDC system is available again, the Investigator must enter all SAE information in the WBDC system as well.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such.**

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for pregnancy discovered before the study patient has received any IP.

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 or 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 to 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal exposure

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

Pregnancy of the patient's partners 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 IP 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 Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) prior to use.

8.4.3 Overdose

Use of durvalumab (MEDI4736) 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 (MEDI4736), 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 eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he/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.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error 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 completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

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

8.4.5 Management of investigational product-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 4.03.

8.4.5.1 Specific toxicity management and dose modification information – Durvalumab and durvalumab + tremelimumab

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 inhibitors, durvalumab [MED4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or 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 anti-cancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document 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 maintained within the Site Master File.

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 aetiology, events should be considered potentially immune-related. In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 7.1 of this protocol and the TMGs). Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines (see the Annex document to this CSP). 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 and the durvalumab + tremelimumab regimen by the reporting Investigator.

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

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

PDx parameters are not evaluated in this study.

8.7 CCI

8.7.1 CCI

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8.7.2 CCI

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8.8 CCI

8.8.1 CCI

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8.8.1.2 CCI

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8.8.4.3 CCI

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8.9 Health economics

Health economic parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No formal statistical hypothesis will be tested in this study.

9.2 Sample size determination

The primary objective of this study is to assess the safety and tolerability of durvalumab (MEDI4736) which is defined as Grade 3 and Grade 4 TRAEs observed within 6 months after the initiation of durvalumab (MEDI4736) treatment. In addition, safety and tolerability of durvalumab (MEDI4736) will be characterized for the cohorts of WHO/ECOG PS 0 to 1 and 2 patients.

This is a safety study and no formal sample size calculation will be done. Between 100 and 120 patients will be enrolled in the WHO/ECOG PS 0 to 1 Cohort and up to 30 patients in the WHO/ECOG PS 2 Cohort depending on recruitment. CCI [redacted]

CCI [redacted]

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[redacted]

9.3 Populations for analyses

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 1 dose of IP. 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

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 (MEDI4736) 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 pre-defined 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 (MEDI4736) to the onset of an AESI pre-defined 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.

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

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.

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

OS (days) = Death date or Censor date – treatment start date +1

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.

9 **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.

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

11 **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

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

The end of response should coincide with the date of progression or death from any cause used for the 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.

12 CCI [redacted]

13 **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 Statistical analysis plan (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 TEAEs will be included. TEAEs 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.

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 TRAEs will be reported for patients overall and separately for the cohorts of WHO/ECOG PS 0 to 1 and 2 patients.

9.5.2 Analysis of the secondary variables

9.5.2.1 Safety variables

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 last dose 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 the last dose 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 pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable, the patient need only have 1 post-dose 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 WHO/ECOG PS 0 to 1 and 2 patients 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 12 and 24 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, 24, and 36 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.

9.5.2.3 Patient-reported outcomes

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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. However, the SC will conduct an early safety evaluation when 10 patients in the WHO/ECOG PS 2 cohort have been treated for a minimum of 6 months or discontinued due to an AE or disease progression, whichever occurs first. At the time of the early safety evaluation, safety data for patients in the WHO/ECOG PS 0 to 1 cohort will also be provided to the SC for completeness in the overall risk/benefit assessment. If needed for publication purposes, an additional early assessment of study data may be conducted when minimum 50 patients in the WHO/ECOG PS 0 to 1 cohort or WHO/ECOG PS 2 cohort have had the opportunity to receive durvalumab (MEDI4736) for a minimum of 6 months.

Details of the early safety evaluations will be documented in the SAP and SC Charter. In addition to the early safety evaluations, during the study, data may be summarized and presented at congresses or conferences.

9.6.1 Steering committee

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 Organisation 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 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 and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, 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 amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

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

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 authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorised 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 (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

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 authorised 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.

Patients must be re-consented for treatment through progression.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorised 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 study, the partner is asked to sign the "Adult Study ICF 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 authorised 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 analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document. AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient's medical information and the genetic files would remain physically separate.

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees 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 CSP and letters to Investigators.

A 6 Dissemination of clinical study data

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 authorised 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 15 years after study completion unless local regulations or institutional policies require a longer retention period. 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. Source data are contained in source documents (original records or certified copies).

A 9 Study and site closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study drug development

A 10 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 multi-centre 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 AE is the development of any untoward medical occurrence 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 unfavourable 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 non-serious 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 event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.
- Adverse Events for malignant tumours 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 judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.
- In Oncology studies, the above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is not the tumour 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 tumour under study). Malignant tumours 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 tumour.

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 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). 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, hospitalisation, disability or incapacity but may jeopardise 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 anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 CTCAE Grade

The grading scales found in the revised NCI CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE 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, 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 a SAE unless it meets the criteria shown in Appendix B, 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 a SAE when it satisfies the criteria shown in Appendix B, 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 aetiology 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 recognised 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

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

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 participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised 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 participant
- Drug not administered as indicated, for example, 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
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

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

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

- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

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

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre will keep full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

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

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

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

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

The Investigator:

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

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and the site is informed.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- Are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, HIV types 1 and 2. They are assigned the following UN number and proper shipping name:

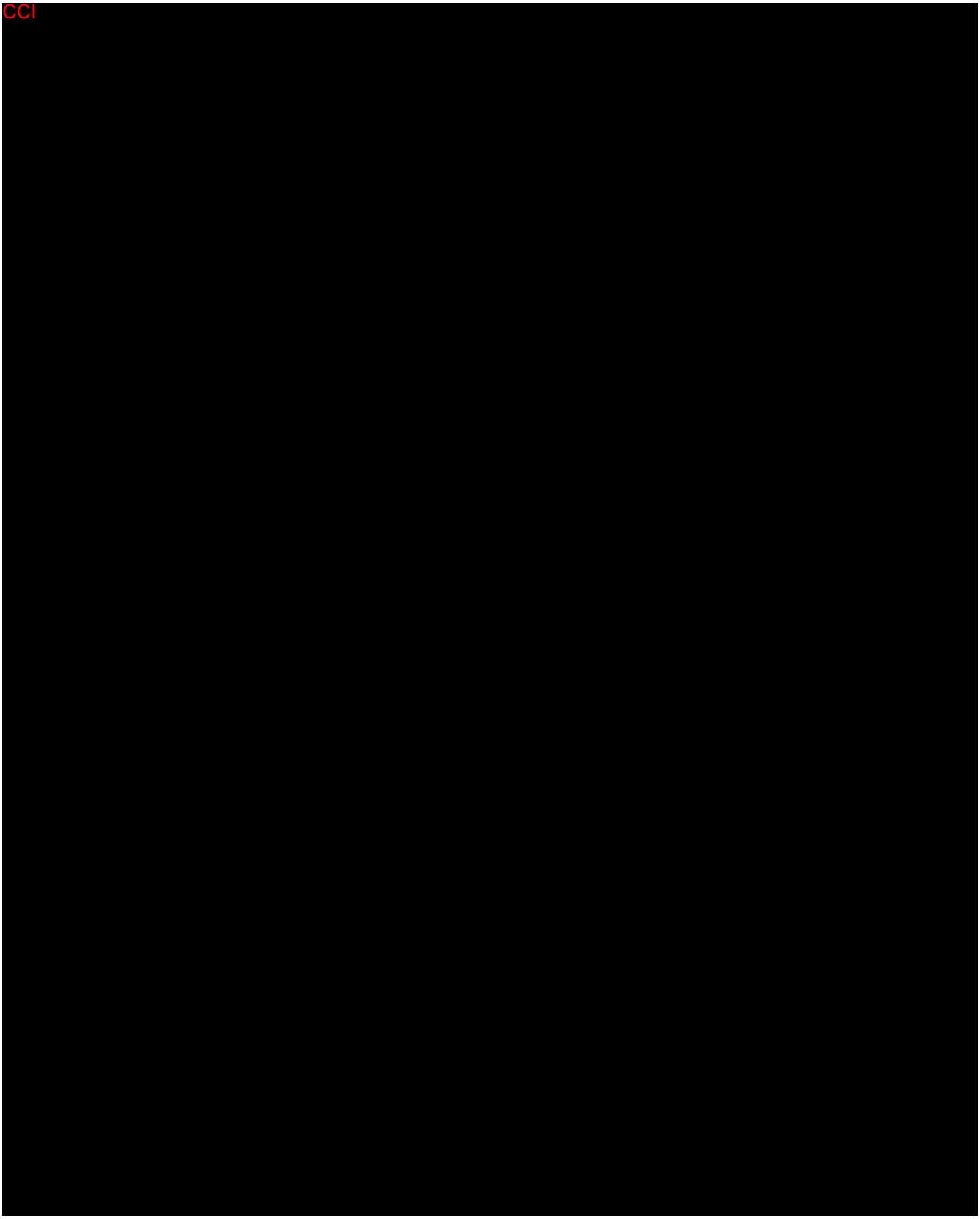
- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

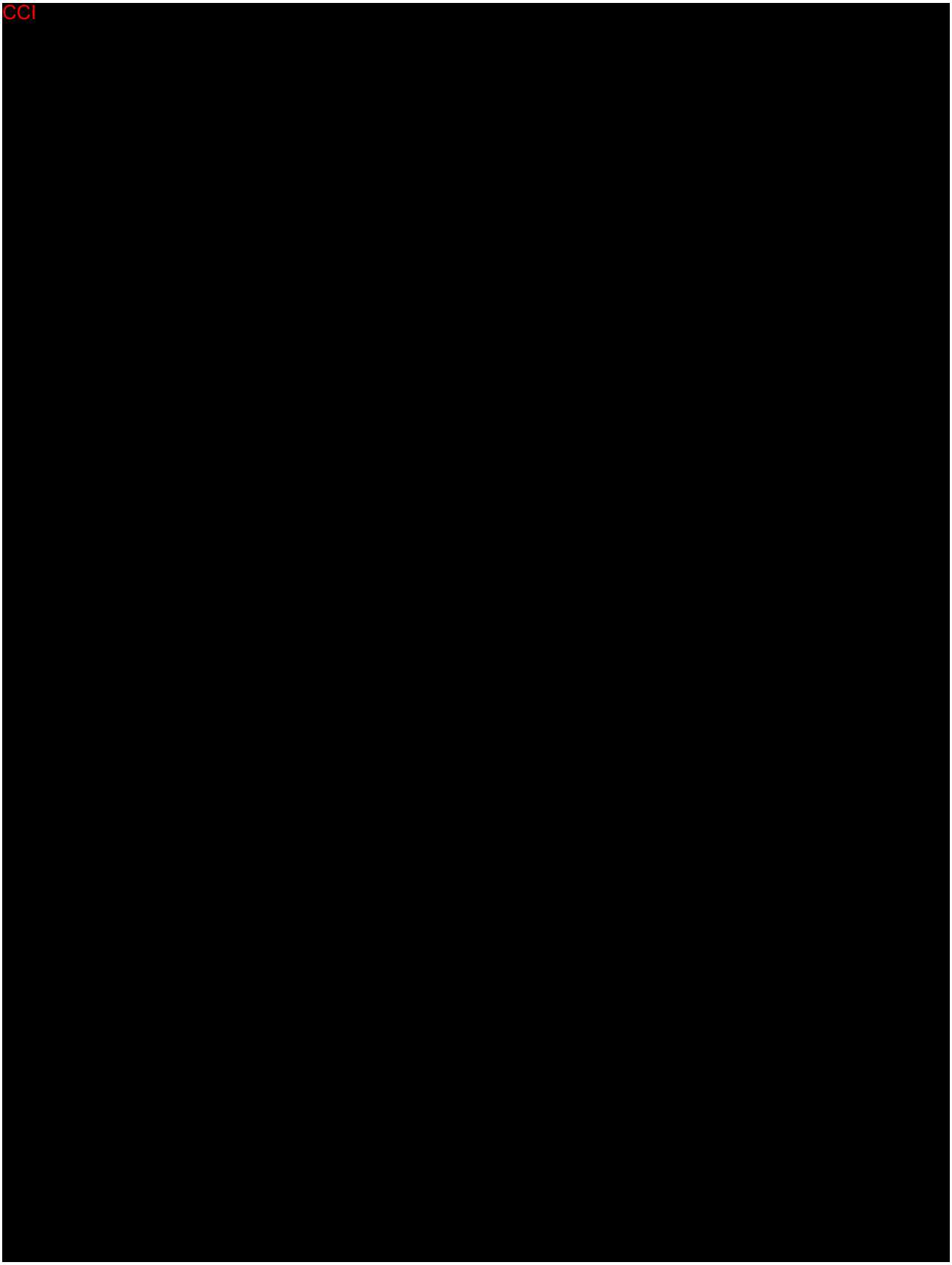
Exempt – all other materials with minimal risk of containing pathogens

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient
- Temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D CCI

CCI

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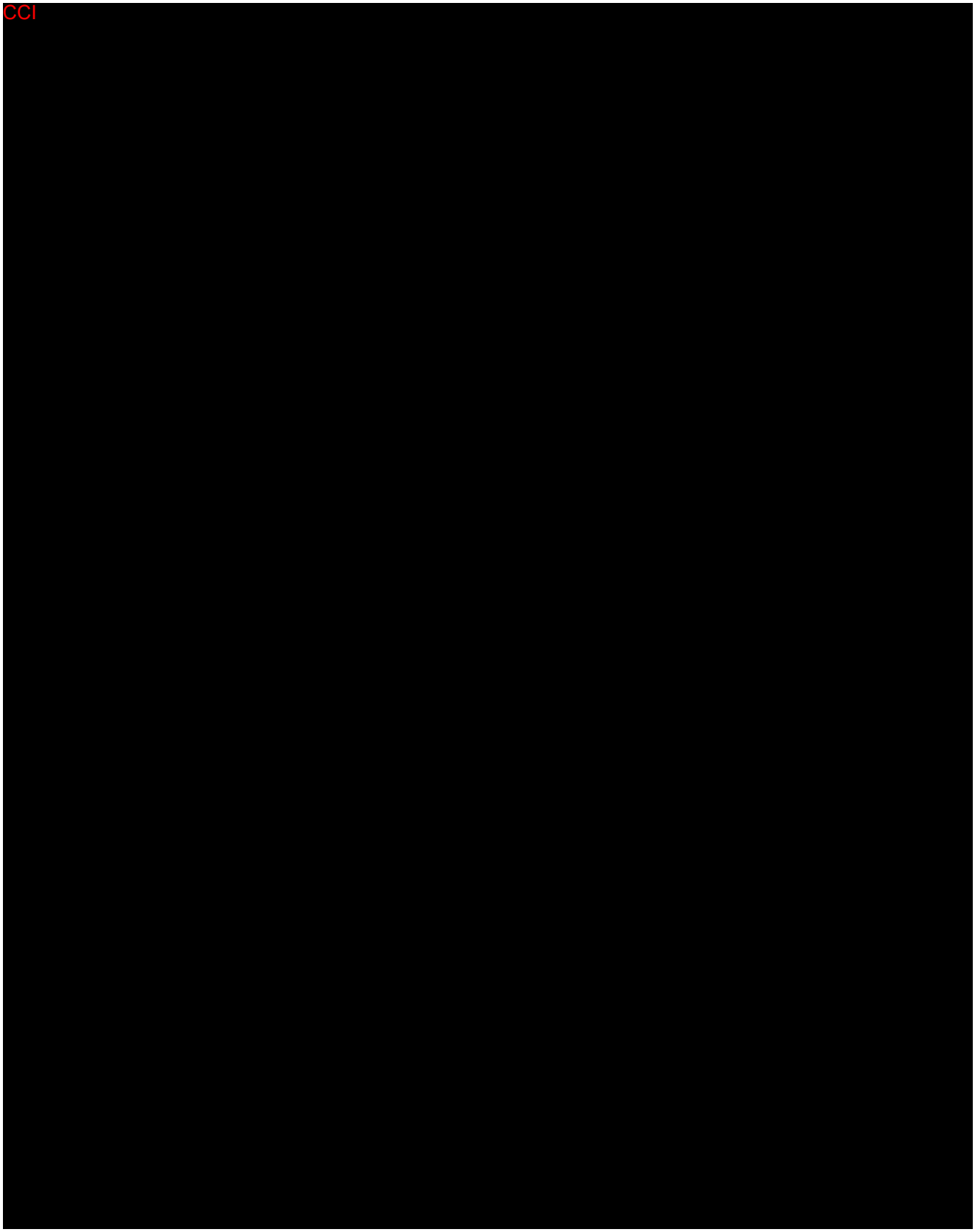
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Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report cases of HL. 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 (Section 8.4.5).

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 potential Hy's law (PHL) criteria at any point during the study.

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 AE and SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's law (PHL)

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

Hy's law (HL)

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
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Appendix E, E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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, 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:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's law criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up 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.
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the 3 Liver CRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

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.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts 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 IP. The AstraZeneca 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.

If 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 AE/SAE, record the AE /SAE in the CRF accordingly and follow the AstraZeneca standard processes

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

- Report an SAE (report term 'Hy's law') according to AstraZeneca Standard processes.
  - The 'Medically Important' 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 3 weeks 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:

- Report an SAE (report term 'Potential Hy's law') applying serious criteria and causality assessment as per above
- 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 met. Update the SAE report according to the outcome of the review 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 drug

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

At the first on-study drug occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the patients' 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, E 5.
- # 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 drug, 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 drug and at first on-study treatment visit, as described in Appendix E, E 6.

If **No**: Follow the process described in Appendix E, E 4.1.

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, E 4.

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 tumour response using RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumours)

Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009) for this study with regard to Investigator assessment of tumour burden including protocol-specific requirements for this study. Additional special guidance is provided for determination of confirmation of radiologic progression.

Patients with measurable disease and/or non-measurable and/or NED assessed at baseline by CT/MRI will be entered in this study.

Definitions of measurable, non-measurable, target and non-target lesions

Measurable:

A lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis[1] diameter of ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

Non-measurable:

- 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[2]).
- Truly non-measurable 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 non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as TLs.

[1] The short axis is defined as the longest axis perpendicular to long axis.
[2] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

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 that it fulfils the criteria for reproducible measurability and is the only lesion available.

Non-target lesions:

Additional measurable lesions not recorded as TLs and non-measurable 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 NLs is provided in Table 14.

Table 14 Summary of imaging modalities for tumour assessment

Target lesions	Non-target lesions	New lesions
CT (preferred) MRI	CT (preferred) MRI Plain X-ray Chest X-ray	CT (preferred) MRI Plain X-ray Chest X-ray Bone scan FDG-PET/CT

CT: Computed tomography; FDG-PET/CT: 18F-Fluoro-deoxyglucose positron emission tomography/computed tomography; 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 NLs.

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 tumour 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 IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV MRI contrast of the abdomen is appropriate. In patients with severely

compromised renal function a non-contrast 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 timepoints per patient.

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumours 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 NLs.

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 1.1 assessment of tumours as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumour size. Tumours 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 tumour assessments as they are not validated in the context of tumour assessment.

Tumour markers

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

Histology and cytology

Histology on tumour biopsy samples will not be used as part of the tumour 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 tumour 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 NLs 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. NLs 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 scan

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scans may be used as a method for identifying NLs, according to the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[3] 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 NLs on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to verify NLs.

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 tumour measurements by RECIST 1.1. In exceptional situations, if a study site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumour 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.

[3] 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.

Tumour response evaluation

Schedule of evaluation

The methods of assessment of tumour 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, NLs at follow-up.

Baseline assessments should be performed no more than 28 days before the date of first IP administration, and ideally should be performed as close as possible to the date of first IP administration. Efficacy by RECIST 1.1 for all patients will be assessed according to the schedules of assessment. 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 target lesions

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. TLs 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, which 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 millimetres. 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 NL.
- 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 1.1 CRF. 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 tumour 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 NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: if the sum of diameters meets the PD criteria, PD overrides NE as a TL response.

TL: Target lesion.

Non-target lesions

Evaluation of non-target lesions

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 study site at each visit (see Table 16).

Table 16 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of 1 or more NTL.
Progression of disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 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 1 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.

NTL: Non-target lesion; TL: Target lesion.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New lesions

Details of any NLs will also be recorded with the date of assessment. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour. If a NL is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the previously NL has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a NL 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 tumour 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	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD 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: Non-target lesion; PD: Progression of disease; PR: Partial response; SD: Stable disease.

Confirmation of radiological progression

A follow-up scan is performed 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 tumour assessments of this follow-up scan. Patients with confirmed radiological PD who continue to receive study drug at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit and will continue to have tumour 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):

- ≥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 NLs 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 tumour evaluation using RECIST 1.1 are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours 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 timepoints. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumours 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 non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised 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 NE from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or NLs, 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

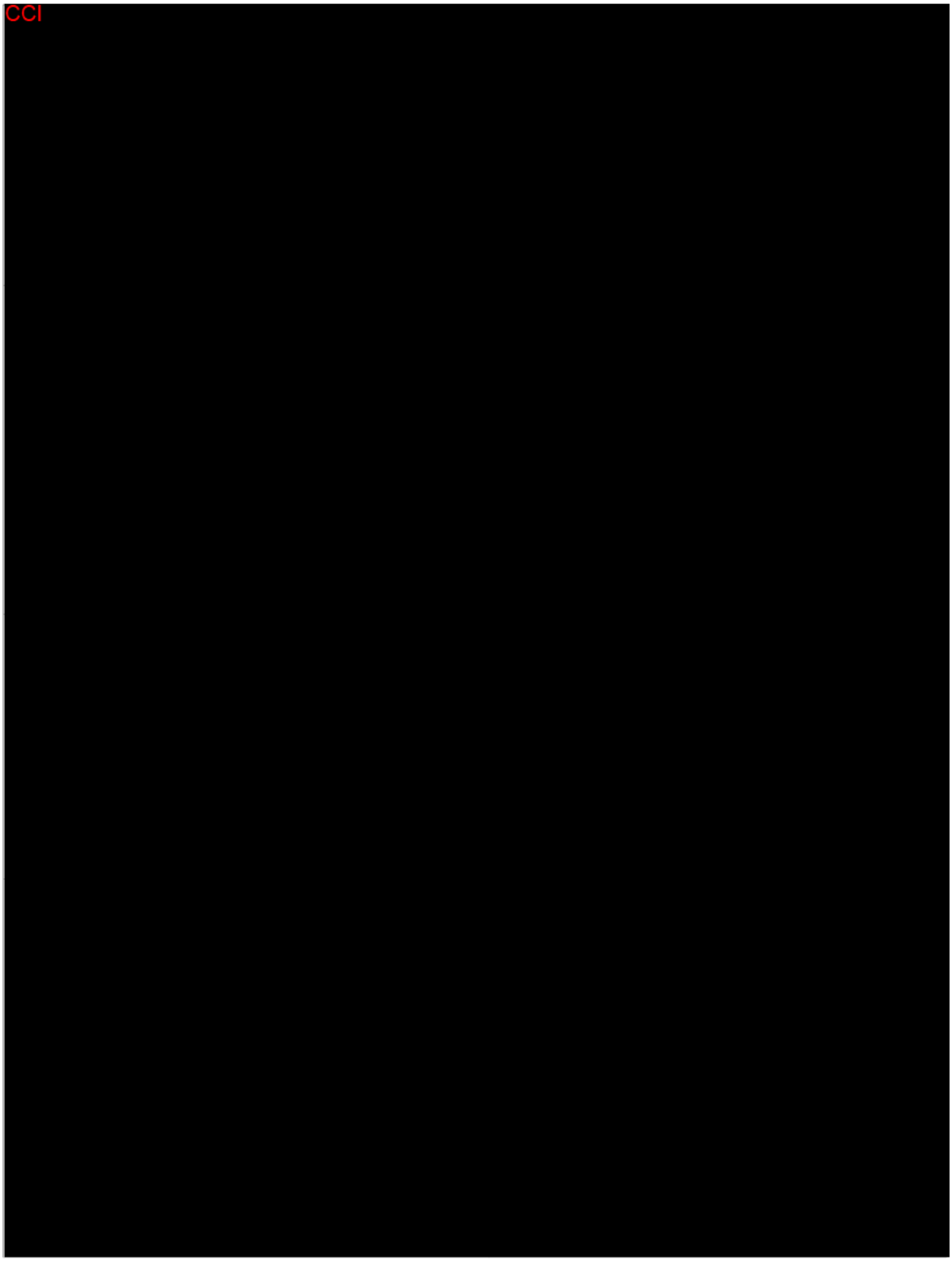
MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be 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 optimised for the specific body part being imaged as well as the scanner utilised. CT of the chest is typically recommended over MRI due to significant motion artefacts (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.

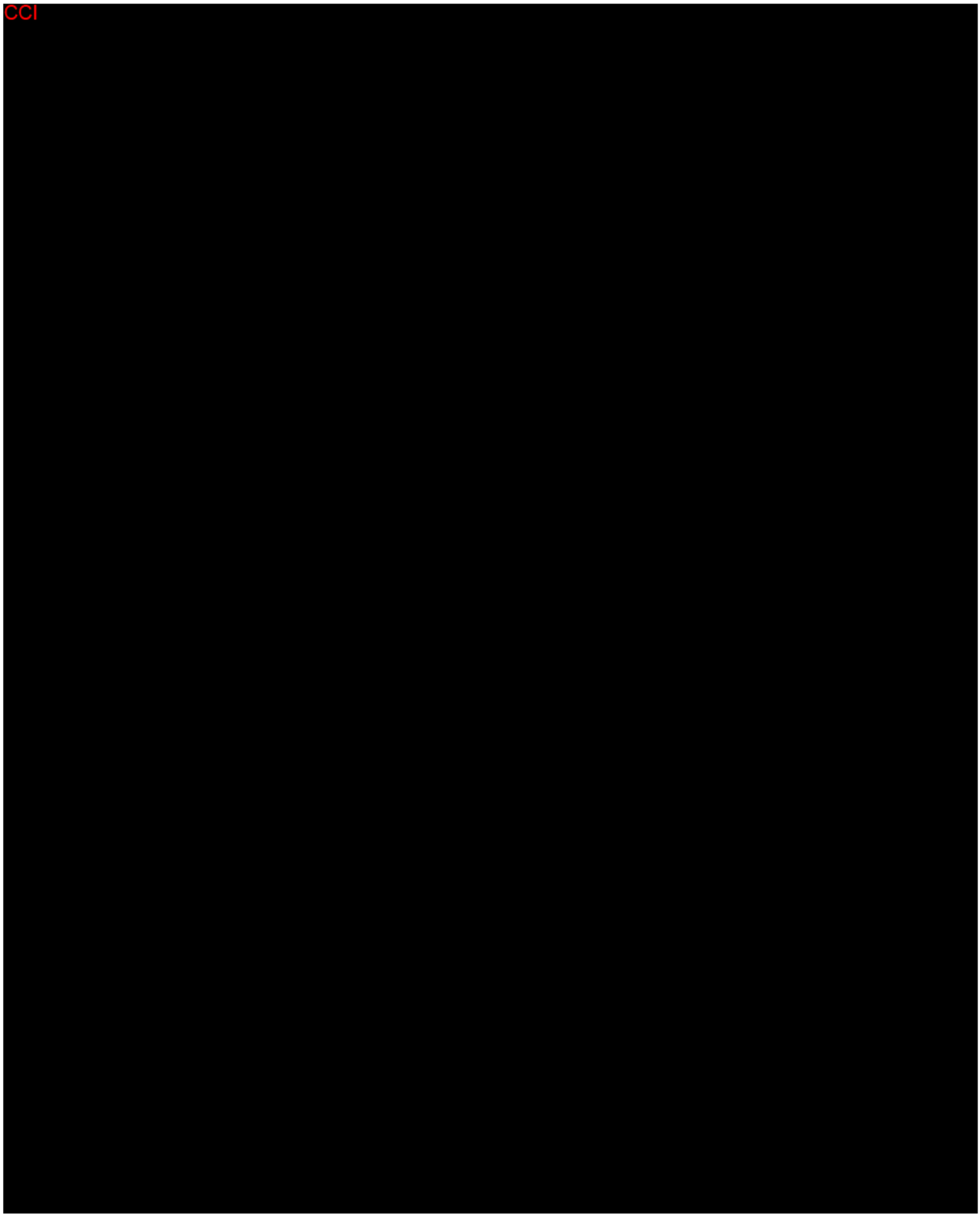
For these reasons, CT is the imaging modality of choice.

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 tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix G Patient-reported outcomes

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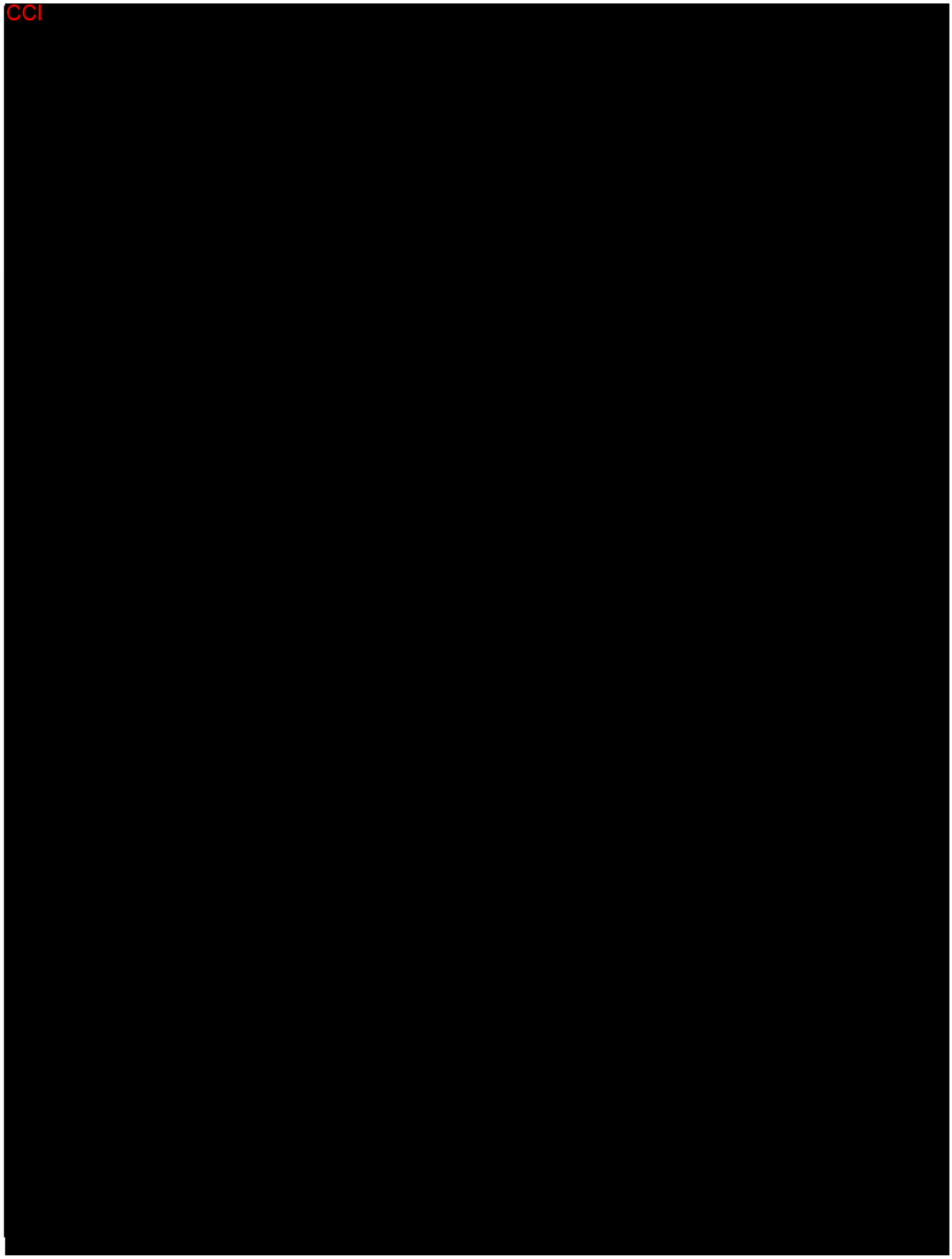
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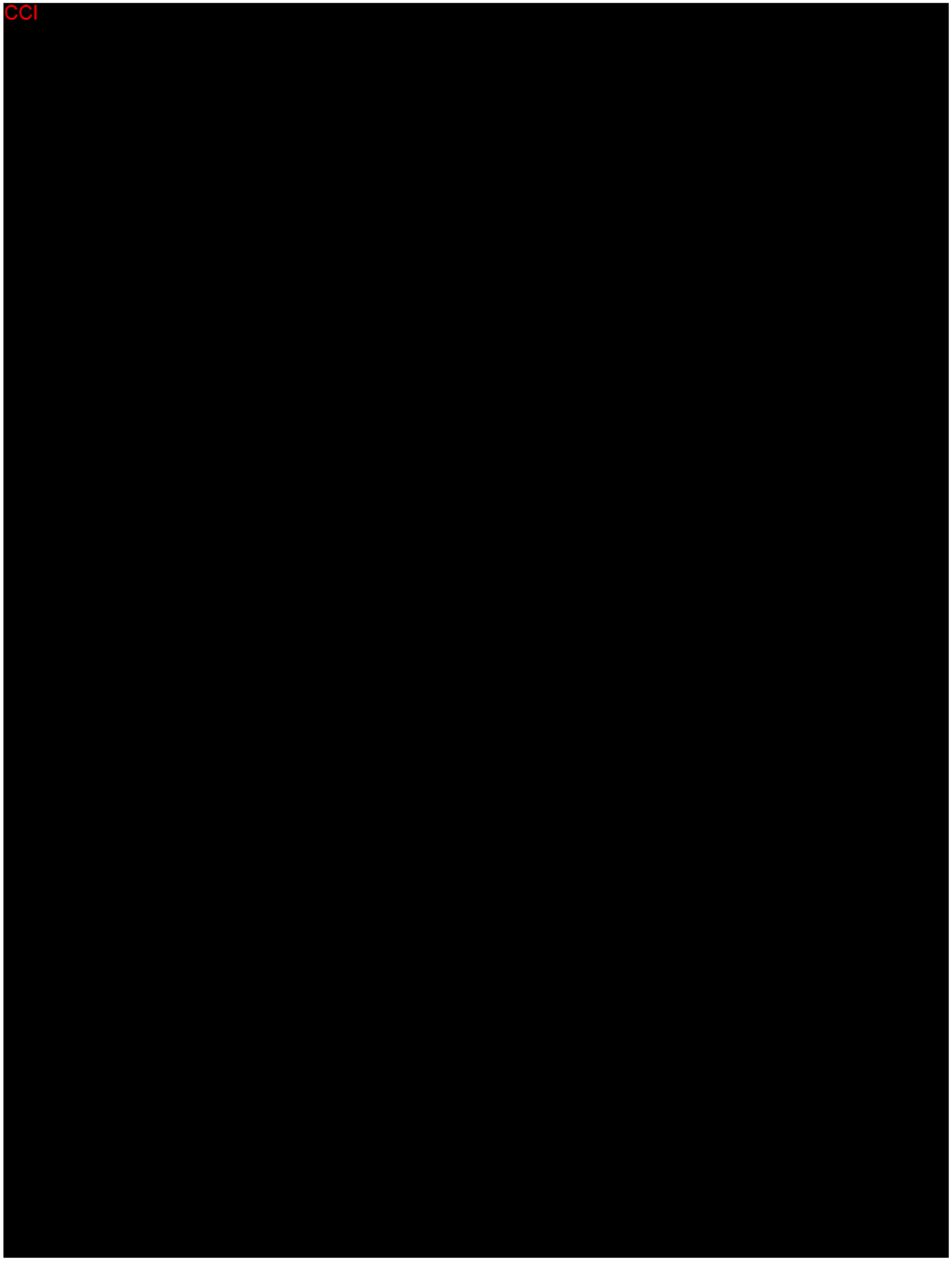

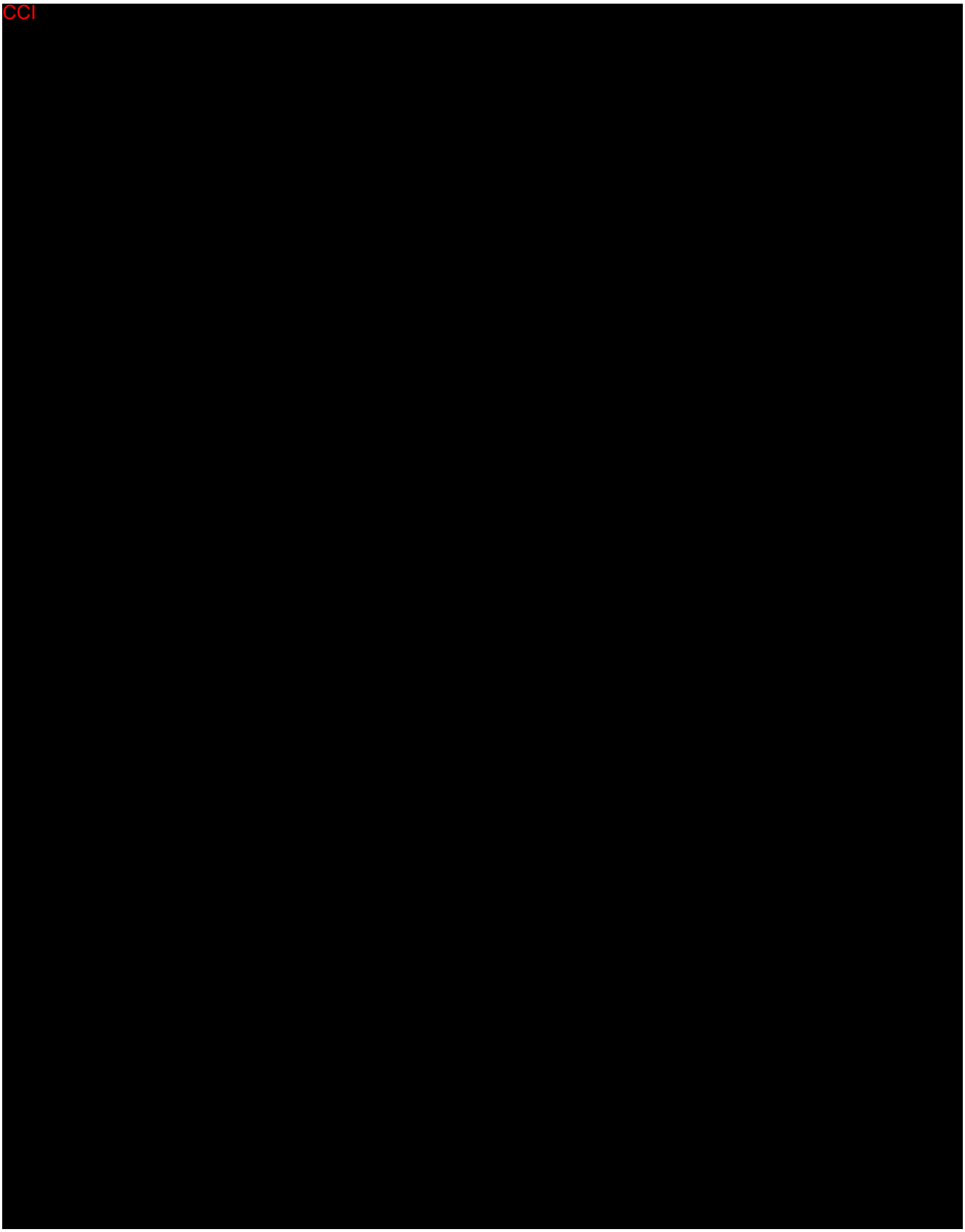
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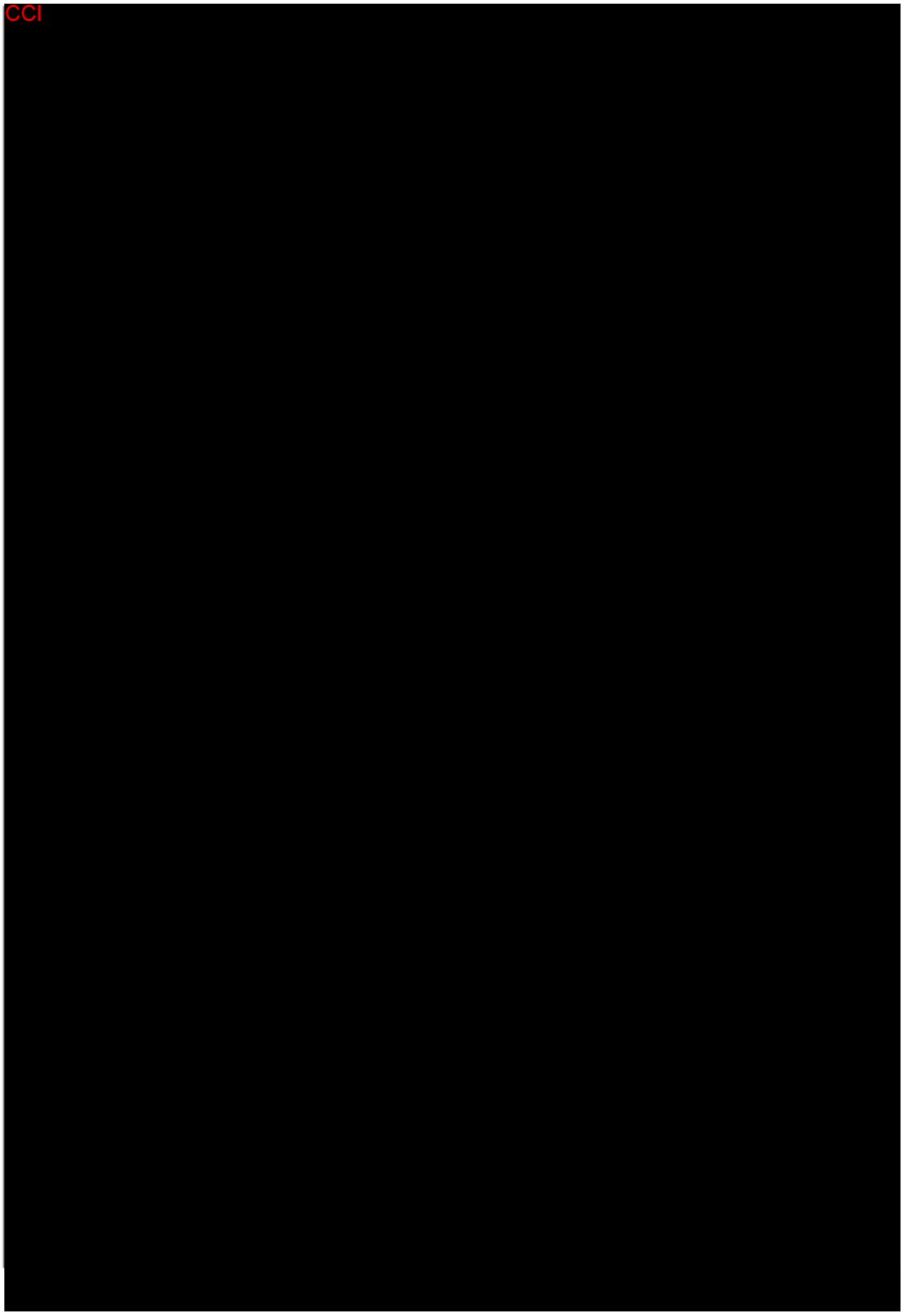
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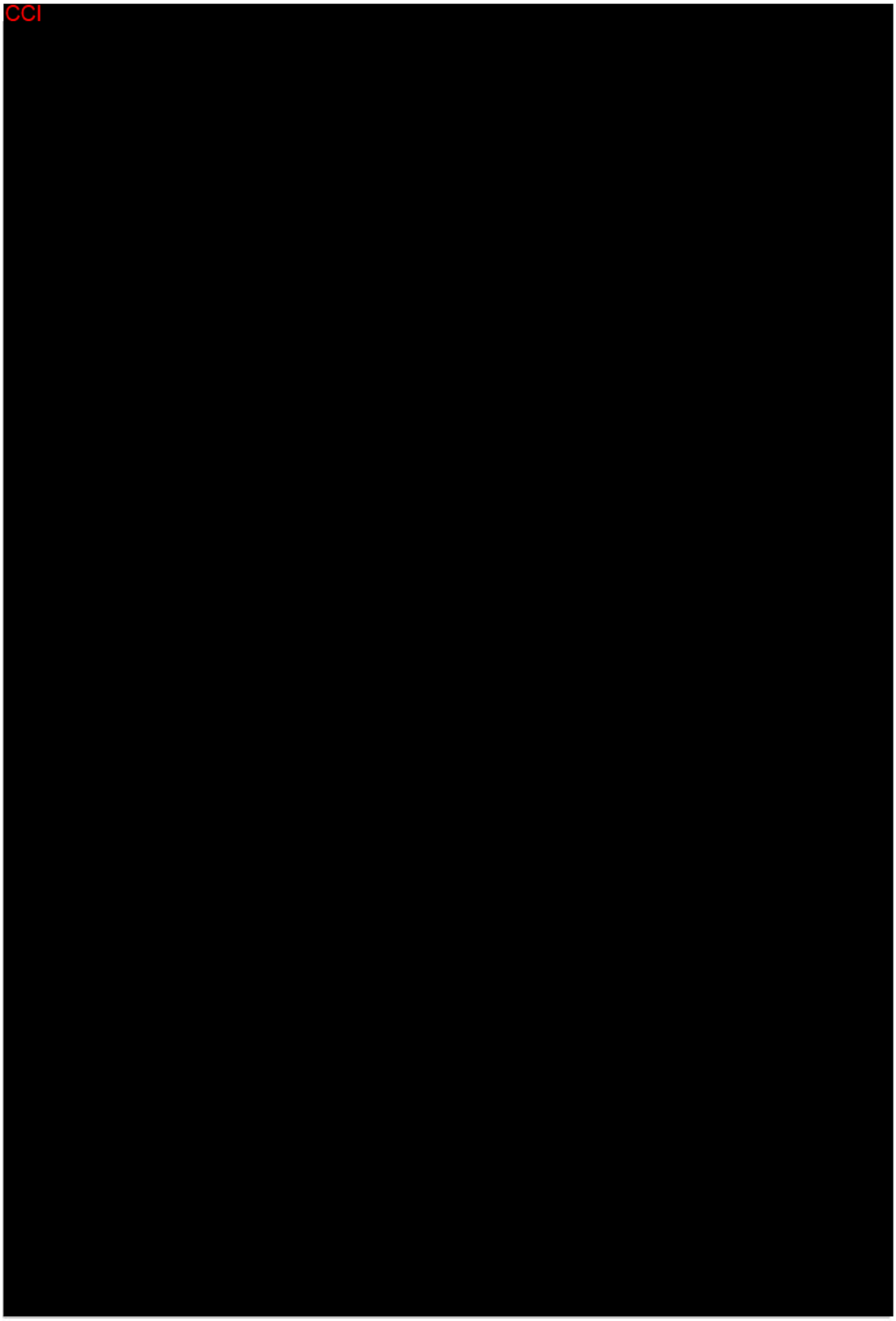
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Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

H 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections H 2 to H 5. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Rescreening of Participants to Reconfirm Study Eligibility

Not applicable.

H 3 Home or Remote Visit to Replace On-site Visit (Where Applicable)

A qualified HCP from the study site or TPV service may visit the participants home/or other remote location as per local Standard Operating Procedures (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

H 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication to be reported and documented.

H 5 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

H 6 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section H 8). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

Notably, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.2, Exclusion Criterion 6).

H 7 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section H 9 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention durvalumab. The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation,

continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

H 8 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the Discontinuation of IP Form completed.

H 9 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

H 9.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

H 9.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab/tremelimumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

H 9.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

H 9.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

H 10 References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

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EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

Appendix I Abbreviations

Abbreviation or special term	Explanation
AchE	Acetylcholine esterase
ACTH	Adrenocorticotropic hormone
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
AUC_{ss}	Area under the plasma concentration versus time curve at steady state
B7-H1	B7 homolog 1
BNP	Brain-type natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
C	Cycle
cCRT	Concurrent chemoradiation therapy
CD	Cluster of differentiation
CI	Confidence interval
$C_{max,ss}$	Maximum drug concentration at steady state
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRT	Chemoradiation therapy
CSP	Clinical Study Protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CCI	CCI
CTLA-4	Cytotoxic T-lymphocyte antigen 4
$C_{trough,ss}$	Trough plasma concentration
DCO	Data cut-off
DILI	Drug induced liver injury

Abbreviation or special term	Explanation
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
E-code	Enrolment number
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
CCI	CCI
CCI	CCI
CCI	CCI
ePRO	Electronic tablet for patient-reported outcomes assessment
CCI	CCI
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDG-PET	^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HbA1c	Haemoglobin A1c
HBc	Hepatitis B core
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCP	Health care professional
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hy's law
HR	Hazard ratio
HRCT	high-resolution computed tomography
HRQoL	Health-related quality of life
IASLC	International Association for the Study of Lung Cancer

Abbreviation or special term	Explanation
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IG	Immunoglobulin
IgG	Immunoglobulin G
ILD	Interstitial lung disease
IM	Intramuscular
imAE	Immune-mediated adverse event
International Coordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally
I-O	Immuno-oncology
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower limit of normal
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism of action
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NL	New lesion
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival

Abbreviation or special term	Explanation
OS12, OS24, OS36	Proportion of patients alive at 12 months, 24 months, 36 months, respectively, from first IP dose administration
PD	Progression of disease
PD-1	Programmed cell death 1
PD-L1, PD-L2	Programmed cell death ligand 1, programmed cell death 1 ligand 2
PDx	Pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
PFS12, PFS24	Proportion of patients progression-free at 12 months and 24 months, respectively, from first IP dose administration
PGx	Pharmacogenetic(s)
PHL	Potential Hy's law
PJP	*Pneumocystis jirovecii pneumonia* (formerly known as *Pneumocystis carinii pneumonia*)
PK	Pharmacokinetic(s)
PO	Per os (by mouth)
PR	Partial response
PRO	Patient-reported outcome(s)
CCI [redacted]	CCI [redacted]
PS	Performance status
PRAE	Possibly-related adverse event
q28d	Every 28 days
q2w ,q3w, q4w, q8w, q12w	Every 2, 3, 4, 8, 12 weeks, respectively
Q	Quarter
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Steering Committee
sCRT	Sequential chemoradiation therapy
SD	Stable disease
SoA	Schedule of assessments

Abbreviation or special term	Explanation
SoC	Standard of care
SOP	Standard Operating Procedure
SpO_2	Peripheral oxygen saturation
sPD-L1	Soluble programmed cell death ligand 1
T3	Triiodothyronine
T4	Thyroxine
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitors
TL	Target lesion
CCI	CCI
TMG	Toxicity Management Guidelines
TNF(-α)	Tumour necrosis factor (alpha)
TPV	Third-party vendor
TRAE	Treatment-related adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organisation
WHO/ECOG PS	World Health Organisation/Eastern Cooperative Oncology Group Performance Status

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