Clinical Study Protocol	
Drug Substance	Durvalumab (MEDI4736)
Study Code	D933KC00001
Version	4.0
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A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab Given Concurrently with Platinum-based Chemoradiation Therapy in Patients with Locally Advanced, Unresectable Non-small Cell Lung Cancer (Stage III) (PACIFIC2)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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Regulatory Agency Identifying Number(s):

EudraCT number: 2017-004397-34

VERSION HISTORY

Version 4.0, 04 Mar 2020

Sections: 1.2, 1.3 (Figure 1), 3, 4.2.1, 8.1, 9.1, 9.2, 9.3 (Table 11), 9.4.2.1, 9.4.2.2, 9.4.8, 9.5, 9.5.1

Updates reflect changes to multiple testing procedure and resulting impact on analysis timelines. Objective response rate (ORR) will now be assessed as a key secondary endpoint. The timeline for the interim analysis (IA) of the primary endpoint of PFS has been updated to occur when approximately CCI events have been observed. In order to ensure adequate maturity for the PFS final analysis (FA), the PFS FA will occur when approximately CCI events have been observed. The first OS IA will occur at the same time of PFS FA, when approximately CCI events are expected. The second OS IA will occur when approximately CCI events have been observed. The timepoint for OS FA has also been updated to occur when approximately CCI events have been observed. The statistical analyses sections have been updated accordingly.

Section 2.3.2.1

Updated to align with Investigator Brochure V14 11Feb2019

Section 6.1.1.4:

Section added to clarify procedures and data collection after final data cut off (DCO)

Section 6.3.2:

Language updated for blinded contract research organization not to have access to the randomization scheme

Section 8.2 Table 8:

Removed footnote d. Calculation of Creatinine Clearance is not done by Data Management.

Section 8.3.12:

Updated to align with Investigator Brochure V14 11Feb2019

Section 8.3.13:

Section added to provide guidance on safety data collection after final DCO

Section 8.4.2:

Removed PREGREP (for reporting pregnancy) and PREGOUT (for reporting pregnancy outcome) eCRF modules as these eCRF modules are not used.

Version 3.0, 10 April 2019

Table 1 and 2:

PGIS evaluation: updated timepoints to align with other PRO questionnaires "CCI CCI (±3 days) after randomisation, then CCI ±1w until CCI, at CCI (relative to the date of randomisation) then CCI ±1w thereafter until PFS2.

Section 4.4:

Removed 'Durvalumab and CCI combo' as this is not included in this study design.

Section 5.2:

Added clarification to Exclusion Criterion 13: Patients with T4 lesions that invade major vascular structures such as pulmonary artery or cardiac tissues are also not eligible.

Table 6:

Moved footer from table 7 to table 6 as the acronyms are applicable to that table.

Version 2.0, 10 September 2018

Various Sections – The protocol has been updated to provide better guidance on radiotherapy

Changes to the protocol are summarised below:

Title : Adding study name : PACIFIC2

Objectives : DCR changed from CCI : No scans expected to be collected at CCI CCI

General : Wording updated: "dual primary endpoint" instead of "co-primary endpoint"

Table 1 :

- Addition of assessment schedule for PFS2 : Based on recent experience, we should continue assessments for PFS 2 until study discontinuation or death
- Final visit removed : redundant information already cover in Table 2
- ePRO : addition of the +/- 3days visit window, changed ePRO collection from "at CCI CCI after PD or IP discontinuation" to "up to PFS 2"
- Footnote l:
    - Pre-dose sample collection clarification : to be collected within 60 minutes prior infusion

- Clarification on time allowed between randomization and first dose. The time between randomization and first dose of IP can be up to 3 days maximum (based on investigator assessment). Every effort should be made to minimize the time between randomization and starting treatment (i.e. on the same day after randomization)

- HOSPAD to be collected until study termination or death instead of PD

Table 2 :

- Addition of assessment schedule for PFS2

- ePRO : addition of the +/- 3days visit window, changed ePRO collection from "at CCI after PD or IP discontinuation" to "up to PFS 2"

- HOSPAD to be collected until study termination or death instead of PD

Table 5 : Study treatments : Induction cycle for the arm Pemetrexed/Carboplatin option removed – considered as non relevant. Addition of optional consolidation cycles of full dose Paclitaxel/Carboplatin.

Table 8 : Clinical chemistry: error corrected for Creatinine. "creatinine clearance" has been changed to "creatinine"

Table 11 : DCR changed from CCI to CCI

Table 13 : Rate of CR and Disease control rate analysis updated from "Fisher's exact" to "analysis using CMH" and to be "Summarized by descriptive statistics", respectively.

Section 4.3.2 : Rationale wording updated

Section 4.4 : Clarification on end of study definition, and guidance in the event that a roll-over or safety extension study is available at time of the final DCO and database closure

Section 4.4.1 : Wording updated: Post final DCO - all SAEs will need to be managed according to section 8.4.1 regardless of study treatment. Post final DCO - statement of death is no longer required. Also updated wording: Patients who are receiving treatment at the time of final DCO may continue receiving durvalumab if the Investigator judges that they are gaining clinical benefit (placebo option was removed)

Section 5.1 :

Inclusion criteria 9 : Wording updated to provide more clarity on the extra DLCO requirement

Inclusion criteria 10 : Reference on liver mets removed

Exclusion criteria 4 & 14 : Wording updated to provide clarity on dividing distant prior cancers, prior lung cancer and cancers with overlapping RT fields

Section 6.1.1.1 : Wording updated on treatment post final DCO

Section 6.1.1.2 : SoC CRT - Induction cycle for the arm Pemetrexed/Carboplatin option removed – considered as non relevant. Addition of optional consolidation cycles of full dose Paclitaxel(175-200 mg/m2)/Carboplatin(AUC5-6)

Sections 6.3.2 and 6.3.3 : Added clarification on unblinding: Additionally, at the request of the Investigator, following discontinuation of IP and RECIST 1.1-defined progression of disease plus the additional regularly scheduled follow-up scan the patient can be unblinded

Section 6.3 : Error corrected – all patients will be centrally randomized only

Section 6.3.2 : Clarification on who will provide the unblinded data to IDMC. Also included additional clarification language: following discontinuation of IP and RECIST 1.1-defined progression of disease plus the additional regularly scheduled follow-up scan the patient can be unblinded. In the setting of rapid clinical progression unblinding should be discussed with the AstraZeneca Global Study Physician and Study Statistician

Section 6.7 : Wording updated on treatment post final DCO

Section 8.1.3 : Addition of PGIS to the Clinical outcome assessments

Section 8.4.5.1 : Toxicity Management guidelines web link updated – and appendix G - Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion related, and Non Immune-mediated Reactions removed

Section 9 : Separation of OS from the final PFS

Section 9.2 : Clarification of what would occur in case of PFS IA not positive

Section 9.3.2 : Safety analysis set: wording changed to "Randomized treatment (durvalumab or matching placebo)" instead of "IP"

Section 9.4.1.1 : RECIST 1.1 BICR definition clarified

DCR at CCI updated to DCR at CCI to match the imaging schedule.

Section 9.4.1.3 : Updated wording: For the Time to HRQoL/function deterioration (QLQ-C30) the wording 'confirmation at a subsequent visit or death' was included as it is written in symptom deterioration.

Section 9.4.2: Table 13 Disease Control Rate updated wording: Summarized by descriptive statistics. This was also updated in Section 9.4.2.7 for DCR.

Section 9.4.2.1 : Typo for maturity at PFS final analysis is corrected from CCI

Section 9.4.2.9 : PFS2 assessment schedule is updated to match the updated SoA.

Section 9.4.2.10 : Typo is corrected as OS is not primary endpoint.

Section 9.4.3 : Language for retreatment summaries is removed as no retreatment is planned in the study

Section 9.5.1 : Removal of PFS IA text duplicate. Clarification on what will happened in case of PFS IA is not positive.

Appendix H : Reworked to provide more detail of the Radiation therapy requirements and recommendations

Version 1.0, 15 December 2017
Initial creation

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

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

For both treatment arms

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

- Patient-reported outcomes (PROs) and tumor efficacy (Response Evaluation Criteria In Solid Tumors [RECIST]) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (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 days prior to dosing.

For durvalumab/placebo treatment

- Patients may delay dosing under certain circumstances.

  – Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1), due to either an immune or a non-immune-related adverse event (AE).

  – If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible (see Section 8.4.5).

  – One cycle is equal to 28 days.

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

Chemoradiation therapy

- Patients may delay and subsequently resume dosing per local standard clinical practice (see Section 8.4.5).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.

Table 1 Schedule of assessments for screening and treatment period

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to PD [a, b]	For details see Section
Week	CCI **to -1**	**0**	CCI **±3 days unless dosing needs to be held for toxicity reasons**				
Day	CCI **to -1**	**1**	CCI **±3 days unless dosing needs to be held for toxicity reasons**				
Informed consent							
Informed consent: study procedures	X						5.1
Consent: genetic sample and analysis (optional) [c]	X						5.1
Study procedures							
Physical exam (full)	X						8.2.2
Targeted physical exam (based on symptoms)		Weekly		X	X	X	8.2.2
Vital signs [d]	X	X	X	X	X	X	8.2.4
ECG [e]	X	As clinically indicated					8.2.3
Concomitant medications	<---------- ---->						6.5
Demography, including baseline characteristics and tobacco use	X						8.2.2
Brain MRI (preferred) or high-quality brain CT with IV contrast	X						8.2.6
Pulmonary function testing [f]	X						5.1
Eligibility criteria	X	X					5.1, 5.2
Radiation plan collection	X						Appendix G 7.1
Laboratory assessments							
Clinical chemistry	X	X [g]	X [h]	X [h]	X [h]	X [h]	Table 8
Hematology	X	X [g]	X [h]	X [h]	X [h]	X [h]	Table 9
TSH (reflex free T3 or free T4 [i])	X	X	X	X	X	X	Table 8
Urinalysis	X	As clinically indicated					Table 10
Hepatitis B and C and HIV	X						8.2.1
Pregnancy test [j]	X	X	X	X	X	X	8.2.1

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to PD [a, b]	For details see Section
Week	CCI to -1	0	CCI ±3 days unless dosing needs to be held for toxicity reasons				
Day	CCI to -1	1	CCI ±3 days unless dosing needs to be held for toxicity reasons				
CCI							8.5
Monitoring							
WHO/ECOG performance status	X	X	X	X	X	X	8.2.5
AE/SAE assessment [m]	<----------					---------->	8.3
Drug accountability		X	All visits				6.2.4
IP administration							
Durvalumab/placebo [n, o]		X	X	X	X	X	6.1
SoC chemotherapy		Dependent on treatment selected; see Table 5					6.1
SoC radiation therapy		5 fractions/week for ~6 weeks (±3 days) (total 60 Gy)					6.1, Appendix G
Other assessments and assays							
CCI							8.5
							8.8
Whole blood for gene expression (PaxGene-RNA CCI	CCI						8.8
CCI							8.8
EORTC QLQ-C30 and QLQ-LC13 [p]	X	CCI (±3 days) after randomisation, then CCI ±1w through CCI (relative to the date of randomisation) and then CCI ±1w thereafter (relative to the date of randomisation) CCI					8.1.3
PGIS [p]	X	CCI (±3 days) after randomisation, then CCI ±1w until CCI CCI (relative to the date of randomisation) then CCI ±1w thereafter CCI					8.1.3

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to PD [a, b]	For details see Section
Week	CCI **to -1**	**0**	CCI **±3 days unless dosing needs to be held for toxicity reasons**				
Day	CCI **to -1**	**1**	CCI **±3 days unless dosing needs to be held for toxicity reasons**				
EQ-5D-5L [p]	X	CCI (±3 days) after randomisation, then CCI ±1w through CCI (relative to the date of randomisation) and then CCI ±1w thereafter (relative to the date of randomisation) until PFS2					8.1.3
Health resource use module (HOSPAD)	X	CCI for the first CCI (relative to the date of randomization) and then CCI thereafter (relative to the date of randomisation) until study termination or death					8.9
CCI							8.8
							8.7
Efficacy evaluations							
Tumor evaluation (CT or MRI) (RECIST 1.1) [b, q]	X	On-study tumor assessments begin CCI ±1w after randomization and continue CCI ±1w through CCI (relative to the date of randomization) and then q12w ±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological progression plus an additional regularly scheduled follow-up scan. The on-study imaging CCI ±1w after randomization, then CCI ±1w through CCI and then CCI ±1w thereafter MUST be followed regardless of any delays in dosing.					8.1

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

[b] Patients will have baseline scans collected no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to the date of randomization. On-study scans will begin CCI ±1w after randomization, then CCI ±1w through CCI (relative to the date of randomization), and then CCI ±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined PD, plus an additional follow-up scan is collected if clinically feasible.

[c] The sample for genetic research will be obtained at CCI If, for any reason, the sample is not drawn at CCI it may be taken at CCI CCI . Only 1 sample should be collected per patient for genetics during the study.

[d] Body weight is recorded at each visit along with vital signs.

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

[f] Pulmonary function testing results for up to CCI prior toscreening are permitted.

[g] If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. Serum or plasma chemistry, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated.

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

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

[j] 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 (ie, SoC CRT, durvalumab, or placebo) and then every CCI . 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

[k] CCI

[l]

[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] Patients with CR, PR, or SD (based on Investigator assessment) at the 16-week tumor evaluation following completion of SoC CRT will continue to receive durvalumab/placebo as consolidation treatment.

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

[q] 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). Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. The follow-up scan collected 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, and this scan is evaluated using the Tumor Assessment Criteria for Scans Following RECIST 1.1-defined PD outlined in 0. If an unscheduled assessment was performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next regularly scheduled visit.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated. The time between randomization and first dose of IP can be up to 3 days maximum (based on Investigator assessment). Every effort should be made to minimize the time between randomization and starting treatment (i.e. on the same day after randomization)

CCI ; AE Adverse event; C Cycle; CR Complete response; CRT Chemoradiation therapy; CT Computerized tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; HIV Human immunodeficiency virus; IM Intramuscular; IP Investigational product; IV Intravenous; LFT Liver function test; MRI Magnetic resonance imaging; PD Progressive disease; CCI ; PR Partial response; PRO Patient-reported outcomes; CCI Every CCI Every CCI Every CCI Every CCI QLQ-C30 30 item core quality of life questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST Response Evaluation Criteria in Solid Tumors version 1.1; SAE Serious adverse event; CCI ; SoC Standard of care; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone; WHO World Health Organization.

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

	Time since last dose of IP								
Evaluation	**Day (±3)**	**Months (±1 week)**						**CCI (±2 weeks)**	**For details, see Section**
	CCI								
Physical examination (full)	X								8.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								8.2.4
Weight	X	X	X		X				8.2.4
CCI									8.2.1
AE/SAE assessment	X	X	X						8.3
Concomitant medications	X	X	X						6.5
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at CCI ; and then at initiation of subsequent anticancer therapy [b]								8.2.5
Second progression assessment [d, e]	Patients who discontinue study drug following progression will be assessed every CCI for a second progression (using the patient's status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death.								8.1
Subsequent anticancer therapy [c] and survival status [f]		X		X	X	X	X	X (every CCI ±2 weeks)	8.1
Hematology	X	X	X						8.2.1
Clinical chemistry	X	X	X						8.2.1
Urinalysis	As clinically indicated								8.2.1
TSH (reflex free T3 or free T4 [g])	X	X	X						8.2.1
CCI									8.5
									8.5
									8.8

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

	Time since last dose of IP								
Evaluation	**Day (±3)**	**Months (±1 week)**						**CCI (±2 weeks)**	**For details, see Section**
	CCI								
Circulating soluble factors (plasma)	X	X		X					8.8
EORTC QLQ-C30 and QLQ-LC13 [i]	CCI (±3 days) after randomisation, then CCI ±1w through CCI (relative to the date of randomisation) and then CCI ±1w thereafter (relative to the date of randomisation) CCI CCI								8.1.3
PGIS [i]	CCI (±3 days) after randomisation, then CCI ±1w until CCI, at CCI (relative to the date of randomisation) then CCI ±1w thereafter until PFS2								8.1.3
EQ-5D-5L [i]	CCI (±3 days) after randomisation, then CCI ±1w through CCI (relative to the date of randomisation) and then CCI ±1w thereafter (relative to the date of randomisation) until PFS2								8.1.3
Health resource use module (HOSPAD)	CCI for the first CCI (relative to the date of randomization) and then CCI thereafter (relative to the date of randomisation) until study termination or death								8.9
Tumor assessment (CT or MRI) (RECIST 1.1) [j]	On-study tumor assessments begin CCI ±1w after randomization and continue CCI ±1w through CCI (relative to the date of randomization) and then CCI ±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological progression plus an additional regularly scheduled follow-up scan. The on-study imaging schedule of CCI ±1w after randomization, then CCI ±1w through CCI, and then CCI ±1w thereafter MUST be followed regardless of any delays in dosing.								8.1

[a] CCI

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

[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] PFS2 assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death.

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

[f] Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for NSCLC (including surgery) post the last dose of IP must be recorded in the eCRF. Every effort should be made to contact patients by telephone to follow and record survival status.

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

[h] CCI and CCI ; ±7 days) after treatment with CCI ends. In addition, a final sample for CCI (±7 days) after treatment with CCI

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

j 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). Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients. The follow-up scan collected 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, and this scan is evaluated using the Tumor Assessment Criteria for Scans Following RECIST 1.1-defined PD outlined in 0. If an unscheduled assessment was performed (eg, to investigate clinical signs/symptoms of progression) 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 randomization).

CCI [redacted]; AE Adverse event; CT Computerized tomography; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; IP Investigational product; IV Intravenous; MRI Magnetic resonance imaging; NSCLC Non-small cell lung cancer; PD Progressive disease; PFS2 Time from randomization to second progression; CCI [redacted]; PRO Patient-reported outcome; CCI [redacted] Every CCI [redacted] Every CCI [redacted] Every CCI [redacted]; QLQ-C30 30 item core quality of life questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST Response Evaluation Criteria in Solid Tumors; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone; WHO World Health Organization.

1.2 Synopsis

International co-ordinating investigator:

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Protocol title: A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab Given Concurrently with Platinum-based Chemoradiation Therapy in Patients with Locally Advanced, Unresectable Non-small Cell Lung Cancer (Stage III)

Rationale: Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers, and 30% of patients present with Stage III disease. While concurrent chemoradiation therapy (cCRT) has been shown to be superior to radiation alone and sequential therapy, the majority of patients inevitably progress (progression-free survival [PFS] of 8 to 12 months; 5-year overall survival [OS] of approximately 15% to 32%). Chemoradiation therapy (CRT)-induced cell death can enhance the ability of the immune system to recognize and respond to the tumor through enhanced antigen release and presentation that, in turn, aids in the priming of immune cells to recognize and eliminate tumor cells. Therefore, triggering or augmenting an antigenic antitumor response with CRT and combining this treatment with anti-programmed cell death ligand 1 (PD-L1) therapy, such as durvalumab, which acts to preserve ongoing immune responses by blocking an immunosuppressive signal, theoretically may result in enhanced antitumor activity by improving local control and decreasing systemic spread. In the PACIFIC study, 1 year of durvalumab as consolidation therapy after achieving stable disease (SD) or better with cCRT demonstrated a PFS benefit of 11.2 months over placebo in patients with Stage III unresectable NSCLC. Initiating durvalumab during cCRT may further enhance outcomes and may provide benefit to those that were never eligible for the PACIFIC study due to disease progression prior to randomization.

Objectives and endpoints

Primary objective:	Endpoint/variables:
To assess the efficacy of durvalumab + SoC CRT compared with placebo + SoC CRT in terms of PFS	PFS using BICR assessments according to RECIST 1.1 [a]

Objectives and endpoints

Secondary objectives:	Endpoint/variables:
To further assess the efficacy of durvalumab + SoC CRT compared with placebo + SoC CRT in terms of ORR, OS, OS24, rate of CR, DoR, CCI CCI, PFS2, and TTDM	ORR using BICR assessments according to RECIST 1.1 OS and OS24 Rate of CR, DoR, DCR, and TTDM using BICR assessments according to RECIST 1.1 CCI as defined by local standard clinical practice
CCI	
To assess symptoms and health-related QoL in patients treated with durvalumab + SoC CRT compared with placebo + SoC CRT using EORTC QLQ-C30 v3 and QLQ-LC13	EORTC QLQ-C30 and QLQ-LC13: Change in symptoms, functioning, and global health status/QoL
Safety objective:	**Endpoint/variables:**
To assess the safety and tolerability profile of durvalumab + SoC CRT compared with placebo + SoC CRT	AEs, physical examinations, vital signs including blood pressure, pulse, electrocardiograms, and laboratory findings including clinical chemistry, hematology, and urinalysis
Exploratory objectives:	**Endpoint/variables:**
CCI	

Objectives and endpoints

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

CCI; AE Adverse event; BICR Blinded Independent Central Review; CR Complete response; CRT Chemoradiation therapy; CCI; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5 dimension, 5-level health state utility index; IP Investigational product; LC13 Lung Cancer Module; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomization; CCI; PFS Progression-free survival; CCI Time from CCI; PGIS Patients' Global Impression of Severity; CCI (s); QLQ-C30 30-item core quality of life questionnaire; QoL Quality of life; RECIST Response Evaluation Criteria In Solid Tumors; SoC Standard of care; TTDM Time to death or distant metastasis.

Overall design:

This is a Phase III, randomized, double-blind, placebo-controlled, multi-center, international study assessing the efficacy and safety of durvalumab given concurrently with platinum-based CRT (durvalumab + standard of care [SoC] CRT) in patients with locally advanced, unresectable NSCLC (Stage III).

Study period:

Estimated date of first patient enrolled: CCI

Estimated date of last patient completed: CCI

Number of patients: Approximately CCI patients with locally advanced, unresectable NSCLC (Stage III) will be recruited and 300 patients randomized in a 2:1 ratio to durvalumab + SoC

CRT or placebo + SoC CRT. Patients will be stratified by age CCI and stage CCI CCI .

Treatments and treatment duration:

All patients will receive 1 of the following platinum-based SoC chemotherapy options, based on Investigator discretion, in addition to radiation therapy: cisplatin/etoposide, carboplatin/paclitaxel, pemetrexed/cisplatin, or pemetrexed/carboplatin. Chemotherapy treatment regimens are outlined in Table 5.

Patients will also receive durvalumab CCI or placebo every CCI via intravenous infusion concurrent with SoC CRT (ie, starting on Cycle 1 Day 1 [±3 days]). Patients with complete response (CR), partial response (PR), or SD following completion of SoC CRT will continue to receive durvalumab/placebo as consolidation treatment. Patients with RECIST 1.1-defined radiological progressive disease at the 16-week tumor evaluation following completion of SoC CRT will proceed to follow-up.

Independent Data Monitoring Committee:

An independent data monitoring committee (IDMC) composed of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule of durvalumab + SoC CRT. The first safety review will take place when the CCI CCI have completed SoC CRT and have had at least CCI of follow-up. The second safety review will take place when the CCI CCI and have had at least CCI of follow-up. Safety reviews will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment.

An additional safety review for CCI patients will take place when CCI CCI have completed SoC CRT and had CCI days of follow-up. This review will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment in CCI

In addition, the IDMC will meet approximately every CCI thereafter to continue safety monitoring. The interim analysis (IA) of the primary objective, PFS and secondary objectives of objective response rate (ORR), CCI and the first and second OS analyses will also be assessed by the IDMC.

Full details of the IDMC procedures, processes, and IAs can be found in the IDMC Charter.

Statistical methods

The primary objective of this study is to assess the efficacy of durvalumab + SoC CRT compared with placebo + SoC CRT in terms of PFS per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by Blinded Independent Central Review (BICR). The key secondary endpoints (ie, those included in the multiple testing procedure) are ORR per RECIST 1.1 as assessed by BICR, OS and OS24.

A hierarchical testing procedure will be used to strongly control type I error. CCI

The study is powered for the primary endpoint of PFS and for the key secondary endpoints of OS and ORR.

There are up to CCI analysis timepoints for PFS. The PFS IA will occur when approximately CCI (information fraction of CCI have occurred. It is estimated that this DCO will occur CCI after the last patient has been randomized. If the CCI for PFS is not positive, the DCO for the PFS final analysis will occur when approximately CCI events have occurred. It is estimated that this DCO will occur CCI after the last patient has been randomized.

If the true PFS HR is CCI the study will provide greater than CCI to demonstrate a statistically significant PFS effect with a 2-sided significance level of 5%; this translates to a CCI in median PFS over CCI on placebo if PFS is exponentially distributed. The smallest treatment effect that would be statistically significant is an CCI at final analysis.

There are up to CCI analysis timepoints for OS. The CCI will occur at the same time of the CCI if the CCI . If the CCI , the CCI will occur when approximately CCI (information fraction of CCI are reached. If the CCI , then the CCI will occur when approximately CCI (information fraction of CCI are reached. Similarly, if CCI then the CCI will occur when approximately CCI events are reached.

If the true CCI , the study will have greater than CCI overall power to demonstrate a statistically significant OS effect with a 5% 2-sided significance level; this translates to a CCI benefit in median OS over CCI on placebo if OS is exponentially distributed. The smallest treatment difference that would be statistically significant is a HR of 0.74 at final analysis.

The study has CCI power to detect a statistically significant difference in CCI with a 2-sided significance level of 0.5%. This assumes the ORR for the patients randomized to placebo + SoC CRT is CCI The smallest treatment effect that would be statistically significant is a difference in ORR of CCI

PFS and OS will be analyzed using a stratified log-rank test adjusting for age CCI and stage (CCI). ORR will be compared between the treatment arms using a Cochran-Mantel-Haenszel test, stratified by age CCI and stage CCI

Safety data will be summarized descriptively.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design

CR Complete response; CRT Chemoradiation therapy; ECOG Eastern Cooperative Oncology Group; n Number of patients; NSCLC Non-small cell lung cancer; ORR Objective response rate; OS Overall survival; PD Progressive disease; PFS Progression-free survival; PR Partial response; SD Stable disease; SoC Standard of care; WHO World Health Organization.

2. INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades, and by 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total) (GLOBOCAN 2012). NSCLC represents approximately 80% to 85% of all lung cancers and 30% of patients present with Stage III disease. Standard treatment for patients with a good performance status (PS) and unresectable Stage III NSCLC had been platinum-based doublet chemotherapy and radiotherapy administered concurrently with curative intent (cCRT). A meta-analysis of concurrent versus sequential CRT demonstrated better outcomes with concurrent therapy, but even with cCRT, 5-year overall survival (OS) ranges between 15% and 32% (ASTRO 2017, Aupérin et al 2010). More recently, the PACIFIC study (D4191C00001) demonstrated that the addition of durvalumab as sequential therapy to platinum-based CRT significantly improves PFS (median PFS 16.8 months with durvalumab compared to 5.6 months with placebo, HR of 0.52; Antonia et al 2017).

The clinical benefit associated with potentiating the proinflammatory effects of CRT observed in the PACIFIC study suggests that giving durvalumab in combination with CRT may yield further clinical benefits, including increasing the response rate to CRT, improving the complete response (CR) rate, and decreasing the number of patients who progress on CRT.

2.1 Study rationale

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

Results of early studies with durvalumab in advanced cancers are consistent with a class effect of early and sustained tumor control that has been observed previously with other inhibitors of the immune checkpoint pathway. A consistent observation across these studies is the long durability of benefits with immune checkpoint inhibitors. For patients who experience an objective response, the duration of response (DoR) is significantly longer with immunotherapy than with chemotherapy alone. However, not all patients benefit from immune checkpoint inhibitors as monotherapy. Hence, studies combining immune checkpoint inhibitors with other established treatment regimens, such as CRT, are needed in order to expand the patient population who might benefit from immune checkpoint inhibitors.

Radiation and CRT have been shown to induce immunogenic cell death. Cell death, from radiation or CRT, enhances the ability of the immune system to recognize and respond to the tumor through enhanced antigen release and presentation (tumor specific T-cell activation; Formenti and Demaria 2013, Weichselbaum et al 2017). In addition, ionizing radiation causes upregulation of various pro-inflammatory signals and cytokines, which play a key role in immune regulatory pathway, leading to improved antitumor immunity. Twyman-Saint Victor et al also showed that radiation enhanced the diversity of the T-cell receptor repertoire of intratumoral T-cells (Twyman-Saint Victor et al 2015). Additionally, both chemotherapy and

radiotherapy can up-regulate the expression of PD-L1 (Butts et al 2014, Deng et al 2014, Zhang et al 2008b). Given these factors, CRT may confer more sensitivity to PD-L1-directed therapy.

The results of the PACIFIC study support the hypothesis that durvalumab added after definitive CRT would provide clinical benefit by potentiating the pro-inflammatory effects of the definitive therapy. However, the PACIFIC study only evaluated patients who had not progressed following recently completed CRT. A significant unmet medical need still exists in patients who were not eligible for the PACIFIC protocol due to progression during or immediately following CRT. The addition of durvalumab at an earlier timepoint may be a way to prevent progression during or shortly after CRT. Also, the addition of durvalumab to CRT may increase the depth of responses, which could translate into longer term clinical benefit.

Furthermore, there is evidence that suggests added benefit may be derived with checkpoint inhibition earlier and in combination with radiation. Verbrugge et al demonstrated that the combination of radiation with concomitant and adjuvant anti-programmed cell death 1 (PD-1) agent can enhance the release of tumor antigens in animal models, and thus synergistically improve the antitumor immunity (Verbrugge et al 2012). In mouse flank tumor models, Deng et al showed that combination with an anti-PD-L1 antibody and a single high-dose radiation showed substantial tumor regression (Deng et al 2014). Additionally, Dovedi and Illidge showed the importance of using radiation therapy concurrently, rather than sequentially, with anti-PD-L1 treatment in providing long-term tumor control (Dovedi and Illidge 2015). Clinically, the addition of a PD-1 directed immunotherapy (pembrolizumab) to chemotherapy demonstrated the ability to significantly increase response rates in non-squamous NSCLC patients without significantly affecting tolerability (Langer et al 2016), and previous radiotherapy has been shown to increase the efficacy of pembrolizumab (Shaverdian et al 2017). This suggests that treatment with durvalumab concurrent with CRT could lead to additional depth of response to CRT that could be associated with longer-term clinical benefit.

Given this, administering durvalumab earlier and in combination with CRT may have added clinical benefit and improve the outcome for more patients.

2.2 Background

2.2.1 Immunotherapies

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

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling Tcell- activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). The PD-1 and PD-L1/PD-L2 belong to the 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 PD1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses -Tcell- proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly overexpressed on tumor cells or on -nontransformed- cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD1 receptors on the activated -Tcells- leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

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

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-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 antitumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008a) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

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

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2 [PD-L2]) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the

inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (IFNγ) (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-celldependent- mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1 and Section 8.3.12. Refer to the current durvalumab Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information including safety, efficacy, and CCI

2.3 Benefit/risk assessment

The following sections include summaries of the potential benefits and risks associated with durvalumab prior to the overall benefit-risk assessment.

2.3.1 Potential benefits

2.3.1.1 Durvalumab as a single agent in metastatic NSCLC

The majority of the safety and efficacy data currently available for durvalumab are based on the first-in-human, single-agent study (Study 1108) in patients with advanced solid tumors, the study of durvalumab monotherapy in NSCLC (Study D4191C00003 [ATLANTIC]), and the study of durvalumab monotherapy in NSCLC following completion of platinum-based chemotherapy concurrent with radiation therapy (the PACIFIC study, described in Section 2.3.1.2). Data from these studies have demonstrated clinical activity of durvalumab therapy in patients with NSCLC. Details pertaining to Study 1108 and ATLANTIC are provided in the durvalumab IB.

2.3.1.2 Durvalumab after completion of CRT in locally advanced NSCLC

The PACIFIC study has demonstrated the efficacy of durvalumab versus placebo in patients with locally advanced, unresectable Stage III NSCLC who had completed treatment with at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy within 1 to 42 days prior to the first dose of IP and had not progressed (Antonia et al 2017). As of the first IA (DCO of 13 February 2017) for the PACIFIC study, durvalumab demonstrated a statistically significant (HR: 0.52; 95% CI: 0.42, 0.65; p-value <0.0001) and clinically meaningful prolongation of PFS (according to Blinded Independent Central Review [BICR] assessment of Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]) compared with placebo. Durvalumab treatment demonstrated a median PFS improvement of 11.2 months when compared with placebo; treatment effects were observed early and sustained over time, as supported by the estimates of the PFS rates at 12 months (55.9% in the durvalumab group and 35.3% in the placebo group) and 18 months (44.2% and 27.0%, respectively). The improvement of PFS is supported by the clinical meaningful incremental objective response rate (ORR) of 12% over placebo (28.4% in the durvalumab group vs 16.0% in the placebo group; nominal p-value <0.001). The responses were durable, with the median DoR not reached in the durvalumab group

compared to 13.8 months in the placebo group. Of the patients who demonstrated response to durvalumab, 72.8% showed ongoing response at both 12 and 18 months after treatment initiation compared with 56.1% and 46.8%, respectively, with placebo. In addition, the median time to death or distant metastasis (TTDM) was longer for the durvalumab group compared to the placebo group (23.2 months in the durvalumab group, compared to 14.6 months in the placebo group; HR: 0.52; 95% confidence interval [CI]: 0.39, 0.69; nominal p-value < 0.0001). The frequency of BICR-assessed new lesions was lower in the durvalumab group (20.4%) compared with that in the placebo group (32.1%), and the incidence of new brain metastases was also lower (5.5% vs 11.0%). In addition, the study achieved statistically significant improvement in overall survival at a planned interim analysis.

Concurrent immunotherapy and chemotherapy

The efficacy of immunotherapy administered concurrently with chemotherapy agents is supported by recent results from the KEYNOTE-021 study (pembrolizumab; PD-1 inhibitor), the CheckMate 012 study (nivolumab; PD-1 inhibitor), and preliminary results from Study D419SC00001 (durvalumab ± tremelimumab, a CTLA-4 inhibitor).

The anti-tumor activity of pembrolizumab administration concurrent with various chemotherapy regimens versus chemotherapy (carboplatin-pemetrexed) alone as first-line treatment for NSCLC (the KEYNOTE-021 study) demonstrated ORRs of 55% (95% CI: 42, 68) versus 29% (95% CI: 18, 41), respectively (p=0.0016), with DoRs of at least 6 months in 92% (95% CI: 73, 98) and 81% (95% CI: 51, 93), respectively (Langer et al 2016).

The antitumor activity of nivolumab administered concurrently with platinum-based doublet chemotherapy as first-line treatment for advanced NSCLC (the CheckMate 012 study) demonstrated ORRs for nivolumab 10 mg/kg plus gemcitabine-cisplatin, nivolumab 10 mg/kg plus pemetrexed-cisplatin, nivolumab 10 mg/kg plus paclitaxel-carboplatin, and nivolumab 5 mg/kg plus paclitaxel-carboplatin of 33%, 47%, 47%, and 43%, respectively, and 24-week PFS rates of 51%, 71%, 38%, and 51%, respectively (Rizvi et al 2016).

The efficacy of durvalumab ± tremelimumab with standard platinum-based chemotherapy in advanced cancers is being generated from 2 ongoing Phase I studies: internal Study D419SC00001 (n=6) and a Phase Ib study (NCT02537418) run by the Canadian Cancer Trials Group (CCTG). Patients in the CCTG study were treated with durvalumab ± tremelimumab at 1 of 4 dose levels concomitantly with either pemetrexed + carboplatin / cisplatin followed by pemetrexed consolidation for nonsquamous histology (45 patients) or gemcitabine + carboplatin/cisplatin for squamous histology (9 patients). Preliminary results from this study indicated that a total of 45 patients (44% male; median age=62 years [range PPD to PPD]; 100% Eastern Cooperative Oncology Group [ECOG] PS ≤1) in the pemetrexed-platinum cohort received a total of 346 treatment cycles while 9 patients (78% male; median age=64 years [range PPD to PPD]; 100% ECOG PS ≤1) in the gemcitabine-platinum group received a total of 55 treatment cycles. The ORR was 57.1% (95% CI: 39.4, 73.7) in 35 evaluable patients receiving pemetrexed-platinum and 37.5% (95% CI: 8.5, 75.5) in 8 evaluable patients receiving gemcitibine-platinum (Juergens et al 2017).

Concurrent immunotherapy and radiation therapy

Currently, over a dozen clinical studies are evaluating anti-PD-1 and anti-PD-L1 antibodies in administration concurrently with (as opposed to after completion of) radiation for cancer treatment, but robust efficacy results are not yet available (Weichselbaum et al 2017). Several non-clinical studies, as described below, suggest that inhibition of the PD-1/PD-L1 checkpoint combined with radiotherapy liberates T cells from immunosuppression, which in turn positively alters the tumor microenvironment owing to killing of suppressive cells via cytokine secretion. Mouse tumor models have been used to demonstrate the synergistic effect of radiotherapy and immunotherapy via checkpoint inhibition in solid tumors (Weichselbaum et al 2017). A preliminary non-clinical report from the Drake laboratory indicates that radiotherapy combined with anti-PD-1 antibody treatment can result in primary tumor control and an abscopal effect (Sharabi et al 2014). More recent data from the same group indicate that this therapy combination results in the induction of endogenous antigen-specific immune responses, resulting in improved local control in single tumor models of melanoma or breast carcinoma (Sharabi et al 2015); however, no experiments on the abscopal effect were reported. Dovedi and Illidge (Dovedi and Illidge 2015) subsequently noted that the timing of anti-PD-L1 blockade is crucial; concurrent radiation and anti-PD-L1 treatment, but not sequential treatment, resulted in long-term tumor control, suggesting that concurrent administration of durvalumab and SoC radiotherapy may have improved clinical benefit over sequential therapy.

2.3.2 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against TCs. By stimulating the immune system however, there is the potential for adverse effects on other 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 which 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 adverse events (AEs) such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypo- and hyper-thyroidism.

2.3.2.1 Durvalumab

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

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

In durvalumab monotherapy clinical studies AEs at an incidence of >20% include events such as fatigue, nausea, decreased appetite, dyspnea and cough. Approximately 10% of patients discontinued the drug due to AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.5.1).

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

2.3.2.2 Durvalumab after completion of CRT

In the PACIFIC study, durvalumab treatment in patients with locally advanced, unresectable Stage III NSCLC who had recently completed CRT demonstrated a well tolerated and manageable safety profile that was consistent with the established safety profile to date with the exception of the events of pneumonitis/radiation pneumonitis (Antonia et al 2017). AEs were reported in 96.8% of patients who received durvalumab and 94.9% who received placebo; Grade 3 or 4 AEs were reported in 29.9% of patients who received durvalumab and 26.1% who received placebo. The most frequently reported Grade 3 or 4 AE was pneumonia (4.4% and 3.8%, respectively). SAEs were reported in 28.6% and 22.6% of patients, respectively, and deaths due to AEs occurred in 4.4% and 5.6% of patients, respectively. Pneumonitis and radiation pneumonitis were notable events in multiple AE categories. There was a numerical increase in these events in the durvalumab group over placebo (33.9% vs 24.8%, respectively, patients with pneumonitis or radiation pneumonitis of any grade), but most of these events were low grade and manageable. Grade 3 or 4 pneumonitis was reported in 3.4% and 2.6% of patients in the durvalumab and placebo groups, respectively. Clinically important Common Terminology Criteria for Adverse Event (CTCAE) Grade 3 and above events were infrequent and balanced between the 2 groups. In addition to pneumonitis, the other adverse events of special interest (AESIs) and immune-mediated adverse events (imAEs) reported in the study were typical of the PD-1/PD-L1 class of immunotherapies and were generally manageable and/or reversible with appropriate treatment guidelines, which included the use of steroids or endocrine therapy, withholding durvalumab until the event resolved, or permanent discontinuation of durvalumab.

2.3.2.3 Concurrent immunotherapy and CRT

Concurrent administration of durvalumab and CRT is CCI [redacted] in patients with advanced solid tumors (estimated date of first patient enrolled: CCI [redacted]). Safety observations from this study will be used to inform decisions regarding safety monitoring for the current proposed study. In addition, an IDMC will assess safety data from the current study CCI [redacted]

CCI and then at least every 6 months thereafter, to ensure patient safety.

Concurrent administration of CRT and other immunotherapies has generally been well tolerated to date.

A retrospective review of patients with metastatic lung cancer treated with PD-1/PD-L1 inhibitors and radiotherapy demonstrated no new safety signals; rates of AEs, including pneumonitis, were comparable between treatment groups (Hwang et al 2017). An ongoing study of pembrolizumab administered concurrently with CRT in 27 patients with Stage III-IVB squamous cell carcinoma of the head and neck has demonstrated no unexpected toxicities and safety generally consistent with CRT administration alone (Powell et al 2017). In addition, during an ongoing study of nivolumab administered concurrently with CRT in patients with Stage IIIA/B NSCLC, a European Thoracic Oncology Platform IDMC review did not observe any additional toxicities compared to CRT alone (ClinicalTrials.gov NCT02434081).

Also, across multiple tumor types, the addition of PD-1/PD-L1 based therapies (including durvalumab) to platinum-based chemotherapy has been shown to be tolerable with a manageable safety profile and no new safety signals (Rizvi et al 2016, Langer et al 2016, Study D419SC00001, NCT02537418).

2.3.3 Overall benefit/risk

The clinical activity associated with potentiating the proinflammatory effects of CRT suggests that giving durvalumab in combination with CRT may have clinical benefits, including increasing the response rate to CRT, improving the CR rate, and decreasing the number of patients who progress on CRT.

Safety observations to date have demonstrated that concurrent administration of CRT and immunotherapy has generally been well tolerated, with toxicities comparable to administration of either agent alone. The safety of concurrent administration of durvalumab and CRT is further supported by results from the PACIFIC study, which showed that durvalumab administered within 42 days of completion of CRT had a well tolerated- and manageable safety profile that was consistent with the established safety profile to date.

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

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/variables:**
To assess the efficacy of durvalumab + SoC CRT compared with placebo + SoC CRT in terms of PFS	PFS using BICR assessments according to RECIST 1.1 [a]
Secondary objectives:	**Endpoint/variables:**
To further assess the efficacy of durvalumab + SoC CRT compared with placebo + SoC CRT in terms of ORR, OS, OS24, rate of CR, DoR, DCR, CCI and TTDM	ORR using BICR assessments according to RECIST 1.1 OS and OS24 Rate of CR, DoR, DCR, and TTDM using BICR assessments according to RECIST 1.1 CCI as defined by local standard clinical practice
CCI [redacted]	
To assess symptoms and health-related QoL in patients treated with durvalumab + SoC CRT compared with placebo + SoC CRT using EORTC QLQ-C30 v3 and QLQ-LC13	EORTC QLQ-C30 and QLQ-LC13: Change in symptoms, functioning, and global health status/QoL
Safety objective:	**Endpoint/variables:**
To assess the safety and tolerability profile of durvalumab + SoC CRT compared with placebo + SoC CRT	AEs, physical examinations, vital signs including blood pressure, pulse, electrocardiograms, and laboratory findings including clinical chemistry, hematology, and urinalysis
Exploratory objectives:	**Endpoint/variables:**
CCI [redacted]	

Table 3 Study objectives

CCI

[a] PFS will be based on programmatically derived PFS by BICR assessment according to RECIST 1.1. See Section 9.4.1.1 for further details.

CCI; AE Adverse event; BICR Blinded Independent Central Review; CR Complete response; CRT Chemoradiation therapy; CCI; DCR Disease control rate; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5 dimension, 5-level health state utility index; IP Investigational product; LC13 Lung Cancer Module; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomization; CCI; PFS Progression-free survival; CCI; PGIS Patients' Global Impression of Severity; CCI (s); QLQ-C30 30-item core quality of life questionnaire; QoL Quality of life; RECIST Response Evaluation Criteria In Solid Tumors; SoC Standard of care; TTDM Time to death or distant metastasis.

4. STUDY DESIGN

4.1 Overall design

This is a Phase III, randomized, double-blind, placebo-controlled, multi-center, international study assessing the efficacy and safety of durvalumab given concurrently with platinum-based

CRT (durvalumab + SoC CRT) in patients with locally advanced, unresectable NSCLC (Stage III). Patients will be stratified by age CCI and stage (CCI).

Approximately CCI patients with locally advanced, unresectable NSCLC (Stage III) who are eligible to receive platinum-based CRT will be enrolled in order to randomize 300 patients in a 2:1 ratio to either durvalumab + SoC CRT or placebo + SoC CRT. Patients with CR, partial response (PR), or stable disease (SD; based on Investigator assessment) at the 16-week tumor evaluation following completion of SoC CRT will continue to receive durvalumab/placebo as consolidation treatment. Patients with RECIST 1.1-defined radiological progressive disease (PD) will proceed to follow-up.

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

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

4.2 Scientific rationale for study design

4.2.1 Rationale for study endpoints (efficacy)

The primary aim of this study is to determine the efficacy of durvalumab (CCI mg CCI via intravenous [IV] infusion) + SoC CRT compared with placebo + SoC CRT.

PFS may serve as a surrogate endpoint for OS when differences between treatment arms are of sufficient magnitude and clinically important (FDA Guidance 2011, Mauguen et al 2013, Pazdur 2008). In particular, a close association of PFS and OS has been observed in stage III NSCLC. However, in the setting of advanced, unresectable NSCLC, the utility of survival as an endpoint may be confounded by subsequent therapies. Specifically, there are currently a number of molecules targeting the PD-1/PD-L1 pathway in late-stage development in patients with first, second, and third line PD-L1-positive and PD-L1-unselected NSCLC. Therefore, PFS will be used as the primary endpoint in this study.

The key secondary efficacy endpoints (ie, those included in the multiple testing procedure) of OS, OS24 and ORR, and other secondary endpoints including rate of CR, DoR, DCR, time CCI CCI and TTDM, will be examined to further evaluate the antitumor effect of durvalumab + SoC CRT versus placebo + SoC CRT.

ORR can be a useful endpoint, because it is a direct measure of the drug's antitumor activity (Pazdur 2008). The use of ORR in the setting of advanced, unresectable NSCLC, especially when the responses are sustained and durable (a key feature of immunotherapy), is justified because it is anticipated that it will serve as an early measure of clinical benefit that may be confirmed by the survival endpoints employed in a randomized confirmatory study. Assessing ORR (and CR rate) will help ascertain the benefit of adding durvalumab during CRT, versus waiting until after CRT. Additionally, for patients treated with immunotherapies, including durvalumab, responses appear to be durable, reinforcing the importance of ORR as a likely surrogate for clinical benefit.

The secondary symptoms and overall health-related quality of life (QoL) endpoints, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire, version 3 (QLQ-C30 v3) and the complementary 13-item Lung Cancer Quality of Life questionnaire (QLQ-LC13) will show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and will aid in understanding of the benefit/risk evaluation. These PRO questionnaires are well established instruments that have been previously included in cancer clinical studies.

Antitumor activity will be assessed according to RECIST 1.1 guidelines. The analysis of PFS and ORR will be based on programmatically derived PFS and ORR based on BICR assessments. Sensitivity analyses will also be performed using data from Site Investigator tumor assessments based on RECIST 1.1.

4.2.2 Rationale for study endpoints (other exploratory endpoints)

Biological samples will be used to explore potential CCI in CCI which may influence the CCI CCI

Blood samples will be taken to allow for research into CCI and CCI of durvalumab, and the relationship between durvalumab CCI exposure and clinical outcomes, efficacy, AEs, and/or safety parameters.

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

4.2.3 Rationale for treatment duration

Treatment in this study will continue until RECIST 1.1-defined PD, or until another discontinuation criterion is met (see Section 7.1). This guidance was supported by data from the CheckMate-153 study presented at the 2017 ESMO Congress, which 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, no new safety signals were observed with durvalumab after 6 months of treatment. Based on these observations, no new safety signals are expected beyond 1 year of treatment with durvalumab, but there exists the potential for additional survival benefit beyond 1 year of treatment. Treatment will be discontinued following RECIST 1.1-defined progression to allow the patient the opportunity to utilize an alternate anticancer treatment.

4.3 Justification for dose

This study will utilize CCI for durvalumab treatment (CCI mg CCI) + SoC CRT followed by durvalumab consolidation (CCI mg CCI). Based on an average body weight of CCI of CCI of durvalumab CCI is equivalent to CCI

4.3.1 Durvalumab monotherapy dose rationale

A durvalumab dose of CCI is supported by in-vitro data, non-clinical activity, clinical CCI, and activity data from CCI

CCI

Based on available CCI from ongoing CCI with doses ranging from CCI to CCI or CCI, durvalumab exhibited non-linear (dose dependent) CCI consistent with target-mediated drug disposition. The CCI approached linearity at CCI CCI suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than CCI The expected half life with doses CCI is approximately CCI. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with CCI. A low level of CCI has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on CCI please see the current IB).

Data from CCI also show an approximately dose-proportional increase in CCI exposure for durvalumab over the dose range of CCI durvalumab CCI or CCI (For further information on CCI observations in CCI please see the current IB).

The observed durvalumab CCI data from the combination study were well in line with the predicted monotherapy CCI data (5th median and 95th percentiles) for a q4w regimen.

A population CCI model was developed using the data from CCI (CCI to CCI CCI or CCI (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both CCI and CCI regimens, as represented by the area under the plasma drug concentration-time curve at steady state (AUC_{ss}; CCI). Median Cmax,ss is expected to be higher with CCI (~1.5 fold) and median Ctrough,ss is expected to be higher with CCI (~1.25 fold). Clinical activity with the CCI CCI dosing regimen is anticipated to be consistent with CCI with the proposed similar dose of CCI expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in CCI, and clinical activity in diverse cancer populations; (c) maintain sufficient CCI exposure in case of CCI impact; and (d) achieve CCI exposure that yielded maximal antitumor activity in animal models.

Given the similar AUC and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the CCI and CCI regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of CCI CCI.

Clinical data

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

4.3.2 Rationale for CCI

A population CCI model was developed for durvalumab using monotherapy data CCI (N=292; doses= CCI to CCI or CCI ; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the CCI of durvalumab (coefficient of ≤0.5). The impact of body WT-based (CCI) and fixed dosing (CCI) of durvalumab was evaluated by comparing CCI (5th, median, and 95th percentiles) using the population PK model. CCI A total of 1000 patients were simulated using body WT distribution of 40 to 120 kg. CCI

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 CCI CCI dosing perform similarly, with CCI being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that CCI performed better for 12 of 18 in terms of reducing the between-patient variability in CCI parameters (Zhang et al 2012).

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

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit or last scheduled procedure shown in the Schedule of Activities (SoA).

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

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over 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 Informed Consent.

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

4.4.1 Treatment after final overall survival data cutoff

At the time of the final data cutoff (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 analysis, 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 in progression-free follow-up (patients who have discontinued study drug treatment and have not progressed) may decide to continue in the study in progression-free follow-up.

Patients who are receiving treatment at the time of final DCO may continue receiving durvalumab 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 treatment beyond the time of the final DCO, Investigators will report serious adverse events (SAEs) to AstraZeneca Patient Safety via paper case report forms (CRFs) until 90 days after the last dose of study treatment, in accordance with Section 8.4.1. Any non-serious AE that is ongoing at the time of this DCO is to be followed up at the discretion of the Investigator and per local practice and in alignment with the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1). Data will not be captured for the purposes of this study outside of being recorded in the patients' source documents.

Following the final DCO, SAE reporting applies only to patients who are active on durvalumab and within 90 days after the last dose. No OS data will be recorded in the study database after final DCO for the study.

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 be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures (refer to Section 5.4).

In this protocol, "enrolled" patients are defined as those who sign an informed consent. "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

5.1 Inclusion criteria

Informed consent

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

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

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

Age

3. 18 years or older at the time of signing the ICF. In Japan, patients must be 20 years or older at the time of signing the ICF.

Type of patient and disease characteristics

4. Histologically or cytologically documented NSCLC who present with locally advanced, unresectable (Stage III) disease (according to Version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology 2016]).

   – Except for overt cT4 disease, nodal status N2 or N3 should be proven by biopsy, via endobronchial ultrasound, mediastinoscopy, or thoracoscopy. Absent biopsy, nodal status should be confirmed with whole body ^{18}F-fluoro-deoxyglucose positron emission tomography, plus contrast-enhanced computed tomography (CT) in addition to or in combination with PET.

   – Mandatory brain magnetic resonance imaging (MRI; preferred) or high-quality brain CT with IV contrast at the time of staging.

5. World Health Organization (WHO)/ Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at enrollment and randomization.

6. Patients with at least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 Target Lesion (TL) at baseline. Tumor assessment by CT or MRI must be performed within CCI prior to randomization.

7. Tumor sample requirements:

   – Mandatory provision of an archived tumor tissue block (or at least CCI CCI (refer to Section 8.8 and the Laboratory Manual for

details). If an archival sample is not available, provision of a recent (≤3 months) tumor biopsy is mandated.

– The provision of an additional recent CCI) tumor biopsy is optional, provided that a biopsy procedure is technically feasible and the procedure is not associated with unacceptable clinical risk.

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

9. Adequate pulmonary function test results as described below:

- Pre- or post-bronchodilator forced expiratory volume 1 of 1.0 L or >40% predicted value

And,

- Diffusing capacity of the lung for carbon monoxide (DLCO) >30% predicted value.

10. Adequate organ and marrow function at enrollment and randomization as defined below:

– Hemoglobin ≥9.0 g/dL

– Absolute neutrophil count >1.5 × 10^9/L

– Platelet count >100 × 10^9/L

– 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.

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

– Measured creatinine clearance (CL) >40 mL/min or calculated CL >40 mL/min as determined by Cockcroft-Gault (using actual body weight)

Males:

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

Females:

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

11. CCI research study (optional)

For inclusion in the optional CCI research study, patients must fulfil the following criteria:

– Provide informed consent for the CCI sampling and analyses.

If a patient declines to participate in the CCI research, there will be no penalty or loss of benefit to the patient. A patient who declines CCI research participation will not be excluded from any other aspect of the main study.

Weight

12. Body weight >30 kg at enrollment and randomization.

Sex

13. Male or female

Reproduction

14. 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:

– 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).

– 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. History of allogeneic organ transplantation.

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

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

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

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

4. History of another primary malignancy except for

   - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence. Patients with a previous history of radiation therapy are eligible provided field overlap is minimal and the risk of toxicity to tissues in the overlapping region(s) is deemed to be acceptable by treating radiation oncologist.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease

5. History of leptomeningeal carcinomatosis

6. History of active primary immunodeficiency.

7. Active infection including **tuberculosis (TB)** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known CCI [redacted] result), **hepatitis C** (HCV), or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the CCI [redacted]) are eligible. Patients CCI [redacted] are eligible only if polymerase chain reaction is CCI [redacted]

8. Mixed small cell and NSCLC histology.

9. Known allergy or hypersensitivity to any of the IPs or any of the IP excipients.

10. Any medical contraindication to treatment with platinum-based doublet chemotherapy as listed in the local labelling.

11. Patients whose radiation treatment plans are likely to encompass a volume of whole lung receiving ≥20 Gy in total (V20) of more than 35% of lung volume. V20s up to 37% will be permitted and viewed as a minor deviation, provided that the treating radiation oncologist believes this level of exposure is within patient tolerance.

12. Planned radiation cardiac dose V50 >25%.

13. Patients who have disease considered for surgical treatment as part of their care plan, such as Pancoast or superior sulcus tumors. Patients with T4 lesions that invade major vascular structures such as pulmonary artery or cardiac tissues are also not eligible.

Prior/concomitant therapy

14. Receipt of prior or current cancer treatment for NSCLC, including but not limited to, radiation therapy, investigational agents, chemotherapy, and mAbs. Prior surgical resection of metachronus NSCLC (ie, Stage I or II) is permitted.

15. Receipt of live attenuated vaccine within CCI prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine while receiving IP and up to CCI after the last dose of IP.

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

17. 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.

18. Current or prior use of immunosuppressive medication within CCI before the first dose of IP. The following are exceptions to this criterion:

    – Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)

    – Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

    – Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

Prior/concurrent clinical study experience

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

20. Previous IP assignment in the present study

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

22. Participation in another clinical study with an IP during the CCI prior to randomization.

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

Other exclusions

24. 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 CCI after the last dose of IP.

25. 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.

26. Genetics research study (optional):

    Exclusion criteria for participation in the optional CCI research component of the study include:

    – Previous allogeneic bone marrow transplant.

    – CCI CCI in 120 days of CCI

5.3 Lifestyle restrictions

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

1. Female patient of child-bearing potential

    – Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non sterilized male partner must use at least 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 IP). Non sterilized male partners of a female of childbearing

potential must use 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 birth control. Female patients should also refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

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

   – Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 4).

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 all 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.

Highly effective methods of contraception, defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 4. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

In addition to the guidelines described above, local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for SoC CRT agents must be followed.

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[b]: Etonogestrel-releasing implants: eg, Implanon® or Norplant® • Intravaginal Devices[b]: Ethinylestradiol/etonogestrel-releasing intravaginal devices: eg, NuvaRing® • Injection[b]: Medroxyprogesterone injection: eg, Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch[b]: Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra® • Minipill[b]: 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
[b] This hormonal method is not approved in Japan.

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

Restrictions relating to concomitant medications are described in Section 6.5.

5.4 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients can be rescreened a single time, but they cannot be re-randomized.

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 chemotherapy and radiation (CRT), durvalumab, and placebo.

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca/MedImmune will supply durvalumab (MEDI4736). SoC agents (chemotherapy and radiation) and the saline solution for the placebo will be supplied locally. Under certain circumstances when local sourcing is not feasible, SoC treatment (chemotherapy) may be supplied centrally through AstraZeneca. See Table 5 for further details on the IPs.

Table 5 Study treatments

	Durvalumab	Placebo	Standard of care[a]				
Study treatment name:	Durvalumab (MEDI4736)	Saline solution	Cisplatin/ Etoposide	Carboplatin/ Paclitaxel	Pemetrexed/ Cisplatin [b]	Pemetrexed/ Carboplatin [b]	Radiation
Dosage formulation:[c]	CCI	Sterile solution of CCI CCI for injection	As sourced locally	As sourced locally	As sourced locally	As sourced locally	As sourced locally
Route of administration	IV	IV	IV	IV	IV	IV	External beam radiation
Dosing instructions:[d]	CCI	Saline volume matching durvalumab volume	Cisplatin CCI on Days 1 and 8 Etoposide CCI CCI cycles **+1 additional induction cycle optional** Concurrent thoracic radiotherapy	Carboplatin AUC 2 and Paclitaxel CCI on CCI - Concurrent thoracic radiotherapy **Optional**:paclitaxel CCI mg/m^2 and carboplatin CCI given either as 1 induction cycle prior to initiation of radiotherapy **OR** as 1-2 consolidation cycles after radiotherapy is completed	Pemetrexed CCI and cisplatin CCI on CCI **+1 additional induction cycle optional**	Pemetrexed CCI	5 fractions/ week for CCI (±3 days) (Total 60 Gy)
Packaging and labelling	Provided in CCI vials, labelled in accordance with GMP Annex 13 and per country regulatory -requirement[f]	Sourced locally by site	Sourced locally by site	Sourced locally by site	Sourced locally by site	Sourced locally by site	Sourced locally by site

Table 5 Study treatments

	Durvalumab	Placebo	Standard of care[a]				
Provider	AstraZeneca	Sourced locally by site[g]	Sourced locally by site[g]	Sourced locally by site[g]	Sourced locally by site[g]	Sourced locally by site[g]	Sourced locally by site

Note: Cycles of durvalumab/placebo are [redacted] cycles of chemotherapy are per local prescribing guidelines.

[a] Under certain circumstances when local sourcing is not feasible, an SoC treatment may be supplied centrally through AstraZeneca.

[b] Patients with non-squamous NSCLC only. Administer vitamin B12 and folic acid as per pemetrexed prescribing instructions.

[c] Refer to Section 6.2 for detailed formulation and preparation instructions for IPs.

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

[e] If a patient's weight falls to 30 kg or below, the patient should receive weight-based dosing equivalent to [redacted] of durvalumab [redacted] until the weight improves to >30 kg, at which point the patient should start receiving the [redacted] of durvalumab [redacted].

[f] 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.

[g] Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally source the drug, which will be labeled with text translated to local language in accordance with regulatory guidelines.

AUC Area under the curve; GMP Good Manufacturing Practice; IV Intravenous; NSCLC Non-small cell lung cancer; [redacted] Every [redacted]; SoC Standard of care.

6.1.1.1 Durvalumab (MEDI4736) or placebo

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

Saline solution will serve as the placebo in this study.

Durvalumab CCI or placebo will be administered CCI via IV infusion (see Table 5) concurrent with SoC CRT (ie, starting on Cycle 1 Day 1 [±3 days]). Patients with CR, PR, or SD (based on Investigator assessment) at the 16-week tumor evaluation following completion of SoC CRT will continue to receive durvalumab/placebo as consolidation treatment until RECIST 1.1-defined PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients with RECIST 1.1-defined radiological PD will proceed to follow-up.

Crossover within the study will not be permitted.

If chemotherapy and/or radiation is discontinued due to treatment-related toxicity, treatment with durvalumab or placebo may continue at the Investigator's discretion when toxicity resolves to Grade 2 or less. Note: if the Investigator feels a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca/MedImmune should be consulted for an exception to this rule. Additional details for dosing delays can be found in Section 8.4.5.

6.1.1.2 SoC CRT

SoC CRT agents will be supplied locally where possible. Patients will receive 1 of the SoC platinum-based chemotherapy options outlined in Table 5, based on Investigator discretion, in addition to radiation therapy (as described in Table 5). Concurrent radiation therapy will be administered according to the guidelines outlined in Appendix G. Treatment with SoC CRT will be concurrent with durvalumab/placebo (ie, starting on Cycle 1 Day 1 [±3 days]). In order to allow adequate time for coordination of radiation therapy, at the discretion of the treating physician, an additional planned "induction" cycle of certain chemotherapy regimens may be administered prior to the initiation of radiotherapy. If an optional induction chemotherapy cycle is administered prior to initiation of radiation therapy, durvalumab/placebo will begin on the same day as induction chemotherapy (Cycle 1 Day 1). For the paclitaxel/carboplatin regimen, investigators have the option of administering 1 induction cycle three weeks before initiating radiotherapy OR administering up to 2 consolidation cycles after completion of radiotherapy (but may NOT administer both induction and consolidation for this regimen). Specific dosing information is detailed in Table 5.

In the event that durvalumab/placebo is discontinued or temporarily held due to treatment-related toxicity, SoC CRT may still be administered as scheduled at the Investigator's discretion.

On days when both durvalumab/placebo and SoC CRT are administered, durvalumab/placebo will be administered first, followed by SoC chemotherapy.

6.1.1.3 Placebo

The saline placebo solution will be administered using an IV bag that is identical in size to the durvalumab solution. A volume of normal saline equal to the volume of durvalumab as specified in Section 6.2 will be added to the IV bag. The IV bag should be covered with an opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel to maintain double-blind conditions.

6.1.1.4 Post Final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician considers they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1).

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over 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 Informed Consent.

Investigators should continue to monitor and document data for all study patients in the database after scheduled DCO for final analysis of the global cohort and final database lock. Dependent on the analysis results of the global cohort, a decision may be made to continue further data collection for a longer period with intent to analyze long-term OS and safety data to fulfill any other potential Health Authority requirements. Any additional long-term analysis may be further clarified through addendum to main statistical analysis plan, which will be developed before DCO for the long-term analysis. Data will be collected until any of following conditions are met:

- Until remaining patients in the study (including patients after discontinuation of study treatment) have discontinued the study OR
- Remaining patients have been transferred to a roll-over study OR
- If the sponsor decides to stop data collection, patients ongoing study treatment at this time and deriving clinical benefit from their assigned treatment will be allowed to continue treatment and only SAEs will be collected

Patients moving to the roll over study will require a new informed consent. The OS data collected in the roll over study may be combined with the OS data from PACIFIC 2 and evaluated as a combined dataset.

6.2 Preparation/handling/storage/accountability

6.2.1 Product preparation of durvalumab

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

- CCI
-

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

6.2.2 Preparation of durvalumab doses for administration with an IV bag

A dose of CCI (for patients >30 kg in weight) will be administered using an IV bag containing CCI, with a final durvalumab (MEDI4736) concentration ranging from CCI, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, CCI mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within CCI. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. The IV bag should be covered with an opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel to maintain double-blind conditions.

If weight falls to ≤30 kg, weight-based dosing at CCI will be administered using an IV bag containing CCI with a final durvalumab (MEDI4736) concentration ranging from CCI, and delivered through an IV administration set with a CCI in-line filter.

The time from needle puncture of vial to start of administration should be up to CCI. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed CCI at room temperature.

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

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

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

6.2.3 Preparation of placebo for administration with an IV bag

The placebo solution will be identical in color to the durvalumab solution and will be administered using an IV bag that is identical in size to the durvalumab IV bag (see Section 6.2.2). A total of 30.0 mL normal saline will be added to the IV bag. Additional preparation and administration details will be identical to those for durvalumab (see Section 6.2.2).

6.2.4 Storage and accountability

The unblinded pharmacist must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved by supply chain before use of the study treatment.

The unblinded pharmacist will ensure that all IP is stored in a secured area, in refrigerated temperatures (2°C to 8°C for durvalumab and according to local guidelines for SoC) 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 unblinded monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Durvalumab storage conditions stated in the IB may be superseded by the label storage.

The IP provided for this study will be used only as directed in the study protocol.

IPs will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The unblinded pharmacist is responsible for managing the IPs from receipt by the study site until the return of all unused IP to AstraZeneca. AstraZeneca will provide the study documents “Procedures for drug accountability” and ‘Procedures for drug storage,” which describes the specific requirements. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.3 Measures to minimize bias: randomization and blinding

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

Patients may be enrolled but not randomized. If a patient is not randomized, the IVRS/IWRS should be contacted to terminate the patient in the system.

If a patient withdraws from the study, then his/her enrolment/randomization code cannot be reused, and they cannot re-enter into the study. Withdrawn patients will not be replaced.

The IVRS/IWRS will also be used to track drug supply.

6.3.1 Procedures for randomization

Patients must not be randomized unless all eligibility criteria have been met.

Patients will be randomized in a 2:1 ratio to either durvalumab + SoC CRT or placebo + SoC CRT. Patients will be stratified by age (CCI) and stage (CCI

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

Patients will be identified to the Centralized Randomization Center per country regulations. Randomization codes will be assigned PPD , within each stratum, as patients become eligible for randomization. The IVRS/IWRS Centralised Randomization Centre will inform the unblinded pharmacist of the kit identification number to be allocated to the patient at the randomization visit.

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

The Investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new kit identification number. The kit identification number dispensed at each visit will correspond to the IP to which the patient was originally randomized.

If a patient discontinues participation in the study, then his/her enrolment/randomization code cannot be reused.

6.3.2 Methods for ensuring blinding

The study will be conducted in a double-blind manner. The diluted durvalumab and placebo (IV saline solution) will be blinded using an opaque sleeve, fastened with tamper-evident tape over the IV bag prior to dispensing to other study personnel to maintain the double-blind conditions.

The patient, the Investigator, and study center staff will be blinded to the durvalumab/placebo allocation. The study center pharmacist will be unblinded to the durvalumab/placebo allocation and will prepare durvalumab or placebo for a patient as specified by the randomization scheme and IVRS (only the unblinded pharmacist will know the randomization/treatment allocation details). Pharmacists will be given specific instructions for durvalumab/placebo preparation and will note if the double-blind conditions have been compromised or the blind has been broken. Lot numbers of durvalumab dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. Other study center staff and monitors will not be given access to lot number information.

No member of the extended study team at AstraZeneca/MedImmune, at the investigational centers, or any blinded contract research organization handling data will have access to the randomization scheme until the time of the final data analysis or any IA data where the study has met 1 of the primary endpoints and a decision is made to unblind the study at that timepoint. At such time, AstraZeneca/MedImmune and any Contract Research Organisation handling data will have access to the randomization scheme. Exceptions are relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca/MedImmune or their designee, where the information is needed to package the durvalumab/placebo; the drug safety departments at AstraZeneca/MedImmune; and the pharmacists required to dispense the durvalumab/placebo at the study site. Investigators will be unblinded to treatment allocation only in cases of medical emergency. Additionally, at the request of the Investigator, following discontinuation of IP and RECIST 1.1-defined progression of disease plus the additional regularly scheduled follow-up scan the patient can be unblinded. In the setting of rapid clinical progression, unblinding should be discussed with the AstraZeneca Global Study Physician and Study Statistician.

The IDMC will be provided with unblinded data for their review via a vendor independent of the rest of the study conduct, analysis, and reporting; AstraZeneca/MedImmune staff and Investigators involved in the study will remain blinded.

6.3.3 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each center.

The treatment code should not be broken by the investigator except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. Additionally, at the request of the Investigator, following discontinuation of IP and RECIST 1.1-defined progression of disease plus the additional regularly scheduled follow-up scan the patient can be unblinded. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to a patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

6.4 Treatment compliance

The administration of all IPs should be recorded in the appropriate sections of the electronic case report form (eCRF).

Any change from the dosing schedule, does 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 unblinded pharmacist is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.5 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study, including the follow-up period following the last dose of IP. Any concomitant medication(s), including herbal preparations, taken during this time will be recorded in the eCRF.

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 the following tables. Refer also to the Dosing Modification and Toxicity Management Guidelines in Section 8.4.5.1. For agents in the SoC CRT arm, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

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 whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Live attenuated vaccines	Should not be given through CCI after the last dose of IP

Prohibited medication/class of drug:	Usage:
Immunosuppressive medications, including but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Short-term premedication for patients receiving SoC CRT, in which the prescribing information or local guidance for the agent requires the use of steroids for documented hypersensitivity reactions, nausea/vomiting, prophylaxis, etc. • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids are 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 CCI post last dose of durvalumab. 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 has been given concomitantly
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE Adverse event; CRT Chemoradiation therapy; CTLA-4 cytotoxic T-lymphocyte antigen 4; EGFR Epidermal growth factor receptor; I-O Immuno-oncology; IP Investigational product; CCI CCI SoC Standard of care; TKI Tyrosine kinase inhibitor.

Table 7 Supportive medications

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

6.5.1 Other concomitant treatment

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

6.5.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either pre-clinically or in patients. As durvalumab is a 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 will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected CCI drug-drug interactions. The mechanism of action of durvalumab involves binding to PD-L1, and therefore significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

6.5.3 Rescue medication

As a result of imAEs that could potentially be experienced by patients on durvalumab, immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into this category are infliximab (for colitis) and mycophenolate (for hepatitis). AstraZeneca supply chain will be responsible for sourcing 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 unblinded pharmacist and stored according to the labelled storage conditions, with temperature excursions reported accordingly by the unblinded pharmacist. If required for use as a result of an immune-mediated adverse event (imAE), then the interactive voice response system (IVRS)/interactive

web response system (IWRS) will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the time. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS.

6.6 Dose modification

Dose modifications are permitted in the management of certain IP-related toxicities as described in Section 8.4.5. In case a dose reduction is necessary, durvalumab/placebo will be administered as described in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1). Modification of SoC CRT will be based on local prescribing and labelling guidelines.

6.7 Treatment after the end of the study

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving durvalumab treatment up to the time that they discontinue the treatment for whatever reason (see Section 6.1).

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

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

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study 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 (see Section 8.4.5.1) or as defined in the local prescribing information for the SoC CRT agents
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent

- Clinical progression and Investigator determination that the patient is no longer benefiting from treatment with IP

- RECIST 1.1-defined radiological PD

In the event that durvalumab/placebo is discontinued due to treatment-related toxicity, SoC CRT may still be administered as scheduled. If SoC CRT is discontinued due to treatment-related toxicity, durvalumab/placebo may continue at the Investigator's discretion when toxicity resolves to Grade 2 or less. Note: if the Investigator feels that a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

7.1.1 Procedures for discontinuation of study treatment

At any time, patients are free to discontinue IP without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. If possible, they will be seen and assessed by an Investigator. AEs will be followed up (see Section 8.3). The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

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

Patients who permanently discontinue study drug for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 assessments performed CCI ±1 week beginning CCI after randomization for the first CCI (relative to the date of randomization), and then CCI ±1 week thereafter until RECIST 1.1-defined PD or death (whichever comes first) as defined in the SoAs.

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 CCI after the prior assessment of PD.

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

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

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

If a patient is withdrawn from study, see Section 7.3.

7.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine

the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. Patients should be considered "potentially lost to follow-up" if contact is lost at any time during the study. 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 key endpoints of PFS/OS, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked; this includes those patients who withdrew consent or are classified as "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)
- withdrawal to the use of any samples (see Appendix C)

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

The Rave 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 treatment.

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

All screening evaluations must be completed and reviewed to confirm that potential 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 utilized for screening or baseline purposes, provided that the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy assessments

This study will evaluate the primary endpoint of PFS. The key secondary endpoints (ie, those included in the multiple testing procedure) are ORR, OS and OS24. Efficacy assessments of PFS, rate of CR, DoR, DCR, and TTDM will be derived (by AstraZeneca) using BICR

assessments according to RECIST 1.1. A sensitivity analysis of PFS will be performed using Investigator assessments.

Tumor assessments utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands), collected during screening/baseline and at regular (follow-up) intervals during study treatment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoAs). 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 until clinical progression/deterioration or radiological progression by RECIST 1.1, and scanning/tumor assessments continue throughout treatment until RECIST 1.1-defined radiological progression plus an additional follow-up scan (if clinically feasible).

The RECIST 1.1 guidelines (0) provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed no more than 28 days before the date of randomization, and ideally should be performed as close as possible to and prior to the date of randomization. The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and Non-Target Lesions (NTLs). On-study images are evaluated for TLs and NTLs chosen at baseline, and for New Lesions (NLs) when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall timepoint responses (CR, PR, SD, PD, or Not Evaluable [NE]).

8.1.1 Central reading of scans

All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization for QC and storage. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter, (also referred to as ‘Imaging Charter’).

8.1.2 Survival assessments

Assessments for survival must be made CCI (±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. These contacts should generally occur within 7 days of the DCO.

8.1.3 Clinical outcome assessments

PRO is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical studies. The following PROs will be administered in this study: EORTC QLQ-C30 v3 (core questionnaire), EORTC QLQ-LC13 (lung cancer module), PGIS and 5-level health state utility index (EQ-5D-5L) (see Appendix H).

8.1.3.1 EORTC QLQ-C30 and QLQ-LC13

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' symptoms, functioning, and health-related quality of life (HRQoL) (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, nausea, and vomiting); a 2-item global HRQoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

The QLQ-LC13 is a well-validated complementary module measuring lung cancer associated symptoms and side effects from conventional chemotherapy and radiotherapy (Bergman et al 1994). The QLQ-LC13 includes questions assessing cough, hemoptysis, dyspnea, site specific pain (symptoms), sore mouth, dysphagia, peripheral neuropathy, alopecia (treatment-related side effects), and pain medication.

8.1.3.2 PGIS

The Patient Global Impression of Severity (PGIS) item is included to assess how a patient perceives his/her overall current severity of cancer symptoms. Patients will choose from response options from "No symptoms" to "Very severe."

8.1.3.3EQ-5D-5L

The EuroQoL 5-Dimension (EQ-5D) is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions as follows: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options ("no problems," "slight problems," "moderate problems," "severe problems," and "extreme problems") that reflect increasing levels of difficulty (EuroQoL Group 2013).

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

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

8.1.3.4 Administration of patient-reported outcomes questionnaires

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

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

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

- It is preferred that PRO questionnaires are completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid biasing the patient's responses to the questions.
- PRO questionnaires must be completed in private by the patient.
- Patient should be given sufficient time to complete the PRO questionnaires at their own speed.
- 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 ePRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the CCI using the materials and training provided in the CCI .
- 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.

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

8.2 Safety assessments

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

8.2.1 Clinical safety laboratory assessments

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

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, units, and reference ranges) will be recorded on the appropriate eCRF.

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

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

The following laboratory variables will be measured:

Table 8 Clinical chemistry

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

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

ALT Alanine aminotransferase; AST Aspartate aminotransferase, T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid Stimulating Hormone.

Table 9 Hematology

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

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 1 of cycle 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.

[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.

Table 10 Urinalysis

Urinalysis should be done at baseline (screening) and then as clinically indicated	
Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

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

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

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.

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 SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal (GI), urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.6.

8.2.3 Electrocardiograms

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

In case of clinically significant ECG abnormalities, including a 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.

8.2.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiratory rate) will be evaluated according to the assessment schedules (see the SoAs). Body weight is also recorded at each visit along with vital signs. The following timepoints for vital signs assessments apply to infusions of durvalumab/placebo. Vital signs assessments related to SoC CRT administration should be performed according to local clinical practice.

First infusion

On the first infusion day, 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 will be collected before, during, and after each durvalumab/placebo infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 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 ±5 minutes)
- A CCI period is recommended after the first infusion of durvalumab/placebo. 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 (CCI after each durvalumab/placebo 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 infusions

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

8.2.5 WHO/ECOG performance status

WHO/ECOG PS will be assessed at the times specified in the SoA based on the following:

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

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

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

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

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

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

8.2.6 Other safety assessments

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

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment (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.
- SpO2
  - Saturation of peripheral oxygen (SpO2)

- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    (ii) Tumor markers: Particular tumor markers that are related to disease progression.
    (iii) Additional Clinical chemistry: C reactive protein (CRP), lactate dehydrogenase (LDH)

Brain MRI/CT

At screening, a brain MRI (preferred) or high-quality brain CT with IV contrast will be performed.

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 or 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 authorized representative).

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

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

AEs and SAEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (90 days after the last dose of IP).

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

Investigators are not obligated to actively seek 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 treatment 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 provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

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 but without further recording in the eCRF. 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
- 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 hospitalization

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

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 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 be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B, 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.

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, anemia vs low hemoglobin 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.

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 Hy's law.

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events 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 include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions 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, and 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 etiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Section 8.4.5.1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the IP/study regimen by the reporting investigator.

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

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5.1). All data 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 durvalumab treatment (or within the 90 days following the last dose of durvalumab 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 not available, then the Investigator or other study site personnel reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

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 of the Clinical Study Protocol.

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 IPs.

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs 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.

8.4.2.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for CCI following the last dose of IP. Please follow the local prescribing information relating to contraception and the time limit for such precautions for SoC CRT agents.

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 CCI 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 Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

8.4.3 Overdose

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

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 8.4.1. For other overdoses, reporting must occur within 30 days.

Refer to the local prescribing information for treatment of cases of overdose for any SoC CRT agents. If any overdose is associated with an AE or SAE, please record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

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 or 5 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.

8.4.5 Management of IP-related toxicities

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, or infections). This includes SoC CRT-induced toxicity.
- In the absence of a clear alternative etiology, all events should be considered potentially immune related, and the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1) should be followed.
- In the event that durvalumab/placebo is discontinued or delayed as part of the Dosing Modification and Toxicity Management Guidelines, SoC CRT may still be administered as scheduled.
- In the event that SoC CRT is discontinued due to treatment-related toxicity, durvalumab/placebo may continue at the Investigators discretion when toxicity resolves to at least Grade 2 or less. Note: if the Investigator feels that a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

If unsure how to manage a patient, please contact the Study Physician at AstraZeneca to discuss individual cases. All toxicities will be graded according to CTCAE version 4.03.

8.4.5.1 Durvalumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the Dosing Modification and Toxicity Management Guidelines. The most current version of these guidelines is also maintained within the Site Master File. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines is available through the following link:

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

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

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

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

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

8.4.5.2 Standard of care agents

Chemotherapies are associated with a number of unwanted effects. SoC CRT-related toxicity management and dose adjustment, including dose delays and reductions, should be performed as indicated in the local prescribing information for the relevant agent. In the event of unfavorable tolerability, patients can switch between the permitted chemotherapy options at any point on study (assuming eligibility for the switched therapy is met).

In the event that an AE can reasonably be attributed to SoC CRT, dose adjustment of SoC CRT should be attempted before modifying the administration of durvalumab/placebo.

Every effort should be made to ensure patients receive all scheduled cycles of SoC CRT across all treatment arms in the study, if conditions allow.

8.5 CCI

8.5.1 Collection of samples

Blood samples for determination of CCI will be obtained according to the assessment schedules (see the SoAs).

Samples for determination of CCI will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate CCI Validation Report.

8.5.2 Collection of samples to measure for the presence of CCI

The presence of CCI will be assessed in serum samples taken according to the assessment schedules (see the SoAs).

Samples will be measured for the presence of CCI and CCI for durvalumab using validated assays. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naïve validation samples will be employed. Samples will analyzed in an AstraZeneca-designated laboratory; additional details are provided in the Laboratory Manual.

8.5.3 Storage and destruction of CCI samples

CCI samples will be disposed of a maximum of 15 years from the end of the study.

CCI samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled CCI samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the Clinical Study Report (CSR).

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

Any CCI samples may be used for CCI (in this case, CCI samples will be shipped to the AstraZeneca-assigned CCI see details in the Laboratory Manual).

8.6 Pharmacodynamics

Pharmacodynamic samples will not be taken during the study

8.7 CCI

8.7.1 Optional CCI sample

A CCI sample for CCI isolation will be collected from patients who have consented to participate in the CCI analysis component of the study. Participation is optional. Patients who do not wish to participate in the CCI research may still participate in the study. The CCI CCI for CCI research will be obtained from the patients prior to CCI CCI

In the event of CCI failure, a replacement CCI sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix D for information regarding CCI research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the Laboratory Manual.

8.8 Biomarkers

By participating in this study, the patient consents to the mandatory collection and use of donated biological samples as described here. Blood and tissue samples will be obtained from all screened patients.

Based on availability of tissue, exploratory biomarkers may be evaluated as described in Section 8.8.1. Also, descriptions of exploratory, peripheral measures are described in this section. Samples will be obtained according to the assessment schedules provided in the SoAs.

Tumor biopsy samples should be formalin fixed and embedded in paraffin.

- Samples should be collected via a core needle (CCI) or be collected as an excisional or incisional tumor biopsy sample.
- Two cores should be placed in formalin and processed to a single paraffin-embedded block, as described in the Laboratory Manual.
- The tumor specimen should be of sufficient quantity to allow for immunohistochemistry analyses (see the Laboratory Manual). Tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. Please consult the Laboratory Manual for specific instructions and guidelines regarding sections. Specimens with limited tumor content and fine-needle aspirates are inadequate.

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

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

The results may be pooled with biomarker data from other CCI studies to CCI and to CCI in CCI versus CCI settings.

Additional information regarding the handling of human biological samples is provided in Appendix C.

8.8.1 Exploratory biomarkers

Baseline measures will be CCI . Note that samples will be obtained from patients randomized to each treatment arm. Comparisons will be made between baseline measures to determine if CCI CCI associated with durvalumab + SoC CRT versus placebo + SoC CRT.

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

The exploratory biomarker plan is described by sample type below.

CCI

Soluble factors - plasma

Plasma will be obtained from all patients as described in the SoAs. The concentrations of a panel of relevant CCI may be assessed. Plasma may also be used to evaluate mutant CCI. Correlations with outcome data may be completed on select candidates and predictive markers with the aim of identifying useful, appropriate cutoffs for

identifying patients likely to receive benefit, or alternatively, for identifying patients likely to suffer drug-related AEs.

Tumor markers

Tissue obtained as part of screening procedures will be analyzed for additional markers by immunohistochemistry. A primary goal is to measure CCI protein expression in an effort to CCI. Based on availability of tissue, a panel of additional, immune-relevant markers expressed on tumor-infiltrating lymphocytes or on CCI may be assessed. Markers of special interest include, but are not limited to, CCI CCI.

Tumor tissue may also be utilized to evaluate other relevant biomarkers, potentially including but not limited to, somatic mutation detection methods for markers, such as tumor mutational burden, and gene expression methodologies to evaluate inflammatory signatures, potentially including but not limited to, CCI.

Management of biomarker data

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

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

8.8.2 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of CCI from the end of study, after which they will be destroyed. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab to generate hypotheses to be tested in future research.

8.8.3 Labeling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix C, C 3 "IATA 6.2 Guidance Document."

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

8.9 Health economics

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

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

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

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

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

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The formal statistical analyses will be performed to test the main hypothesis:

- H0: No difference between durvalumab + SoC CRT and placebo + SoC CRT
- H1: Difference between durvalumab + SoC CRT and placebo + SoC CRT

The primary objective of this study is to assess the efficacy of durvalumab + SoC CRT compared with placebo + SoC CRT in terms of PFS (per RECIST 1.1 as assessed by BICR). The key secondary endpoints (ie, those included in the multiple testing procedure) are ORR (per RECIST 1.1 as assessed by BICR), OS, and OS24.

The study will be considered positive (a success) if the PFS analysis results are statistically significant.

9.2 Sample size determination

The study will plan to enroll approximately CCI patients in order to randomize 300 eligible patients 2:1 to durvalumab + SoC CRT or placebo + SoC CRT. The randomization will be stratified by age CCI) and stage CCI

The study is powered for the primary endpoint (PFS) and for the key secondary endpoints of ORR and OS. Details of the sample size calculations are shown below. For the multiple testing procedure, refer to Section 9.4.8, and for details of the alpha spending, refer to Section 9.5.

There are up to CCI will occur when approximately CCI of CCI PFS events (information fraction of CCI have occurred. It is estimated that this DCO will occur CCI after the last patient has been randomized. If the CCI is not positive, the DCO for the CCI will occur when approximately CCI events have occurred. It is estimated that this DCO will occur CCI after the last patient has been randomized.

If the true PFS HR is CCI the study will provide greater than CCI power to demonstrate a statistically significant PFS effect with a 2-sided significance level of 5%; this translates to a CCI CCI benefit in median PFS over CCI on placebo if PFS CCI. The smallest treatment effect that would be statistically significant is an HR of CCI at final analysis.

There are up to CCI will occur at the CCI of the CCI if the CCI . If the CCI , the CCI will occur when approximately CCI (information fraction of CCI are reached. If the CCI , then the CCI will occur when approximately CCI (information fraction of CCI are reached. Similarly, if CCI , then the DCO for the CCI analysis will occur when approximately CCI events are reached.

If the true OS HR is CCI the study will have greater than CCI overall power to demonstrate a statistically significant OS effect with a 5% 2-sided significance level; this translates to a CCI if OS is CCI . The smallest treatment difference that would be statistically significant is a HR of CCI at final analysis.

The study has CCI power to detect a statistically significant difference in CCI with a 2-sided significance level of CCI. This assumes the ORR for the patients randomized to placebo + SoC CRT is CCI. The smallest treatment effect that would be statistically significant is a difference in ORR of CCI.

9.3 Populations for analyses

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

Table 11 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy Data	
PFS	FAS (ITT population)
ORR, OS, OS24, CR rate, DoR, DCR at CCI, PRO endpoints, and TTDM	FAS (ITT population)
Demography	FAS (ITT population)
PK data	PK analysis set
Safety Data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
Vital Signs	Safety analysis set
ADA	ADA analysis set

ADA Anti-drug antibody; CR Complete response; DCR Disease control rate; DoR Duration of response; FAS Full analysis set; ITT Intent-to-Treat; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; CCI; PK Pharmacokinetic; PRO Patient-reported outcomes; TTDM Time to death or distant metastasis

9.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients. The FAS will be used for all efficacy analyses (including PROs). Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment will be included in the analysis in the treatment arm to which they were randomized.

9.3.2 Safety analysis set

The safety analysis set will consist of all patients who received at least 1 dose of randomized treatment (durvalumab or matching placebo). Safety data will be summarized using the safety analysis set according to treatment received, that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

9.3.3 CCI

All patients who receive at least 1 dose of durvalumab or placebo per the protocol, for whom any post-dose data are available and do not violate or deviate from the protocol in ways that would significantly affect the CCI analyses, will be included in the CCI analysis set. All patients who have non-missing baseline CCI and at least 1 non-missing post-baseline CCI result will be included in the CCI analysis set. The population will be defined by the study team physician, CCI and statistician prior to any analyses being performed.

9.4 Statistical analyses

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

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

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

Efficacy and PRO data will be summarized and analyzed based on the FAS. CCI data will be summarized and analyzed based on the CCI analysis set. Safety data will be summarized using the safety analysis set.

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

9.4.1 Outcome measures for analysis

9.4.1.1 Calculation or derivation of efficacy variables

The analysis of PFS, ORR, rate of CR, DoR, DCR, and TTDM will be based on BICR tumor assessments according to RECIST 1.1. OS will be evaluated from all-cause mortality. Additionally, CCI will be defined by local standard clinical practice.

A CCI of PFS and ORR will be performed using the Investigator tumor assessments.

RECIST 1.1 based endpoints

Blinded Independent Central Review of RECIST 1.1-based assessments

The BICR of radiological images (including those at unscheduled visits or outside visit windows) will be carried out using RECIST 1.1. The images will be reviewed by 2 independent radiologists using RECIST 1.1 criteria. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). If any of the overall visit responses (CR, PR, SD, PD, or NE) differ between the 2 primary radiologists, the case will be adjudicated by a third independent radiologist who will choose all assessments of the primary reviewer with which they agree more. If no differences in overall visit responses are identified,

then the assessments from the primary radiologist who completed their review of baseline scans first will be used for the analysis. Endpoints (of PFS, ORR, rate of CR, DoR, DCR, and TTDM) will be derived from the overall visit responses.

Further details of the BICR will be documented in the Independent Review (Imaging) Charter.

Investigator RECIST 1.1-based assessments

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

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD, depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the CCI prior to randomization. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE, unless there is evidence of progression, in which case the response will be assigned as PD.

Please refer to 0 for the definitions of CR, PR, no evidence of disease (NED), NE, SD, and PD.

Progression-free survival

PFS (per RECIST 1.1 as assessed by the BICR) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 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 RECIST 1.1 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 RECIST 1.1 assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have baseline data, he or she will be censored at Day 1 unless he or she dies within 2 visits of baseline, then they will be treated as an event with date of death as the event date.

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

RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For BICR assessments, the date of progression will be determined based on the earliest scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of the reviewer who read baseline first if there is no adjudication.
- For Investigator assessments, the date of progression will be determined based on the earliest of the RECIST 1.1 assessment/scan dates of the component that indicates progression.

- When censoring a patient for PFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Note: For TLs, only the latest scan date within an imaging visit window is recorded in the RECIST 1.1 eCRF out of all scans performed at that assessment for the TLs, and similarly for NTLs, only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

A sensitivity analysis of PFS will be performed using Investigator assessments according to RECIST 1.1.

Objective response rate

ORR (per RECIST 1.1 as assessed by BICR) is defined as the number (%) of patients with a confirmed response of CR or PR.

A confirmed response of CR or PR means that a response of CR or PR is recorded at 1 visit and confirmed by repeat imaging not less than CCI after the visit when the response was first observed, with no evidence of progression between the initial and CR/PR confirmation visit. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

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

Overall survival

OS is defined as the time from the date of randomization until death due to any cause. 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.

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

Proportion of patients alive at 24 months (OS24)

The proportion of patients alive at 24 months (ie, OS24) will be defined as the Kaplan-Meier estimate of OS at 24 months. In addition, the proportion of patients alive at 12 months (ie, OS12) will be presented. This will be defined as the Kaplan-Meier estimate of OS at 12 months.

Rate of complete response

The rate of CR (per RECIST 1.1 as assessed by BICR) is defined as the number (%) of patients with at least 1 visit response of CR, which is subsequently confirmed. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in

the assessment of rate of CR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the rate of CR.

Duration of response

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

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

Disease control rate

DCR at CCI (per RECIST 1.1 as assessed by BICR) is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first CCI (to allow for late assessment within the assessment window) or who have SD for at least CCI after randomization (to allow for an early assessment within the ±1 week assessment window). Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the DCR.

Time to death or distant metastasis

TTDM will be defined as the time from the date of randomization until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any NL that is outside of the radiation field according to RECIST 1.1 or proven by biopsy. Patients who have not developed distant metastasis or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient has distant metastasis or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 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 they die within 2 visits of baseline.

CCI

CCI will be defined as the CCI will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: CCI CCI. The site will be asked whether the patient has had a CCI on a regular basis (q12w ±1 week) following CCI used for the CCI CCI and the status recorded. Patients alive and for whom a CCI CCI has not been observed should be censored at the last time known to be alive and

without CCI , that is, censored at the latest of the CCI assessment date if the patient has not had a CCI .

9.4.1.2 Calculation or derivation of safety variables

Adverse events

Data from all cycles of randomized treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred term and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of IP may be included in the AE summaries, but the majority of the AE summaries will omit the AEs observed after a patient has received further therapy for cancer. Further details will be provided in the Statistical Analysis Plan (SAP). Any AE that occurs after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

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

Other significant adverse events (OAEs)

During the evaluation of the AE data, an AstraZeneca/MedImmune medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs. Examples of these are marked hematological and other laboratory abnormalities and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

Safety assessments

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 start of IP.

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, in other words, 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.

9.4.1.3 Calculation or derivation of patient-reported outcome variables – EORTC QLQ-C30 and QLQ-LC13

Symptoms and overall quality of life will be assessed using the PRO questionnaires, EORTC QLQ-C30 and QLQ-LC13 (secondary endpoints). All questionnaires will be scored according to published guidelines or the developer's guidelines, if published guidelines are not available. All PRO analyses will be based on the FAS. The clinical meaningfulness threshold of the PRO analyses described below will be provided in the SAP.

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

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

Higher scores on the global health status/QoL and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

Changes in score compared with baseline will be evaluated. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of ≥10 for scales/items from the QLQ-C30 and the QLQ-LC13 (Osoba et al 1998). For example, a clinically meaningful deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline of ≥10. A clinically meaningful improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable or worsening as shown in Table 12.

Table 12 Visit responses for symptoms and HRQoL

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

EORTC European Organisation for Research and Treatment of Cancer; QLQ C30 30 item core quality of life questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; QoL Quality of life.

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

For each of the symptoms scales/items in the EORTC QLQ-C30 and QLQ-LC13, time to symptom deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from IP or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by EORTC QLQ-C30 and QLQ-LC13) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1.

The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores of ≤90.

Time to HRQoL/function deterioration (QLQ-C30)

For HRQoL and function (as measured by EORTC QLQ-C30), time to deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration (a decrease in the score from baseline of ≥10) that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from IP or receives another anticancer therapy prior to HRQoL/function deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the HRQoL/function change could be evaluated.

Patients whose HRQoL or function have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the HRQoL/function could be evaluated. Also, if HRQoL deteriorates after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where HRQoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1.

The population for the analysis of time to QoL/function deterioration will include a subset of the ITT population who have baseline scores of ≥10.

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

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

The denominator will consist of a subset of the ITT population who have a baseline symptom score of >10.

HRQoL/function improvement rate (QLQ-C30)

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

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

9.4.1.4 Calculation or derivation of patient-reported outcome variables–PGIS

PGIS data will be presented using summaries and descriptive statistics. Further details will be provided in the SAP.

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

The health state utility will be assessed using the EQ-5D-5L (exploratory). The index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; see Section 8.1.3.3). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity

(no problems, slight problems, moderate problems, severe problems, and extreme problems). A unique EQ-5D health state is referred to by a 5-digit code, allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where value sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied (Oemar and Janssen 2013). In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analog scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

9.4.2 Efficacy analyses

Efficacy data will be summarized and analyzed using the FAS. All outputs will be summarized by treatment arm for all randomized patients (Intent-to-Treat population).

The following table (Table 13) details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint.

Table 13 Formal statistical analyses to be conducted and pre-planned sensitivity analyses

Endpoints analyzed	Notes
Progression-free survival	Primary analysis using stratified log-rank test using BICR assessments (RECIST 1.1) Sensitivity analyses using BICR assessments (RECIST 1.1) 1) Interval censored analysis – evaluation time bias 2) Analysis using alternative censoring rules – attrition bias CCI stratified log-rank test using site Investigator assessments (RECIST 1.1) – CCI
Objective response rate	Primary analysis using CMH test, stratified by age CCI CCI) and stage CCI Sensitivity analysis using a CMH test repeated using the site Investigator data based on RECIST 1.1 As a sensitivity analysis the ORR analyzed using logistic regression adjusting for the same factors as for PFS
Overall survival	Stratified log-rank test Sensitivity analysis using a Kaplan-Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias
Proportion of patients alive at 24 months	Kaplan-Meier estimates of survival at 24 months and p-value (following the method described by Klein et al 2007)

Endpoints analyzed	Notes
Rate of CR	Analysis using CMH test using BICR assessment RECIST 1.1 data Sensitivity analysis using the CMH test using site Investigator tumor data (RECIST 1.1)
Duration of response	Kaplan-Meier estimates
Disease control rate	Summarized by descriptive statistics
Time to death or distant metastasis	Stratified log-rank test using BICR data (RECIST 1.1)
CCI [redacted]	CCI [redacted]
CCI [redacted] in key symptoms (EORTC QLQ-C30 and QLQ-LC13)	Mixed model repeated measures analysis
HRQoL/Function improvement rate (EORTC QLQ-C30 endpoints)	Summarized by descriptive statistics
Symptom improvement rate (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Logistic regression
Time to HRQoL/Function deterioration (EORTC QLQ-C30 endpoints)	Stratified log-rank test
Time to symptom deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Stratified log-rank test

BICR Blinded Independent Central Review; CMH Cochran-Mantel-Haenszel; EORTC European Organisation for Research and Treatment of Cancer; HRQoL Health-related quality of life; ORR Objective response rate; PFS Progression-free survival; PFS2 Time from randomization to second progression; QLQ-C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1.

9.4.2.1 Primary endpoint: Progression-free survival

PFS based on the BICR data will be analyzed using a stratified log-rank test adjusting for by age CCI [redacted]) and stage CCI [redacted] The p-value will be obtained from the stratified log-rank test.

The HR and its CI can be estimated from the Cox proportional hazards model (Cox 1972).

Kaplan Meier plots of PFS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment.

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analyzed. For patients whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010).

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2, or more, non-evaluable tumor assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

Ascertainment bias will be assessed by analyzing site Investigator data. The stratified log-rank test will be repeated on the programmatically derived PFS using the site Investigator data based upon RECIST.

If there is an important discrepancy between the primary analysis using the BICR and this sensitivity analysis using site Investigator data assessments, then the proportion of patients with site but no central progression will be summarized; such patients have the potential to introduce bias in the central review due to informative censoring. An approach that imputes an event at the next visit in the central review analysis may help inform the most likely HR value (Fleischer et al 2011), but only if an important discrepancy exists.

Subgroup analyses will be conducted comparing PFS between treatments in the following subgroups of the FAS (but not limited to):

- Planned chemotherapy treatment regimen (identified prior to randomization)
- Planned radiation therapy (intensity-modulated radiation therapy vs 3-dimensional conformal radiation therapy) (identified prior to randomization)
- Region
- Race/ethnicity
- Sex
- Age[redacted]
- Smoking status
- Stage[redacted]
- Histology
- [redacted]

- CCI
- Planning target volume (PTV)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic factors.

For each subgroup, the HR (for the treatment comparisons of interest) and 95% CI will be calculated from a Cox proportional hazards model that contains treatment. These will be presented on a forest plot including the HR and 95% CI.

No adjustment to the significance level for sensitivity or subgroup analyses will be made, since all these analyses will be considered supportive of the primary analysis of PFS.

Unless there is a marked difference between the results of the statistical analyses of the PFS from the BICR tumor data and that of the site Investigator, the subgroup analyses will only be performed upon the PFS endpoint using BICR data.

Cox proportional hazards modelling will be employed to assess the effect of covariates on the HR estimate.

Interactions between treatment and stratification factor will also be tested to rule out any qualitative interaction using the approach of Gail and Simon (Gail and Simon 1985).

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 10 events in a subgroup), the relationship between that subgroup and PFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

Censoring rules will be provided in the SAP.

9.4.2.2 Objective response rate

The ORR will be based on BICR data. The ORR will be compared between treatment arms using a Cochran-Mantel-Haenszel (CMH) test, stratified by age CCI and stage CCI CCI. As a sensitivity analysis, the ORR will be analyzed using logistic regression adjusting for the same factors as for PFS.

The analysis of ORR using a CMH test will be repeated using the site Investigator data based on RECIST 1.1 as a sensitivity analysis to confirm the results of the primary analysis.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). Overall visit response data will be listed and summarized over time for all patients (ie, the FAS). For each treatment arm, the BoR will be summarized by n (%) for each category (CR, PR, NED, SD, PD, and NE). No formal statistical analyses are planned for BoR.

9.4.2.3 Overall survival

OS will be analyzed using a stratified log-rank test, using the same methodology as described for the primary PFS endpoint. The effect of treatment will be estimated by the HR together with its corresponding 95% CI. Kaplan Meier plots of OS will be presented by treatment arm. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS for each treatment. Subgroup analyses maybe performed if there are a sufficient number of OS events.

9.4.2.4 Proportion of patients alive at 24 months

The proportion of patients alive at 24 months (ie, OS24) will be summarized (using the Kaplan-Meier curve) and presented by treatment arm. For each treatment arm, the survival rate at 24 months based on Kaplan-Meier method will be presented, along with its 95% CI. The computation of the CI will be based on a log(-log(.)) transformation. It will be compared between treatments by using the Kaplan-Meier estimator of survival at 24 months for each treatment to obtain the HR. The HR and CI will be presented.

For the comparison between treatments, the test will be based on the method described in Klein 2007 (Klein et al 2007). The test statistic and its variance estimate are as follows:

- test statistic = $\ln \frac{\ln \hat{S}_1(t)}{\ln \hat{S}_2(t)}$
- variance estimate = $\frac{\hat{\sigma}_1(t)^2}{\ln^2 S_1(t)} + \frac{\hat{\sigma}_2(t)^2}{\ln^2 S_2(t)}$

where $\hat{\sigma}_i(t)^2 = \sum_{t_i \le t} \frac{d_i}{n_i(n_i - d_i)}$ is the variance derived from Greenwood's formula $S(t)$ and can be estimated from standard software packages, where d_i and n_i refer to the number of deaths and patients at risk for each risk set.

- The z-statistic is then calculated as: $\frac{\text{test statistic}}{\sqrt{\text{variance estimate}}}$

For the stratified analysis, the test statistic and its variance estimate in each strata will be combined by weighting inversely proportionately according to each within stratum variance (Whitehead and Whitehead 1991). A Z-test will be performed, and the p-value from the test will be presented.

9.4.2.5 Rate of complete response

Rate of CR will be analyzed in the same way as for ORR.

9.4.2.6 Duration of response

Kaplan-Meier estimates will be provided for the DoR in responding patients (ie, median DoR and 95% CIs) by treatment arm, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached).

9.4.2.7 Disease control rate

DCR will be summarized using descriptive statistics by treatment arm.

9.4.2.8 Time to death or distant metastasis

TTDM will be analyzed using identical methods as outlined for the analysis of PFS and adjusting for the same set of covariates, but no subgroup analysis will be performed. Medians and Kaplan-Meier plots will be presented to support the analysis.

CCI

9.4.2.10 Patient-reported outcomes: EORTC QLQ-C30 and QLQ-LC13

Five symptoms have been identified as primary:

- Dyspnea: multi-item scale based on 3 questions ("Were you short of breath when you rested; walked; climbed stairs" – QLQ-LC13),
- Cough: 1 item ("How much did you cough?" – QLQ-LC13),
- Chest pain: 1 item ("Have you had pain in your chest" – QLQ-LC13).
- Fatigue: multi-item based on 3 questions ("Did you need rest; Have you felt weak; Were you tired" – QLQ-C30)
- Appetite loss: 1 item ("Have you lacked appetite" – QLQ-C30)

The physical functioning and overall health status domains of the EORTC CT30 are furthermore pre-specified endpoints of interest.

Mixed models repeated measures (MMRM) analysis

Change from baseline in dyspnea, cough, and chest pain scores as assessed by the EORTC QLQ-LC13 and fatigue and appetite loss as assessed by the EORTC QLQ-C30 will be the primary analysis and assessment of PRO outcome measures. The analysis will be performed using a linear mixed model for repeated measures (MMRM) analysis of change from baseline in the scores for each assessment timepoint and the Bonferroni-Holm procedure for adjusting the significance level will be used to aid interpretation. Therefore, the 5 endpoints will be tested at a 1% significance level.

Time to deterioration

Time to symptom and function/HRQoL deterioration will be analyzed for each of the symptom scales/items, function scales, and global health status/QoL in EORTC QLQ-C30 and QLQ-LC13. This will be achieved by comparing between treatment arms using a stratified log-rank test as described for the primary analysis of PFS. The HR and 95% CI for each scale/item will be presented graphically on a forest plot.

For each of the symptom scales/items, functional scales, and global health status/QoL, time to deterioration will be presented using a Kaplan-Meier plot. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death and the median time to deterioration will also be provided for each treatment arm.

Symptom and function/HRQoL improvement rate

A summary of the symptom improvement rate for all symptom scales/items in EORTC QLQ-C30 and QLQ-LC13 will be produced. Similarly, a summary of function/HRQoL improvement rate for each of the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL will be produced.

Symptom improvement rates will be analyzed by comparing between treatment arms using a logistic regression model. The odds ratio and 95% CI for each scale/item will be presented graphically on a forest plot. If there are very few responses in 1 treatment arm, a Fisher's exact test will be considered.

Change from baseline

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score, and each functional domain will be reported by assessment timepoint for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each assessment timepoint for each ordinal item (in terms of the proportion of patients in the categories of improvement, stable, and deterioration as defined in Table 12) will also be produced for each treatment arm.

EuroQol-5-Dimension 5-Level questionnaire

Descriptive statistics will be reported for the health state domain (eg, proportion in each domain) and the visual analog scale by visit, as well as the change in the visual analog scale value and the derived utility index value from baseline. To support future economic evaluations, additional appropriate analyses may be undertaken, for example, mean health state utility pre- and post-treatment and pre- and post-progression.

9.4.2.11 Health care resource use

An exploratory health economic analysis of hospital episodes including type of contact (hospitalization, outpatient, day case), reason, length of stay by ward type (including intensive care unit), and procedures and tests may be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of SoC CRT given

concurrently with durvalumab. This would include providing descriptive statistics as appropriate, including means, median, and ranges.

9.4.3 Safety analyses

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

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, urinalysis, vital signs, and ECGs. Exposure to CRT, durvalumab, and placebo will be summarized. Time on study and CRT/durvalumab/placebo dose interruptions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.4.4 CCI

Durvalumab concentration data will be listed for each patient and each dosing day, and a summary will be provided for all evaluable patients. Data collected in this study may be utilized to perform population CCI analysis.

9.4.5 CCI analysis

CCI results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable CCI. The CCI titer and presence of neutralizing CCI will be reported for samples confirmed positive for the presence of CCI The effect of CCI, pharmacodynamics, efficacy, and safety will be evaluated, if data allow.

9.4.6 CCI relationships

If the data are suitable, the relationship between durvalumab CCI CCI may be investigated graphically or using appropriate data modeling approach.

9.4.7 Biomarker data

The relationship of CCI expression and, if appropriate, of exploratory biomarkers to clinical outcomes (including but not restricted to PFS) may be presented.

9.4.8 Methods for multiplicity control

The multiple testing procedure (Figure 2) will define which significance levels should be applied to the interpretation of the raw p-values for the primary endpoints of PFS and the key secondary endpoints, ORR, OS and OS24. The family-wise error rate is strongly controlled at 5% for these endpoints.

The testing procedure is CCI The overall 5% type I error will be first assigned to the CCI is significant at CCI or the CCI , an alpha level of CCI will be allocated to the CCI will be allocated to the CCI analysis. If the CCI , then the CCI alpha will be CCI endpoint. If the OS analysis is significant at either the IAs or the final analysis, then the available alpha for OS will be recycled to the OS24 endpoint.

If the OS24 analysis is significant, then the available alpha for OS24 will be recycled to the ORR endpoint. This detail is not shown in Figure 2 and will be included in study Statistical Analysis Plan.

Formal statistical testing of ORR will occur when PFS is statistically significant. If additional alpha is recycled to ORR at later timepoint, the formal testing of ORR will be based on the data at the time when PFS is statistically significant.

Formal statistical testing of OS24 will occur after 24 month of LSI and when OS is statistically significant.

For the PFS endpoint, CCI , and the alpha level will be controlled at the CCI CCI by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach. For the OS endpoint, CCI CCI , and the alpha level will be controlled CCI by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach. The O'Brien Fleming boundaries for the CCI will be adjusted depending on the alpha used for the endpoint.

Figure 2 CCI

9.5 Interim analyses

Interim monitoring for safety will be conducted by the IDMC. Details of the plan and communication process will be provided in the SAP and the IDMC charter.

CCI

The alpha level allocated to PFS will be controlled at the interim and primary timepoints by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the significance level applied at the interim depends upon the proportion of information available. With the alpha level of 5%, if CCI of PFS events required at the time of the primary PFS analysis are available at the time of the interim (ie, CCI CCI events have occurred), the 2-sided significance level to be applied for the PFS IA would be CCI and the 2-sided significance level to be applied for the primary PFS analysis would be CCI.

In addition, CCI will be performed CCI. The CCI CCI when approximately CCI of the final number of OS events is expected to be reached (approximately CCI OS events). The CCI is when CCI of the final number of events is expected to be reached (approximately CCI OS events). It is expected that recruitment will have completed prior to the results of the IAs being available.

The alpha level allocated to OS will depend on the results of the PFS and ORR analysis (see Section 9.4.8). It will be controlled at the interim and primary timepoint by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the significance level applied at the IA depends upon the proportion of information available. For example, if the alpha level is CCI and if CCI and CCI of OS events required at the time of the CCI analysis are available at the time of the IA (ie, CCI and CCI events have occurred), the 2-sided significance level to be applied for the CCI would be CCI and CCI respectively, and the 2-sided significance level to be applied for the CCI analysis would be CCI.

9.5.1 Independent Data Monitoring Committee

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 study protocol and letters to Investigators.

A data monitoring committee will be utilized for this study. Section A 5 provides more details on the rationale for and the remit of the committee.

An IDMC composed of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule of durvalumab + SoC CRT. The first safety review will take place when the first CCI The second safety review will take place when the first CCI Safety reviews will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment.

An additional safety review for CCI patients will take place when the first CCI patients in CCI have completed SoC CRT and had CCI of follow-up. This review will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment in CCI

The IDMC will also meet approximately every CCI thereafter to continue safety monitoring.

In addition:

- The IDMC will review the efficacy data for the primary PFS IA and if PFS is positive, ORR analysis ORR, CR, and DCR.
- The IDMC will review the efficacy data for the CCI, at the time of the CCI CCI, else when approximately CCI have been observed.

- The IDMC will review the efficacy data when approximately CCI OS events have occurred at the time of the CCI , if CCI .

Full details of the IDMC procedures, processes, and IAs can be found in the IDMC Charter.

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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 Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, 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.

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 patients partner becomes pregnant during or within 90 days after the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or 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 on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

A description of this clinical trial 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 trial 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 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 multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event 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

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one 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.

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 judgement 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 jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement 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 National Cancer Institute 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 recognized feature of overdose of the drug?

- Is there a known mechanism?

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

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

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

B 8 Medication error

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 recognize 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 AZ 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 center 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 AZ-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 analyzed, 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 organization(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 organization(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, Human immunodeficiency virus 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 trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial 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

D 1 Use/analysis of CCI

CCI may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a CCI will be collected for CCI analysis from consenting patients.

AstraZeneca intends to collect, analyse, and store CCI for CCI research to explore how CCI may affect clinical parameters, risk and prognosis of diseases, and the response to medications. CCI research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of CCI samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and, possibly, to CCI guided treatment strategies.

CCI research may consist of the analysis of the structure of the patient´s CCI ie, the CCI CCI.

The results of CCI analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the CCI samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on durvalumab continues but no longer than 15 years or other period as per local requirements.

D 2 CCI research plan and procedures

Selection of CCI research population

Study selection record

All patients will be asked to participate in this CCI research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this CCI research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**: Provide informed consent for the CCI sampling and analyses.

Exclusion criteria
Exclusion from this CCI research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous CCI
- CCI in 120 days of CCI sample collection

Withdrawal of consent for CCI research:
Patients may withdraw from this CCI research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for CCI research
The CCI sample for CCI research will be collected from the patients CCI at the CCI CCI. Although CCI, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at the CCI, it may be taken at CCI. Only one sample should be collected CCI for CCI during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples
The processes adopted for the coding and storage of samples for CCI analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of CCI, from the date of last patient last visit, after which they will be destroyed. CCI is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of CCI CCI replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca CCI laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the CCI

The link between the patient enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant CCI for analysis, facilitate correlation of CCI results with CCI data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements
The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The CCI component of this study is optional and the patient may participate in other components of the main study without participating in the CCI component. To participate in the CCI component of the study the patient must sign and date both the consent form for the main study and the CCI component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the CCI aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual CCI results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent CCI data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the CCI 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 also have access to his or her CCI data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

Any CCI data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as CCI CCI from CCI of individuals with a CCI from this CCI research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the CCI data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the CCI research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

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 Hy's law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1).

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets 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 Hy's law (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 investigational medicinal product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (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)

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

Hy's law (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, 0 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, 0 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 Clinical Study Protocol.

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 three 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 CCI 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 AZ standard processes

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

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

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the 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 B, B 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 total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

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

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

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

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

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease), or did the patient meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix E, 0.

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, 0.

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 total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

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

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) guidelines (Eisenhauer et al 2009) for this study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for evaluation of scans following a RECIST 1.1-defined PD scan using confirmation of radiologic progression criteria.

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

Only patients with measurable target disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

Measurable:

A lesion, not previously irradiated per the protocol prior to randomization, 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 computed tomography (CT) or magnetic resonance imaging (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, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Brain metastasis

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

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 as target lesions (TLs).

Target lesions:

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

Prior irradiated lesions may be considered measurable and selected as TLs provided they fulfill the other criteria for measurability. Tumor lesions selected for screening biopsy should not be selected as TLs, unless imaging occurred at least CCI after biopsy, allowing time for healing.

Non-target lesions:

Additional measurable and non-measurable lesions (or sites of disease) not recorded as TL should be identified as Non-Target Lesion (NTL) at baseline.

Methods of assessment
The same method of assessment on the same imaging technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided in Table 14, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

Table 14 Summary of methods of assessment

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

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

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

It is recommended that CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to IV CT contrast, a noncontrast- CT examination of the chest and an MRI with IV 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 lesions or surface tumors (by visual inspection or manual palpation) will not be used for RECIST assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

X-ray

Chest X-ray

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

Plain X-ray

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

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

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

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

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

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the RECIST 1.1 tumor response assessments in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to new lesions or progression of NTLs, respectively.

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

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

FDG-PET scan
^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[3] not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline or prior FDG-PET scan available, and no evidence of new lesions on CT/MRI scans, then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to verify new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically-based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT examination is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT

[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.

introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

Tumor response evaluation

Schedule of evaluation

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

Baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to the start of IP. Efficacy by RECIST 1.1 for all patients will be assessed according to the schedules of assessments. 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.

For patients who discontinue IP due to toxicity in the absence of evidence of disease progression, tumor assessments should be continued according to the original imaging schedule.

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 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 millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

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

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

Evaluation of target lesions

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

Table 15 Evaluation of target lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis 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 shrinkage 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 sum on study (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.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg missing anatomy) or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; 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 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 one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; 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 stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as RECIST 1.1 progression. The finding of a new lesion should be unequivocal; ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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

Symptomatic deterioration
Symptomatic deterioration is not a descriptor of a radiological response; it is a reason for stopping study therapy.

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

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

Table 17 Overall visit response

Target lesions	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, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no target and/or non-target lesions at baseline).

Tumor Assessment Criteria for Scans Following RECIST 1.1-defined PD

A follow-up scan is requested after an initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than CCI after the prior assessment of PD. Additional guidance is provided below for evaluation of scans following a RECIST 1.1-defined PD scan, whereby the subsequent scan would be considered as PD if any the following criteria are met:

- ≥20% increase in the sum diameters of TLs compared with the nadir, with an absolute increase of at least 5 mm in sum of diameters compared to nadir (as per RECIST 1.1 definition)
- *and/or* significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint (as per RECIST 1.1 definition)

- *and/or* significant progression (worsening) of pre-existing new lesions at the follow-up scan timepoint compared with the immediate prior timepoint

- *and/or* additional (brand) new unequivocal lesions at the follow-up scan timepoint (as per RECIST 1.1 definition)

Central review
If specified, all images will be collected, quality checked, and stored centrally by an Imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the Investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the Investigator.

Further details of the BICR will be documented in the Independent Review Charter, (also referred to as 'Imaging Charter').

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

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

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

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up timepoints. This will enable better consistency not only of tumor measurements but also identification of new disease.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very

important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor 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 not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise 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, 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 5mm contiguous slice thickness and this guideline presumes a minimum 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 artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

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

References

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

Appendix G Radiation therapy: requirements and recommendations

G 1 Overview

Patients will be treated to a dose of 60 Gy in 30 fractions (2 Gy/fraction) using photons of 6 to 10 MeV. Motion assessment is **required**, with motion management depending on the results of the motion assessment. Daily image-guided radiotherapy (IGRT) is **required**. Either intensity-modulated radiation therapy (IMRT) or 3D-conformal radiotherapy (3D-CRT) is allowed, though IMRT is preferred (Chun et al. 2017).

G 2 Simulation

G 2.1 Immobilization

Some form of immobilization is **required**, with attention to patient comfort to prevent intra-fraction motion. Patients must be immobilized in a stable position using the participating institutions's standard of practice. A variety of immobilization systems may be used, including, but not limited to, alpha-cradle, vacuum bag, thermoplastic molds, stereotactic frames and rigid pillows.

G 2.2 Planning computed tomography (CT)

The treatment planning CT is **required** for defining target volumes and organs-at-risk (OARs). CT thickness should be a maximum of 0.3 cm, and the CT should be acquired with the patient in the same position and using the same immobilization device as will be used for treatment. All tissues receiving radiation should be included in the CT limits, extending from the bottom of the cricoid cartilage through the liver. The field of view must be large enough so that none of the patient's anatomy along the path of the treatment beams is cut off. The type of CT(s) acquired (free-breathing, breath-hold, etc.) will dictated by the motion assessment and motion management techniques chosen (see section H 2.3).

IV contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, IV contrast should be given during the planning CT unless medically-contraindicated. If contrast is used, the densities should be over-ridden or the contrast scan must be registered to a non-contrast scan for treatment planning purposes.

A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is encouraged for treatment planning. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the treatment planning CT scan.

G 2.3 Motion assessment and motion management

Motion assessment is **required** for this protocol to determine what motion management strategies are needed. For the purposes of this protocol, motion assessment is defined as a method to *measure* the end-to-end target motion under the influence of respiration, while motion management is defined as a method to *minimize* the influence of intra-fractional tumor motion on the delivered dose.

Motion assessment

Motion assessment is **required**. Four-dimensional CT (4DCT) simulation is the preferred method for motion assessment. Fluoroscopy, using either a conventional simulator or the fluoroscopic imaging capabilities of the linear accelerator itseld, is also acceptable.

If the end-to-end target motion is ≤ 10 mm, intra-fractional motion may be accounted for in the design of the target through the creation of an ITV (see section H 3.1). Additional motion management approaches may still be used at the discretion of the participating institution.

If the end-to-end target motion is > 10 mm, accounting for motion with an ITV alone is discouraged. In such instances, it is recommended that more effective motion management strategies (examples given below) be employed.

Motion management

Acceptable forms of motion management include the following:

- ITV defined using a 4DCT
- ITV defined using fluoroscopy
- Abdominal compression
- Active breathing control (e.g. Elekta ABC device)
- Active breath hold
- Free-breathing gating (e.g. Varian RPM system)
- Gated breath hold
- *Other*, provided the participating institution can provide evidence that the motion management method employed reduces the effective motion of the target to ≤ 10 mm.

G 3 Definition of target and organs-at-risk (OARs)

G 3.1 Target definitions

NOTE: The current ICRU 62 guidelines suggest that contouring should proceed from GTV → CTV → ITV → PTV. Given the difficulty in visualizing microscopic disease when considering a moving tumor, this protocol will employ the more widely used approach of contouring from GTV → ITV → CTV → PTV.

- **GTV**: The GTV is all known **gross disease** including the primary tumor and involved lymph nodes (≥1 cm short axis diameter) as demonstrated on the treatment planning CT, and modified as deemed necessary based on PET and other imaging studies.

- **ITV**: The ITV is the GTV plus a margin to account for tumor motion. For the preferred method of using a 4DCT, the ITV will be the union of the GTVs on all respiratory correlated images and/or the ITV may be contoured directly using maximum intensity projection (MIP) images. Even if using a MIP, the delineated ITV will be compared with the actual position of the GTV on each of the respiratory

correlated CTs and modified, if necessary, to encompass the extent of motion of the GTV. If fluoroscopy is used for motion assessment, the ITV will be the GTV plus up to 10 mm of margin in any direction (anisotropic margins) encompassing tumor motion. The ITV may also be modified as deemed necessary based on PET and other clinical studies that may better distinguish the true GTV from other near unit-density tissues. (If a breath-hold technique is used, ITV is the union of the GTVs on 3 breath hold scans).

- **CTV**: The CTV accounts for subclinical involvement around the GTV. The CTV is the ITV plus a 5 – 10 mm margin for microscopic extensions of the tumor (CTV = ITV + 5 to 10 mm) without extending into uninvolved organs such as the esophagus, heart, or bone.

- **PTV**: The PTV is the CTV plus a margin to ensure that the prescribed dose is actually delivered to the CTV. This margin accounts for variations in treatment delivery, including variations in setup between treatments. The CTV is expanded isotropically by 5 mm to generate the PTV (PTV = CTV + 5 mm). Note that this 5 mm margin assumes that daily IGRT is employed, a protocol requirement (see section H 6.1).

G 3.2 Target delineation

The simulation CT scan images will be used for target delineation and treatment planning. The proper lung window should be used for target delineation in the lung parenchyma, and proper soft tissue window should be used to delineate the nodal disease.

If a pre-treatment PET/CT and/or contrast CT images was performed, these should be fused with the simulation images to help with target delineation. Table 18 provides additional guidance on target delineation based on the simulation images and motion management strategy.

Table 18 Summary of motion management options, scans for dose calculations, and target delineation

Motion management	Scans	Scan to be used for dose calculation	Images from which the target volume contours are to be generated
4DCT simulation with free breathing	1 free breathing scan, 1 4D scan (10 imaging data sets)	Average of all phases	MIP or union of the GTVs on all phases
4DCT simulation with free breathing gating	1 free breathing scan, 1 4D scan (10 imaging data sets)	Average of the beam-on phases (eg, 40%-60%)	Union of GTVs contoured at each breathing phase while the beam will be on
4DCT simulation with breath hold (with or without ABC)	Repeat breath hold scan 3 times to assess reproducibility of the breath hold	Select 1 scan for dose calculation	Union of GTVs contoured at each breath hold scan

Table 18 Summary of motion management options, scans for dose calculations, and target delineation

Motion management	Scans	Scan to be used for dose calculation	Images from which the target volume contours are to be generated
Single-slice CT Simulation (4DCT not available)	1 free breathing scan, 1 end-inhale scan at end tidal volume, 1 end-exhale scan at end tidal volume	Free-breathing scan used for dose calculation	Union of GTVs of end-inhale and end-exhale volumes

G 3.3 OAR delineation

The simulation CT scan images will be used for OAR delineation. The OARs to be contoured include the spinal canal, both right and left lungs, the heart, the esophagus, and the brachial plexus for upper lobe tumors,. The liver and kidneys will also be contoured if these OARs will be in the beam path.

The spinal canal will be contoured based on the bony limits of the spinal canal (not the spinal cord). The spinal canal should be contoured starting from the top of C1 (or the first CT slice) down through the bottom of L2 (or the last CT slice). The neural foramina should not be included.

Both lungs should be contoured using pulmonary windows. The right and left lungs will be contoured separately, but will be considered as one structure for lung dosimetry. All inflated and collapsed, fibrotic and emphysematic lungs should be contoured, small vessels extending beyond the hilar regions should be included.

The heart will be contoured along with the pericardial sac. The superior aspect (or base) will begin at the level of the inferior aspect of the pulmonary artery passing the midline and extend inferiorly to the apex of the heart.

The esophagus should be contoured from the beginning at the level just below the cricoid to its entrance to the stomach at GE junction. The esophagus will be contoured using mediastinal window/level on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia.

For the brachial plexus, only the ipsilateral brachial plexus is required, and is only required for upper lobe tumors. This will include the spinal nerves exiting the neural foramina from top of C5 to top of T2.

When the beam path is projected to pass through the liver, the entire liver should be contoured. The gallbladder should be excluded from the liver contour, and the inferior vena cava should be excluded when it is discrete from the liver.

When the beam path is projected to pass through one or both of the kidneys, both kidneys should be contoured. The kidney contours should include both the renal cortex and renal pelvis.

Table 19 provides the nomenclature to be used for this protocol.

G 4 Definition of structures

Table 19 Structure names

Standard Name	Description	Validation
GTV	Primary tumor and involved nodes	Required
ITV	Primary tumor and involved nodes inclusive of tumor motion	Required
CTV_6000	ITV + 5 to 10 mm margin, excluding anatomic boundaries to tumor spread	Required
PTV_6000	CTV + 5 mm margin	Required
Spine_Canal	Spinal canal	Required
Lung_R	Right lung	Required
Lung_L	Left lung	Required
Lungs	(Lung_R + Lung_L) – GTV	Required
Heart	Whole heart	Required
Esophagus	Esophagus	Required
BrachialPlexus	Brachial plexus	Required for upper lobe tumors
Liver	Whole liver	Required if within beam path
Kidney_R	Right kidney	Required if within beam path
Kidney_L	Left kidney	Required if within beam path

G 5 Compliance criteria

G 5.1 Target dose

Compliance criteria for dose to targets are shown in Table 20.

G 5.2 Missed treatment days/elapsed days

Missed treatments can be compensated for by delivering additional twice-daily fractions (within a minimum interfraction interval of 6 hours), by treating on Saturday or Sunday, or by adding fractions to the end of treatment.

Treatment breaks should be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Compliance criteria for treatment duration and treatment interruptions are shown in Table 20.

Table 20 Target and treatment time compliance criteria

Metric	Per protocol	Variation acceptable[a]
PTV_6000 coverage	≥95% covered by 100% prescribed dose	≥95% covered by ≥95% prescribed dose
PTV_6000 hot spots	<110% of prescribed dose to no more than 0.03 cc inside PTV	≥110% but <115% of prescribed dose to no more than 0.03 cc inside PTV
PTV_6000 cold spots	≤95% of prescribed dose to no more than 0.03 cc inside PTV	<95% but ≥93% of prescribed dose to no more than 0.03 cc inside PTV
Overall RT treatment time	≤ 42 days	43 - 56 days
RT treatment days interrupted (other than holidays)	0	≤5

[a] Values not meeting the Variation Acceptable limits will be classified as Deviation Unacceptable.

G 5.3 Dose to OARs

Compliance criteria for OARs are shown in Table 21.

Table 21 Recommended dose acceptance criteria for OARs

	Per protocol	Variation acceptable [a]
Lungs	V20 ≤ 35% Mean lung dose ≤ 20 Gy V5 ≤ 60%	V20 ≤ 37% Mean lung dose ≤ 22 Gy V5 ≤ 65%
Esophagus	Maximum dose: 66 Gy	Maximum dose: 69 Gy
Brachial plexus	V66 ≤ 0.5 cc	V69 ≤ 0.5 cc
Spine_Canal	V50 < 0.03 cc	V52 < 0.03 cc
Heart	V50 ≤ 25% V45 ≤ 35% V30 ≤ 50%	V50 ≤ 30% V45 ≤ 40% V30 ≤ 55%

[a]Values not meeting the Variation Acceptable limits will be classified as Deviation Unacceptable.

G 6 Treatment delivery

G 6.1 Image-guided radiation therapy (IGRT)

Daily IGRT, consisting of images and appropriate image alignment software tool, is required for treatment on this protocol. Patients will be treated only on units with image-guidance capabilities.

Daily IGRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (kV) images, e.g., ExacTrac, on-board imagers or similar systems
- Linear-accelerator mounted kV and MV conebeam CT images
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy)
- Linear-accelerator on-board MV portal imaging, though less desired than the above options.

G 7 RT quality assurance reviews

G 7.1 Pre-treatment review

Radiation plans will be collected and subject to centralized review to assess compliance with the protocol requirements. Final radiation reports will also be collected.

G 8 References

Chun et al. 2017
Chun SG, Hu C, Choy H, Kiomaki RU, Timmerman RD, Schild SE, et al. Impact of intensity-modulated radiation therapy technique for locally-advanced non-small-cell lung cancer: A secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. J Clin Oncol 2017; 35(1):56-62.

Appendix H Patient-reported outcomes

Patient Reported Outcome Questionnaire was removed due to copyrights.

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Patient Reported Outcome Questionnaire was removed due to copyrights.

Study Number:		Site Number:
Subject Number:	Visit Number:	Assessment Date:

Patient Global Impression of Severity for Cancer Symptoms

Overall, how would you rate the severity of your cancer symptoms today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Patient Reported Outcome Questionnaire was removed due to copyrights.

Appendix I Abbreviations

Abbreviation or special term	Explanation
4D CT	four-dimensional computed tomography
CCI	[redacted]
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{ss}	area under the concentration versus time curve at steady state
B7-H1	B7 homolog 1
BICR	Blinded Independent Central Review
BoR	best objective response
BP	blood pressure
cCRT	concurrent chemoradiation therapy
CCTG	Canadian Cancer Trials Group
CD	cluster of differentiation
CI	confidence interval
CL	creatinine clearance
$Cmax_{ss}$	maximum drug concentration at steady state
CR	complete response
CRF	case report form
CRP	C reactive protein
CRT	chemoradiation therapy
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CCI	[redacted]
CTLA-4	cytotoxic T-lymphocyte antigen 4
CTV	clinical target volume
DCO	data cutoff
DCR	disease control rate
DoR	duration of response

Abbreviation or special term	Explanation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOI	end of infusion
EORTC	European Organisation for Research and Treatment of Cancer
EQ 5D-5L	EuroQoL 5 dimension, 5-level health state utility index
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GI	gastrointestinal
GTV	gross tumor volume
CCI	[redacted]
HBV	hepatitis B
HCV	hepatitis C
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFNγ	interferon gamma
IgG	immunoglobulin G
IGRT	image-guided radiation therapy
ILD	interstitial lung disease
IMRT	intensity-modulated radiation therapy

Abbreviation or special term	Explanation
International Co-ordinating 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.
imAE	immune-mediated adverse event
IP	investigational product
irAE	immune-related adverse event
IRB	Institutional Review Board
ITT	Intent-to-Treat
ITV	internal target volume
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LDH	lactate dehydrogenase
LIMS	laboratory information management system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MIP	maximum intensity projection
MLD	maximum lung dose
MRI	magnetic resonance imaging
NE	not evaluable
NED	no evidence of disease
NL	New Lesion
NSCLC	non-small cell lung cancer
NTL(s)	non-target lesion(s)
OAE	other significant adverse event
ORR	objective response rate
OS	overall survival
OS24	proportion of patients alive at 24 months from randomization
PD	progressive disease
CCI [redacted]	
PET	positron emission tomography
PFS	progression-free survival

Abbreviation or special term	Explanation
CCI	[redacted]
PGIS	Patients' Global Impression of Severity
CCI	[redacted]
PR	partial response
PRO	patient-reported outcome
PS	performance status
PTV	planning target volume
CCI	[redacted]
QA	quality assurance
QLQ-C30	30-item core quality of life questionnaire
QLQ-LC13	13-item lung cancer quality of life questionnaire
QoL	quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBE	relative biological effectiveness
RECIST	Response Evaluation Criteria In Solid Tumors
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SoA	schedule of activities
SoC	standard of care
CCI	[redacted]
T-cell	T lymphocyte
TCs	tumor cells
TL(s)	target lesion(s)
TMG	Toxicity Management Guidelines
TNF-α	tumor necrosis factor alpha
TTDM	time to death or distant metastasis
ULN	upper limit of normal

Abbreviation or special term	Explanation
US	United States
WHO	World Health Organization
WT	body weight

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