Clinical Study Protocol

Drug Substance	Durvalumab
Study Code	D910MC00001
Version	2.0
Date	02 August 2022

A Phase III, Randomized, Multicenter, Double-blind, Placebo-controlled Study of Durvalumab for the Treatment of Stage II-III NSCLC Patients with Minimal Residual Disease Following Surgery and Curative Intent Therapy (MERMAID-2)

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 (Version 2.0)	02 August 2022
Original Protocol (Version 1.0)	05 June 2020

Overall Rationale for the Amendment:

Considering the approval of neoadjuvant and adjuvant immunotherapy options for patients with resectable Stage II-III NSCLC, as described in Section 10.1, AstraZeneca has decided to close enrollment to MERMAID-2 (D910MC00001) early. This amendment describes the procedures required for all patients who have signed informed consent for the study and ensures that eligible patients have access to open-label durvalumab where appropriate. Section 10 serves as the new reference point for the study following amendment implementation (CSP v2.0) at site.

Section # and name	Description of change	Brief rationale
Section 1.2, Synopsis; Section 3, Objectives and Endpoints; Section 8.7.2.3, Collection of stools for microbiome testing (OPTIONAL); Section 8.8, Medical resource utilization and health economics	Text added and changes made to some objectives and endpoints and their analyses; objectives and endpoints have been reordered	Following AstraZeneca's decision to close enrollment, study objectives and endpoints have been updated as all analyses of the objectives and endpoints will be descriptive only and considered exploratory; medical resource utilization and health economics will no longer be analyzed
Section 4.3, End of study definition	End of study definition has been updated in Section 10.3.3	End of study definition is now defined as when the last subject has received their last dose of open-label durvalumab
Section 5, Study Population	Note added to clarify that enrolment is closed and there will be no randomizations after CSP v2.0 implementation	AstraZeneca decided to close enrolment; no patients will be randomized after CSP v2.0 implementation
Section 6, Study Treatments	Clarified that placebo will no longer be administered	Patients and Investigators will be unblinded to study treatment; placebo will no longer be administered
Section 6.3, Treatment compliance	Clarified that IP administration following signature of informed consent (ICF3) should be recorded in source documents rather than the eCRF	To clarify where IP administration should be recorded after CSP v2.0 amendment implementation and patient signature of informed consent (ICF3)

Section 6.4, Concomitant therapy	Section updated throughout to reflect concomitant therapy restrictions for CSP v2.0; removal of rescue medication section	To update concomitant therapy text; removed section regarding rescue medication as it will no longer be centrally supplied and sites are to follow toxicity management guidelines
Section 6.5, Dose modification; Section 8.3.12, Adverse events of special interest; Section 8.3.13 Safety data to be collected following the final DCO of the study; Section 8.4.5, Specific toxicity management and dose modification information – Durvalumab	Deletion of Dosing Modification and Toxicity Management Guidelines link	Removal of Toxicity Management Guidelines web portal as web portal has been decommissioned. Guidelines are distributed directly to the sites
Section 7.1, Discontinuation of study treatment	Text updated for patients receiving durvalumab	To remove duration of study treatment (26 cycles) that is no longer applicable for patient receiving open-label durvalumab
Section 8.4.5, Specific toxicity management and dose modification information – Durvalumab	Removed language not relevant for CSP amendment	Removal of reference to study-specific assessments (imaging and ePRO) and relation to dose delay
Section 9, Statistical Considerations	Clarified that all analyses of the objectives and endpoints will be descriptive only and considered exploratory and that interim analysis and medical resource use analysis will not be performed	Aligns with the considerations added in Section 10.4
New Section 10, Rationale and Procedures Following CSP v2.0 Approval	Addition of guidance for patient eligibility for open-label durvalumab and discontinuation of patients from study	To clarify the next steps for patients, including the option to receive open-label durvalumab (where appropriate) or discontinuation from the study
Throughout	Notations indicating which sections/text that are applicable/no longer applicable following CSP v2.0 implementation and to cross-reference to Section 10 and its subsections	To clearly present which sections/text are applicable/redundant
Throughout	Minor editorial and formatting revisions, and minor changes to ensure the consistency between sections or clarifications	To ensure consistency throughout the protocol

IP investigational product; CSP Clinical Study Protocol.

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

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1 PROTOCOL SUMMARY

From CSP v2.0 implementation at site, please use Section 10 as a reference point for the study. This study has closed enrolment early and patients will either start open-label durvalumab or be discontinued from the study.

The protocol summary below refers to the original study design.

1.1 Schedule of activities (SoA)

This study will employ a multi-tiered consent and screening process for patients with histologically confirmed resectable non-small cell lung cancer (NSCLC) (World Health Organization [WHO] 2015 classification) (Stage IIA to select [ie, T3N2 or T4N2] Stage IIIB; according to Version 8.0 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology v8.0]).

Table 1 includes the procedures conducted during the first screening period (initiated by the signing of Informed Consent Form 1 [ICF1]). The primary purpose of this screening period is to determine the minimal residual disease (MRD) status of the patient. This is done by whole exome sequencing (WES) of the patient's resected tumor tissue and germline blood sample to identify tumor-specific DNA variants. A personalized panel comprised of the patient's tumor variants is then created and used to identify circulating tumor DNA (ctDNA) extracted from the patient's plasma. The patient is considered MRD-positive (MRD+) if the panel detects ctDNA. This assay requires mandatory genetic testing.

Following this first screening, eligible patients will be enrolled in a 96-week surveillance period and monitored for the emergence of MRD. Surveillance will begin the day the plasma sample used to determine a patient's MRD status post-curative intent therapy is **collected**. During this surveillance period, the patient may or may not become eligible for randomization into the study. Patients who are MRD+ at the start of surveillance or become MRD+ during the 96-week surveillance period may be eligible for the second screening (see Section 5.1.2). The procedures for the second screening and treatment period are presented in Table 2 and initiated with the signing of ICF2a. The primary purpose of the second screening is to ensure that all eligibility criteria are met prior to randomization. Patients who successfully complete the second screening are eligible for randomization into the study, where patients may receive up to a total of 24 months (26 cycles) of treatment with investigational product (IP).

Table 3 includes the procedures for the follow-up period for patients who discontinue treatment with IP due to toxicity or Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1-defined disease recurrence or who complete the full 24 months (26 cycles) of IP treatment.

Up to 142 MRD- patients who complete their 96-week surveillance period without becoming MRD+ or experiencing disease recurrence may be eligible for entry into an observation period initiated by the signing of ICF2b. Patients in the observation group will be followed up for disease-free survival (DFS) for an additional 24 months or until primary DFS analysis (whichever occurs first), after which these patients will be followed for overall survival (OS) until the end of the study. Table 4 includes the procedures for this observation period.

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

For durvalumab or placebo monotherapy:

- Patients may delay dosing under certain circumstances.
  Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (See Section 8.4.5), 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.
  Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of disease (RECIST) and Patient-reported Outcome (PRO) assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see current Investigator Brochure [IB] for durvalumab).

Table 1 Schedule of assessments for first screening and surveillance (initiated by the signing of ICF1)

	First screening period[a]	Surveillance		For details, see Section
	Prior to start of surveillance	**Start of surveillance[b] 8w ± 1w after completion of adjuvant therapy or 12w ± 1w post-surgery**	**Up to 96 weeks or until emergence of MRD or disease recurrence**	
ICF1[a,c]	X			5.1
Eligibility, including complete information on curative intent therapy[d]	X	X		5.1, 5.2 Table 5, Table 6
Demography, including disease characteristics (at diagnosis) and tobacco use	X			5.1
Whole blood sample for WES/development of personalized panel	X			8.7.1.2
Resected tumor tissue sample for WES/development of personalized panel[e]	X			8.7.1.2
Resected tumor tissue sample for central *EGFR/ALK* testing[e,f]	X			8.7.1.1
Resected tumor tissue sample sent for prospective PD-L1 testing[e,g]	X			8.7.1.3
Resected tumor tissue collected for exploratory analyses[e]	X			8.7.2.2
Plasma sample collection for MRD evaluation and exploratory analyses		X[h] **Start of surveillance is the date of this plasma collection**	q6w ± 3d[i,j]	5.1.1 8.7.2.1
Pre-surgical plasma sample collection for exploratory analyses (if ICF1 is signed prior to surgery)	X			8.7.2.1
Pregnancy test[k]	X	X	q12w ± 1w	8.2.1

Table 1 Schedule of assessments for first screening and surveillance (initiated by the signing of ICF1)

	First screening period[a]	Surveillance		
	Prior to start of surveillance	Start of surveillance[b] 8w ± 1w after completion of adjuvant therapy or 12w ± 1w post-surgery	Up to 96 weeks or until emergence of MRD or disease recurrence	For details, see Section
SAE assessments[l]	X	X	X	8.3
Concomitant medications/medical history[l]	X	X	X	6.4, 8.2.2
Concomitant procedures[l]	X	X	X	5.1, 5.2
Disease assessments (RECIST 1.1)	X[m,n]		q12w ± 1w[j,n,o,p]	8.1, Appendix G
Tumor biopsy (optional)[q]			At recurrence	8.7.2.2

[a] The first screening period will be initiated with the signing of ICF1. Patients should sign and date ICF1 before surgery or as soon as possible post-surgery (including during adjuvant therapy, if administered) to allow resected tumor tissue and whole blood samples to be sent to the diagnostic lab and enable development of the personalized panel for MRD detection. In order for the personalized panel to be ready for prior to the start of surveillance, these samples must be sent as soon as possible after ICF1 is signed but **no later than** 1-2 weeks post-completion of adjuvant therapy or 3-5 weeks post-surgery. Patients who are screen failures of MERMAID-1 (D910LC00001) and subsequently enroll in this study (MERMAID-2; D910MC00001) may be allowed to use a previously developed personalized panel for MRD detection, as well as results of previous PD-L1 and/or *EGFR/ALK* testing (see section 5.4 for details).

[b] Start of surveillance is defined as the day the first post-curative intent therapy plasma sample is **collected** in order to determine a patient's MRD status (ie, 8w ± 1w after completion of adjuvant therapy or 12w ± 1w post-surgery).

[c] Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including first screening evaluations and start of surveillance. ICF1 will be signed **either** prior to surveillance or at the start of surveillance.

[d] Curative intent therapy (complete resection ± neoadjuvant and/or adjuvant therapy) are SoC and not considered study procedures. However, information pertaining to curative intent therapy must be made available during the first screening period for evaluation of study eligibility. Eligibility must also be reviewed at the start of surveillance to ensure the patient is able to participate in this study.

[e] The indicated tumor tissue samples come from the tumor which was removed during surgery. Separate rows indicate that portions of this singular surgical sample will undergo different tests or analyses performed at different locations. FFPE samples of resected tumor tissue will be collected.

[f] Results from local *EGFR/ALK* testing of either a pre-surgery biopsy or the resected tumor tissue may be used for this study, provided testing was performed using a well-validated, local regulatory-approved kit. If local testing will be done on either the pre-surgery biopsy (if available) or resected tumor tissue, *EGFR/ALK* testing does not need to be repeated by the central lab.

[g] PD-L1 testing will be done prospectively for screened patients using resected tumor tissue as this information is required prior to randomization for stratification.

[h] A patient determined to be MRD- at the start of surveillance (based on the plasma sample collected 8w ± 1w post-completion of adjuvant therapy [if administered] or 12w± 1w post-surgery [if adjuvant therapy is not given]) will continue in surveillance. If testing of this first plasma sample returns an MRD+ result, the patient may be eligible to continue to the second screening (initiated with the signing of ICF2a). The plasma sample at the start of surveillance should be collected as indicated in the schedule, even if creation of the personalized panel for MRD detection is delayed. **Note:** a patient who received prior neoadjuvant immunotherapy **must** be MRD- based on analysis of this first plasma sample in order to continue in the study.

[i] If a plasma sample taken during surveillance returns as MRD+, the patient may be eligible to sign ICF2a and continue to the second screening period (see Table 2).

[j] In order to minimize any delay in randomization in the event that a patient is determined to be MRD+, the Investigator should proactively schedule CT and/or MRI scans of the chest/abdomen and brain to coincide within the weeks following q6w plasma collection visits that are not aligned with the q12w CT scan schedule (ie, Week 6, 18, 30, etc, relative to the start of surveillance). A CT or MRI scan of the brain should also be proactively scheduled to occur within the week following the q12w CT scan.

[k] 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 start of surveillance and then every 12w ± 1w. Pregnancy test results should be reviewed by the treating physician or Investigator prior to a visit where a surveillance scan will be performed.

[l] Any SAEs reported after ICF1 has been signed (ie, during first screening and surveillance) should be recorded in the eCRF. Medical history should only be recorded in the eCRF if an SAE is reported. All prior anti-cancer medications or prior radiotherapy should be recorded for all patients after ICF1 is signed; all other concomitant medications should only be recorded in the eCRF if an SAE is reported.

[m] After the completion of curative intent therapy, a CT scan of the chest and abdomen (including liver and adrenal glands) **and** a brain MRI (preferred) or brain CT with IV contrast should be performed per local clinical practice with timing according to Investigator discretion. If a post-therapy scan is unavailable, these scans must be performed prior to the start of surveillance.

[n] Contrast-enhanced CT scan of the chest and abdomen (including liver and adrenal glands) is required. Brain MRI (preferred) or brain CT with IV contrast may be performed only if clinically indicated. Brain MRI (preferred) or brain CT with IV contrast may be performed if clinically indicated.

[o] If scans conducted during the first screening or during surveillance demonstrates evidence of RECIST 1.1-defined disease recurrence and/or metastatic disease, the patient is considered a screen failure (section 5.5) and is no longer eligible to participate in the study. In this case, the final scans along with the date of disease recurrence or metastatic disease should be captured in the eCRF.

[p] Before an MRD+ patient can be randomized, a contrast-enhanced CT scan of the chest and abdomen (including liver and adrenal glands) **and** a brain MRI (preferred) or brain CT with IV contrast needs to be performed to confirm no evidence of RECIST 1.1-defined disease recurrence and/or metastasis. These scans do not need to be repeated during the second screening period if the post-curative intent therapy scans were conducted within 28 days ± 7 days **prior to** randomization. If a patient becomes MRD+ during surveillance, the CT scan of the chest and abdomen conducted during surveillance may be used as the baseline scan, provided it was performed within 28 days ± 7 days **prior to** randomization. A brain MRI (preferred) or brain CT with IV contrast must also be performed prior to randomization. If the previously performed scans fall outside of this window, additional scans of the chest, abdomen, and brain must be performed **before** the patient is randomized to confirm no evidence of disease recurrence and/or metastasis.

[q] FFPE samples of recurrent tumor biopsy will be collected from consenting patients.

ALK Anaplastic lymphoma kinase; CT Computed tomography; D Day; eCRF Electronic case report form; *EGFR* Epidermal growth factor receptor; FFPE Formalin-fixed paraffin-embedded; ICF1 Informed consent form 1; IV intravenous; MRD Minimal residual disease; MRI Magnetic resonance imaging; PD-L1 Programmed cell death ligand-1; q6w Every 6 weeks; q12w Every 12 weeks; RECIST Response Evaluation Criteria in Solid Tumors; SAE Serious adverse event; SoC Standard of care; w Week; WES Whole exome sequencing.

Table 2 Schedule of assessments for second screening and 24-month durvalumab/placebo treatment period (initiated by the signing of ICF2a)

	Second screening period[a]	C1	C2	C3	C4	C5	C6	C7 to C26 or until RECIST 1.1-defined disease recurrence	For details, see Section
Week	**-4 to -1**	**0**	**q4w ± 3d unless dosing needs to be held for toxicity reasons**						
Day	**-28 to -1**	**1[b]**	**q28d ± 3d unless dosing needs to be held for toxicity reasons**						
ICF2a[c]	X								5.1
Informed consent for **optional** genetic analysis (Gx)	X								5.1.2
Study procedures									
Medical history	X								8.2.2
Physical exam (full)	X								8.2.3
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	X	8.2.3
Vital signs[d]	X	X	X	X	X	X	X	X	8.2.4
ECG[e]	X	As clinically indicated							8.2.5
Concomitant medications	<----------							---------->	6.4
Eligibility criteria	X								5.1, 5.2 Table 5 Table 6
Laboratory Assessments									
Clinical chemistry[f]	X	X[f]	X	X	X	X	X	X	Table 11
Hematology[f]	X	X[f]	X	X	X	X	X	X	Table 12
TSH (reflex free T3 or free T4[g])	X	X[h]	X	X	X	X	X	X	Table 11

Table 2 Schedule of assessments for second screening and 24-month durvalumab/placebo treatment period (initiated by the signing of ICF2a)

	Second screening period[a]	C1	C2	C3	C4	C5	C6	C7 to C26 or until RECIST 1.1-defined disease recurrence	For details, see Section
Week	**-4 to -1**	**0**	**q4w ± 3d unless dosing needs to be held for toxicity reasons**						
Day	**-28 to -1**	**1[b]**	**q28d ± 3d unless dosing needs to be held for toxicity reasons**						
Urinalysis	X	As clinically indicated							8.2.1
Hepatitis B and C and HIV	X								8.2.8
Pregnancy test[i]	X	X	X	X	X	X	X	X	8.2.1
Monitoring									
WHO/ECOG performance status	X	X	X	X	X	X	X	X	8.2.7
AE/SAE assessment[j]	<----------							---------->	8.3
Patient follow-up contact / Patient review for safety		Recommended phone contact midway through Cycles 1, 2, and 3: Days 14 of C1, 2, and 3							8.2.6
IP administration									
Durvalumab/placebo[k,l]		X	X	X	X	X	X	X	6
Other assessments and assays									
Plasma sample for exploratory analyses[m]		Sample collected pre-dose on Day 1 of each treatment cycle							8.7.1.2
Whole blood for gene expression (PaxGene mRNA)		X[n]			X[n]			C26 or recurrence[o]	8.7.2
Serum for soluble biomarkers		X[n]			X			C26 or recurrence[o]	8.7.2

Table 2 Schedule of assessments for second screening and 24-month durvalumab/placebo treatment period (initiated by the signing of ICF2a)

	Second screening period[a]	C1	C2	C3	C4	C5	C6	C7 to C26 or until RECIST 1.1-defined disease recurrence	For details, see Section
Week	**-4 to -1**	**0**	**q4w ± 3d unless dosing needs to be held for toxicity reasons**						
Day	**-28 to -1**	**1[b]**	**q28d ± 3d unless dosing needs to be held for toxicity reasons**						
Stool sample collection for microbiome analysis (optional)[p]	X				X			C26 or recurrence[o]	8.7
CCI , CCI , CCI , CCI , CCI , CCI		X	X	X	X	X	X	q4w	8.1.4
Health resource use (HOSPAD module)[r]		To be completed at each hospitalization							
Optional Gx sample (DNA element for long-term storage/future use)[s]		X							8.6.2
Efficacy evaluations									
Disease assessments (RECIST 1.1)	X[t]	Disease assessments occur q8w ± 1w until Week 48, then q12w ± 1w (relative to the date of randomization) until appearance of RECIST 1.1-defined disease recurrence or completion of the study.[u,v,w] Upon detection of RECIST 1.1-defined disease recurrence, an additional follow-up CT scan should be performed 4-8w later[x] and evaluated using post-progression radiological criteria.							8.1 Appendix G
Tumor biopsy (optional)[x,y]		At recurrence							8.7.2.2

[a] In order to minimize the time an MRD+ patient is in second screening (ie, the time from receiving an MRD+ result to being randomized and starting treatment), a patient may sign ICF2a as soon as MRD+ test results are received. In addition, the Investigator should proactively schedule CT and/or MRI scans of the chest/abdomen and brain to coincide within the weeks following q6w plasma collection visits that are not aligned with the q12w CT scan schedule (ie, Week 6, 18, 30, etc, relative to the start of surveillance). A CT or MRI scan of the brain should also be proactively scheduled to occur within the week following the q12w CT scan.

[b] Every effort should be made to minimize the time between randomization and starting treatment (ie, within 3 days of randomization).

[c] Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures. The procedures outlined in this table will be initiated with the signing of ICF2a.

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

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

[f] Collected prior to dosing of each cycle and as clinically indicated. Serum or plasma clinical chemistry (including LFT monitoring) and hematology and urinalysis, may be performed more frequently if clinically indicated. If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

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

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

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

[k] Durvalumab or placebo will be administered on Day 1 of each cycle.

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

[m] After database lock for primary DFS analysis (see section 6.1.3), plasma samples for exploratory analyses will no longer be collected.

[n] Pre-dose same day as infusion.

[o] See Table 3 for details regarding the collection of samples from patients who complete treatment or who discontinue treatment due to disease recurrence.

[p] Optional stool samples will be requested from sites in North America (ie, Canada and the United States) and Europe **only**. Kits for collecting stool samples should be given to patients at the previous visit and samples may be collected from consenting patients at home or in the clinic. Sample should be collected no more than 3 days before the scheduled visit and sample brought to the site as appropriate.

[q] [redacted]

[r] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.

[s] The sample for optional genetic research will be obtained at Day 1 pre-dose (at or after randomization). If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for optional genetics during the study. This sample is separate from the mandatory genetic component of the study.

[t] Before an MRD+ patient can be randomized, a contrast-enhanced CT scan of the chest and abdomen (including liver and adrenal glands) **and** a brain MRI (preferred) or brain CT with IV contrast must be performed to confirm no evidence of RECIST 1.1-defined disease recurrence and/or metastasis. If a patient is MRD+ at the start of surveillance, the post-curative intent therapy scans (described in Table 1) may be used as baseline scans provided they were conducted within 28 days ± 7 days **prior to** randomization. If a patient becomes MRD+ during surveillance, a CT scan of the chest and abdomen conducted during surveillance may be used as the baseline scan, provided it was performed within 28 days ± 7 days **prior to** randomization. If the baseline CT scan is negative for RECIST 1.1-defined disease recurrence, a brain MRI (preferred) or brain CT with IV contrast **must** be performed prior to randomization to confirm no evidence of metastatic disease. If previously performed scans fall outside of this window, additional scans of the chest, abdomen, and brain must be performed **before** the patient is randomized.

[u] The on-study schedule of q8w ± 1w until Week 48 and then q12w± 1w thereafter (relative to the date of randomization) **must** be followed regardless of any delays in dosing.

[v] Contrast-enhanced CT scan of the chest and abdomen (including liver and adrenal glands) is required. Brain MRI (preferred) or brain CT with IV contrast may be performed only if clinically indicated.

[w] After database lock for primary DFS analysis, efficacy scans will be collected in accordance with local clinical practice (see Section 6.1.3).

[x] Treatment can continue until the results of the additional scan conducted 4-8 weeks later confirms disease recurrence.

[y] FFPE samples of recurrent tumor biopsy will be collected from consenting patients.

AE Adverse event; C Cycle; C1D1 Cycle 1, Day 1; CT computed tomography; D Day; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; CCI ; CCI ; FFPE Formalin-fixed paraffin-embedded; Gx Genomics research; HIV Human immunodeficiency virus; HOSPAD Hospital resource use module; ICF2a Informed consent form 2a; IP Investigational product; IV intravenous; LFT Liver function test; MRI magnetic resonance imaging; mRNA Messenger ribonucleic acid; CCI ; CCI ; CCI ; q28d Every 28 days; q4w Every 4 weeks; q8w Every 8 weeks; q12w Every 12 weeks; CCI ; CCI ; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization; w Week.

Table 3 Schedule of assessments for patients who have completed or discontinued treatment

Evaluation	Time since last dose of IP			
	Weeks			
	4 (± 3d)[a]	12 (± 1w)	q12w ± 1w until primary DFS analysis[b] or until disease recurrence	For details, see Section
Physical examination (full)	X			8.2.3
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X			8.2.4
Pregnancy test[c]	X	X	X	8.2.1
AE/SAE assessment	X[d]			8.3
Concomitant medications	X			6.4
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at 30 and 90 days; and then at initiation of subsequent anticancer therapy[e]			8.2.7
Subsequent anticancer therapy[f] and progression assessment[g]	<----------			8.1
Survival status		X	X[h]	8.1.3
Hematology	X	X		Table 12
Clinical chemistry	X	X		Table 11
TSH (reflex free T3 or free T4[i])	X	X		Table 11
Plasma samples for exploratory analyses	q12w ± 1w (preferably to coincide with time of scan) Sample at time of RECIST 1.1-defined disease recurrence (if applicable)[j]			8.7.2.1
CCI, CCI, CCI, CCI[k]	To be completed q4w until PFS event following disease recurrence (ie, a DFS event), study discontinuation, or death (whichever occurs first) PRO data collection will stop at the time of primary DFS analysis			8.1.4
Health resource use (HOSPAD)[l]	To be completed at each hospitalization until PFS event following disease recurrence (ie, a DFS event), initiation of subsequent therapy, study discontinuation, or death (whichever occurs first)			

Table 3 Schedule of assessments for patients who have completed or discontinued treatment

Evaluation	Time since last dose of IP			
	Weeks			
	4 (± 3d)[a]	12 (± 1w)	q12w ± 1w until primary DFS analysis[b] or until disease recurrence	For details, see Section
Disease assessment (RECIST 1.1)	Disease assessments occur q8w ± 1w until Week 48, then q12w ± 1w (relative to the date of randomization) until appearance of RECIST 1.1-defined disease recurrence or completion of the study.[m,n] Upon detection of RECIST 1.1-defined disease recurrence, an additional follow-up CT scan should be performed 4-8w later and evaluated using post-progression radiological criteria.[o]			8.1 Appendix G
Tumor biopsy sample (optional)[p]	At recurrence[j]			8.7.2.2

[a] Patients who discontinue treatment due to disease recurrence will continue to be followed for OS and subsequent therapy until the end of the study. See footnote k for details regarding the timing of final sample collection.

[b] After database lock for primary DFS analysis, all patients remaining on study will continue for OS follow-up including collection of data on safety and subsequent therapies. Plasma samples for exploratory analyses will no longer be collected. Efficacy scans will be collected in accordance with local clinical practice. See Section 6.1.3 for details.

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

[d] SAEs that occur after the 90-day safety follow-up period and that the Principal Investigator deems to be significant or related to IP should be reported.

[e] 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.

[f] Details of any treatment for NSCLC (including surgery and radiotherapy) post the last dose of IP must be recorded in the eCRF through the completion of the study.

[g] Post-recurrence progression (PFS) will be assessed by the Investigator per local clinical practice (See section 8.1.1.3).

[h] Patients may be contacted in the week following data cut-offs to confirm survival status.

[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 patients who discontinued treatment due to disease recurrence, the last plasma sample should be collected with the optional biopsy of recurrent tumor (if provided) at the visit 4 weeks post-last dose of IP. For patients who complete treatment, but who later experience disease recurrence, these plasma and tumor biopsy samples should be collected as close to the time of disease recurrence as possible (ie, at the time the additional follow-up scan is performed approximately 4-8 weeks after the first radiographic evidence of RECIST 1.1-defined disease recurrence).

[k] CCI

[l] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.

[m] On-study schedule of q12w ± 1w (relative to the date of randomization) **must** be followed.

[n] Contrast-enhanced CT scan of the chest and abdomen (including liver and adrenal glands) is required. Brain MRI (preferred) or brain CT with IV contrast may be performed only if clinically indicated.
[o] Post-progression scans will be performed per local clinical practice.
[p] FFPE sample of recurrent tumor biopsy will be collected from consenting patients.

d Day; DFS disease-free survival; ECOG Eastern Cooperative Oncology Group; eCRF Case report form; CCI [redacted]; CCI [redacted]; FFPE Formalin-fixed paraffin-embedded; HOSPAD Hospital resource use module; IP investigational product; NSCLC non-small cell lung cancer; OS Overall survival; CCI [redacted]; q8w Every 8 weeks; q12w Every 12 weeks; RECIST Response Evaluation Criteria in Solid Tumors; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization; w Week.

Table 4 Schedule of assessments for observation period (initiated by the signing of ICF2b)

	Up to 24 months or until RECIST 1.1-defined disease recurrence or primary DFS analysis (whichever occurs first)[a]	**For details, see Section**
ICF2b[b]	X	5.1
Medical history	To be collected on or by the first observation visit	8.2.2
Pregnancy test[c]	X	
SAEs	<----------	8.3
Subsequent anticancer therapy	<----------	8.1.3
Survival status	q12w ± 1w	8.1.3
Plasma sample for exploratory analyses[c]	q12w ± 1w coinciding with scans and at time of disease recurrence, or until discontinuation from the study	8.7.2.1
Disease assessment (RECIST 1.1)[d]	Follow-up disease assessments occur q12w ± 1w (relative to the date of surveillance completion) until appearance of RECIST 1.1-defined disease recurrence or end of the study[e,f]. Upon detection of disease recurrence, an additional follow-up scan should be performed 4-8w later and evaluated using post-progression radiological criteria[g]	8.1 Appendix G
Tumor biopsy sample (optional)[h]	At recurrence	8.7.2.2

[a] Patients in observation will adhere to this schedule of assessments until (1) completion of 24 months in observation; (2) disease recurrence; or (3) until primary DFS analysis; after which, these patients will be followed for OS (including subsequent therapy) until the end of the study.
[b] Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures. The procedures outlined in this table will be initiated by the signing of ICF2b.
[c] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.
[d] After database lock for primary DFS analysis (See Section 6.1.3), plasma samples for exploratory analyses will no longer be collected. Scans will be collected in accordance with local practice.
[e] Scan schedule of q12w ± 1w (relative to the date of randomization) must be followed while a patient is in observation.
[f] Contrast-enhanced CT scan of the chest and abdomen (including liver and adrenal glands) is required. Brain MRI (preferred) or brain CT with IV contrast may be performed only if clinically indicated.
[g] Post-progression scans will be performed per local clinical practice.
[h] FFPE samples of recurrent tumor biopsy will be collected from consenting patients.

CT computed tomography; DFS disease-free survival; ICF2b Informed consent form 2b; IV intravenous; MRI magnetic resonance imaging; OS Overall survival; q12w Every 12 weeks; RECIST Response Evaluation Criteria in Solid Tumors; SAE Serious adverse event; w Week(s).

1.2 Synopsis

From CSP v2.0 implementation at site, please use to Section 10 as a reference point for the study. This study has closed enrolment early and patients will either start open-label durvalumab or be discontinued from the study.

The synopsis below refers to the original study design. The objectives and endpoints have been updated for CSP v2.0. All analyses of the objectives and endpoints will be descriptive only and considered exploratory.

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Protocol Title: A Phase III, Randomized, Multicenter, Double-blind, Placebo-controlled, Study of Durvalumab for the Treatment of Stage II-III NSCLC Patients with Minimal Residual Disease Following Surgery and Curative Intent Therapy

Short Title: MERMAID-2

Rationale:

Up to 30% of patients with non-small cell lung cancer (NSCLC) present with surgically resectable disease (Molina et al 2008). For patients with stage II-IIIA and select stage IIIB disease, surgery and adjuvant standard of care (SoC) chemotherapy results in 5-year disease-free survival (DFS) rates of only ~40% (Wakelee et al 2017). Long-term survival is improved through administration of chemotherapy in the immediate post-operative setting (Pignon et al 2008), yet chemotherapy in the first-line metastatic setting results in no long-term survival benefit and progression-free survival (PFS) benefits of only a small number of months (Cochrane Review 2000). In contrast, immunotherapy agents have transformed the treatment landscape in the first-line setting (Garon et al 2019) and provides a rationale to conduct studies to intercept relapsing NSCLC with immunotherapy prior to the emergence of therapeutic resistance that characterizes overt metastatic disease.

There is evidence that detection of minimal residual disease (MRD) through detection of circulating tumor DNA (ctDNA) post-surgery can accurately predict recurrence (Abbosh et al 2017, Chaudhuri et al 2017). In the TRACERx study, the presence or absence of MRD was evaluated via ctDNA detection in plasma samples taken from patients who had undergone surgery for stage III NSCLC. In 13 of 14 patients who underwent surgical resection of their tumors and subsequently suffered post-operative relapse of their disease, MRD was detected via ctDNA before or at the point of clinically evident disease recurrence (through SoC imaging or presentation of symptoms) (Abbosh et al 2017). In all 12 patients who did not experience post-operative disease recurrence, MRD was not detected following surgery (Abbosh et al 2017). Detection of MRD at a time when there is no radiologic evidence of disease provides an opportunity for earlier therapeutic intervention (Abbosh et al 2018). Patients with MRD (MRD-positive [MRD+]) experience inferior recurrence-free survival compared to patients without detectable MRD (MRD-negative [MRD-]). Therefore, MRD+ patients could benefit from earlier intervention and escalation of additional adjuvant therapy (including immunotherapy); furthermore, MRD- patients (the majority of whom are cured by surgery alone) could be spared from additional treatment and the resulting unnecessary toxicity.

Immunotherapy has changed the landscape of advanced NSCLC (Martinez et al 2019). First-line treatment of metastatic NSCLC with anti-programmed cell death-1 (anti-PD-1) or anti-programmed cell death ligand 1 (anti-PD-L1) monotherapy has demonstrated an overall survival (OS) benefit compared with chemotherapy alone in patients whose tumors expressed PD-L1 (Garon et al 2019, Mok et al 2019, Reck et al 2016, Spigel et al 2019). In the second- or third-line metastatic setting, it has further been established that immune-oncologic (IO) therapy can provide clinical benefit irrespective of PD-L1 status (Rittmeyer et al 2017). However, even with these improvements, most patients will experience disease progression and ultimately die.

Durvalumab can be effective in situations of residual cancer as evidenced by improved PFS and OS observed with durvalumab versus placebo following definitive concurrent chemoradiation in the PACIFIC study (Antonia et al 2018, Gray et al 2019). Moreover, intervention with combination chemotherapy and immunotherapy versus chemotherapy alone improves PFS and OS in advanced NSCLC (Gandhi et al 2018, Gadgeel et al 2019, Paz-Ares et al 2018). These data suggest that earlier intervention with immunotherapy as adjuvant therapy following curative intent treatment could improve outcomes in early-stage NSCLC, prevent progression, and circumvent the need to expose patients to potentially more toxic chemotherapy regimens in the metastatic setting.

This study is being conducted to evaluate the efficacy and safety of durvalumab adjuvant therapy compared to placebo in patients with completely resected stage II-III NSCLC who

have undergone curative intent therapy (complete resection ± neoadjuvant and/or adjuvant therapy), and who become MRD+ during a 96-week surveillance period.

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab compared to placebo as measured by DFS in all randomized patients	DFS in FAS (using Investigator assessments according to RECIST 1.1)
Secondary/Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability profile of durvalumab monotherapy compared with placebo	AEs, physical examinations, vital signs, and laboratory findings
Exploratory objectives:	**Endpoint/variable:**
To assess the efficacy of durvalumab compared to placebo as measured by DFS in the PD-L1 TC≥1% analysis set	DFS in PD-L1 TC≥1% (using Investigator assessments according to RECIST 1.1)
To assess the efficacy of durvalumab compared to placebo on post-recurrence outcomes	PFS (using local standard practice) CCI [redacted] CCI [redacted]
To assess the efficacy of durvalumab compared to placebo as measured by OS in the PD-L1 TC≥1% analysis set and in all randomized patients	OS in PD-L1 TC≥1% and in FAS
To assess patient-reported symptoms, functioning, and HRQoL in patients treated with durvalumab compared to placebo	Change from baseline and time to deterioration in EORTC QLQ-C30 and EORTC QLQ-LC13
To investigate the relationship between a patient's baseline PD-L1 TC expression and efficacy of study treatments	IHC analysis of PD-L1 TC expression and spatial distribution within the tumor microenvironment relative to efficacy outcomes (ie, DFS, OS)
To assess the efficacy of durvalumab monotherapy to clear ctDNA compared to placebo	ctDNA endpoints, as defined by: • Best overall clearance rate (number converted at any time) • Best confirmed clearance rate (as above but confirmed at subsequent visit) • Time to ctDNA clearance • Duration of ctDNA clearance • Time to ctDNA recurrence • Time to confirmed ctDNA recurrence • Changes in variant allele frequencies (VAF) following treatment
To assess the relationship between treatment effect on DFS and treatment effect on ctDNA endpoints	ctDNA endpoints (as defined above) and DFS
To assess the association of TMB with efficacy of durvalumab compared with placebo, and other biomarker subpopulations	DFS, OS, and other efficacy endpoints in patients according to TMB in subpopulations including, but not limited to, PD-L1 TC≥1%, ctDNA endpoints, etc.

To investigate biomarkers in tumor and periphery at baseline, on treatment, post-treatment and/or at recurrence wherever feasible to identify markers related to disease, mechanism of action of the drug and/or their associations with response and clinical endpoints.	Exploratory markers, which may include, but are not limited to: tumor, immune, and/or stromal cell gene and protein expression profiles within the peripheral and tumoral compartments. TMB and somatic mutations in tissue and/or blood/plasma. Changes in RNA, DNA or protein Attributes of tumor microenvironment that could be assessed using various methods which may include, but not limited to, high content imaging, multiplex RNA/DNA/protein analysis with spatial resolution such as Mass Spec or other technologies.
To evaluate patient-reported treatment-related symptoms using PRO-CTCAE To assess the patient´s global impression of symptoms severity, and global treatment tolerability	Pre-specified items on the PRO-CTCAE Patient global assessments
To explore the impact of treatment and disease	CCI , descriptor, and VAS
To assess alternative methodologies for determining MRD	MRD determinations in screened patients
To assess prognostic value of ctDNA quantification at baseline	ctDNA quantification vs binary MRD classification (+/-) to DFS and other efficacy endpoints
To assess prognostic value of MRD classification by comparing outcomes of randomized (MRD+) placebo-treated patients to those of patients in surveillance and/or observation	• MRD status as determined at screening and various timepoints post-curative intent therapy • DFS and other efficacy endpoints • Time from surgery to DFS • Site of relapse • Second primary NSCLC

AE Adverse event; ctDNA Circulating tumor DNA; DFS Disease-free survival; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; EORTC QLQ-LC13 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items; FAS Full analysis set; HRQoL Health-related quality of life; IHC Immunohistochemistry; mRNA Messenger ribonucleic acid; MRD Minimal residual disease; OS Overall survival; PD-L1 Programmed cell death ligand 1; PD-L1 TC≥1% Expression of PD-L1 on tumor membrane, at any intensity, in ≥1% of tumor cells; PFS Progression-free survival; RECIST Response Evaluation Criteria in Solid Tumors; SAS Safety analysis set; TC Tumor cells: CCI ; TMB tumor mutational burden; CCI ; VAS Visual analog scale.

Overall design:

This is a Phase III, randomized, multicenter, double-blind, placebo-controlled, study to evaluate the efficacy and safety of durvalumab adjuvant therapy compared to placebo in patients with completely resected stage II-III NSCLC who have undergone curative intent therapy (complete resection ± neoadjuvant and/or adjuvant therapy), who have no evidence of Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1-defined disease recurrence, and who become MRD+ during a 96-week surveillance period.

The study will screen approximately CCI patients and randomize approximately CCI MRD+ patients with stage II-III NSCLC (according to IASLC Staging Manual in Thoracic Oncology v8.0) (select stage IIIB [ie, T3N2 or T4N2] patients) whose tumors are epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) wild type, and who have completed curative intent therapy. Randomized patients will include approximately CCI PD-L1 TC≥1% and CCI PD-L1 TC<1% patients. The study will be conducted in approximately 250 centers globally.

This study will employ a multi-tiered consent and screening process. Table 1 includes the procedures for the first screening (initiated by the signing of Informed Consent Form 1 [ICF1]) and surveillance of eligible patients. Table 2 includes the procedures for the second screening (initiated by the signing of Informed Consent Form 2a [ICF2a]) and randomization to treatment with investigational product (IP). Table 3 includes the procedures for the follow-up period, which is for randomized patients who discontinue treatment with IP due to toxicity or RECIST 1.1-defined disease recurrence or who have completed 24 months (26 cycles) of treatment with IP.

Resected tumor tissue collected during the first screening will be evaluated for *EGFR/ALK* and programmed death ligand-1 (PD-L1) tumor cell (TC) expression by a central reference laboratory. Patients whose tumor tissue tests positive for *EGFR* mutations and/or *ALK* translocations will be excluded from the study. In addition, PD-L1 status must be known prior to, and is required for, randomization.

- ***Note**:* Results from local *EGFR/ALK* testing of either a pre-surgery biopsy or the resected tumor tissue performed as part of standard care may be used for this study, provided testing was performed using a well-validated, local regulatory-approved kit.

This study requires mandatory genetic testing. During the first screening period (Table 1), whole exome sequencing (WES) of the patient's tumor is performed on the resected tumor tissue and derived tumor-specific DNA variants are identified by removing background germline variants, determined by WES of the patient's whole blood sample. A personalized panel is then created, comprised of up to 50 of the patient's tumor variants expressed at high frequency. This panel is then used to identify the presence of these tumor-specific variants on DNA extracted from a patient's plasma. The patient is considered MRD+ if the panel detects patient-specific tumor variants.

- ***Note:*** In order to initiate surveillance within the appropriate timeframe, samples of resected tumor tissue and whole blood should be sent to the diagnostic laboratory as soon as possible. These samples are critical for WES and the creation of the personalized panel for MRD detection. These samples must be sent **no later than** to 1-2 weeks after completion of adjuvant therapy (including post-operative radiotherapy (PORT), if administered) or 3-5 weeks after surgery (if no adjuvant therapy is administered).

A plasma sample will be collected approximately 8 weeks after completion of adjuvant therapy (including PORT, if administered) or approximately 12 weeks after surgery (if no adjuvant therapy is given), marking the **start of surveillance**. This sample will be used to determine a patient's MRD status and **must** be collected at the indicated timepoint, even if creation of the personalized panel for MRD detection and/or results from PD-L1 testing are delayed.

Eligible patients will be enrolled and monitored for the emergence of MRD during a 96-week surveillance period. During surveillance, the patient will be evaluated for MRD every 6 weeks (q6w) and will receive computed tomography (CT) scans every 12 weeks [q12w] for up to 96 weeks (Table 1). The duration of the surveillance period was selected based on 5-year DFS data across historic adjuvant studies (ANITA [Douillard et al 2006], BLT [Waller et al 2004], E1505 [Wakelee et al 2017], IALT Wakelee et al 2017], JBR.10 [Winton et al 2005]) in which DFS events were observed to be highest in years 1 and 2 and then plateaued. The 96-week surveillance strategy is expected to capture approximately 82% of NSCLC patients who suffer clinical relapse post-surgical resection, based on historical adjuvant studies. The predicted prevalence of patients with MRD is approximately 22% with 96-week surveillance. Tumor doubling times in metastatic solid tumors can be as low as 47 days (reported in colorectal liver metastases; Wiggans et al 2016). Data internally available to the Sponsor demonstrated that plasma sampling q6w to assess MRD status should capture approximately CCI of tumors with an estimated tumor burden CCI. This assumption is based on an estimated CCI tumor doubling time in relapsing NSCLC and the observation that 1 cm^3 of tumor burden results in an estimated ctDNA fraction in blood of ~0.01% (Abbosh et al 2017), close to the limit of detection of the MRD assay.

The premise of the MERMAID-2 study is to identify patients with the lowest possible tumor burden through detection of MRD and to provide treatment to these patients at an earlier timepoint. The window between detection of MRD and clinical relapse is short. Therefore, it is critical to minimize the time between the receipt of an MRD+ test result and randomization of a patient.

Patients who become MRD+ during surveillance (including cases where analysis of the first plasma sample collected [marking the start of surveillance] returns an MRD+ status) will undergo a second screening period, initiated by the signing of ICF2a (Table 2). **Note:** Patients who received prior neoadjuvant immunotherapy **must** be MRD- based on analysis of the first plasma sample collected (which marks the start of surveillance).

Patients should sign ICF2a as soon as their MRD+ result is available to immediately enter the second screening period. To ensure the duration of the second screening period is as short as possible, and to prevent any unforeseen delays in scheduling necessary scans, Investigator should proactively schedule CT and/or magnetic resonance imaging (MRI) scans of the

chest/abdomen and brain within 2 weeks following each q6w plasma collection. Thus, the baseline scans necessary to confirm eligibility will already be scheduled if testing of the plasma sample returns an MRD+ status.

Once all additional inclusion and none of the exclusion criteria are met, patients will be eligible for randomization. Patients must be randomized as soon as possible after eligibility criteria are confirmed, and treatment **must** begin within 3 days of randomization (Table 2).

Approximately 284 MRD+ patients will be randomized 1:1 to treatment with durvalumab monotherapy 1500 mg or placebo every 4 weeks (q4w) intravenously (IV). Patients will be treated for up to a total of 24 months (26 cycles), until disease recurrence, or until other specific treatment discontinuation criteria are met (whichever comes first). The study will be fully blinded.

Based on internal Sponsor data from stage II-III resected patients, it is estimated that CCI of randomized patients will be PD-L1 TC≥1%. To ensure that the target of CCI PD-L1 TC≥1% patients are randomized in the study, enrollment of PD-L1 TC<1% patients into surveillance will end once CCI PD-L1 TC<1% patients have been randomized. The remaining PD-L1 TC<1% patients will be immediately withdrawn from surveillance. Additional data will not be collected on these patients. Patients who are determined to be PD-L1 TC<1% during the first screening will not be eligible to continue to surveillance and will be considered screen failures (see Section 5.5). Please note that any PD-L1 TC <1% patient who is already in the observation arm will remain in the study.

Similarly, enrollment into the study will end once 284 MRD+ patients are randomized. Patients in surveillance will be immediately withdrawn from the study and additional data will not be collected on these patients. Please note that patients already in the observation arm will remain in the study.

Note: In the event the Sponsor withdraws patients from surveillance because the applicable cohort(s) have been filled, these patients may continue to receive CT scans every 12 weeks until 96 weeks have elapsed (relative to the start of surveillance) to honor the patient's consent to q12w scans or until disease recurrence or primary DFS analysis (whichever occurs first). No additional data will be collected on these patients.

Up to 142 of the patients who complete their 96-week surveillance period, remain MRD-, and have no evidence of RECIST 1.1-defined disease recurrence may be eligible for entry into an observation period initiated by the signing of a separate informed consent (ICF2b; Table 4). These patients will be followed for serious adverse events (SAEs), DFS, OS, subsequent anticancer therapy, and MRD assessments for 24 months or until primary DFS analysis (whichever occurs first) after which patients will be followed for OS until the end of the study. Data from this cohort of patients will be compared to the patients randomized to placebo to

support the hypothesis that MRD can be used as a prognostic biomarker to identify patients at high risk of disease recurrence prior to radiologic evidence of disease.

Patients with evidence of RECIST 1.1-defined disease recurrence using Investigator assessments during the surveillance period will not be eligible for randomization and will no longer be followed as part of the study; however, data pertaining to their recurrence must be captured (see section 5.5).

Study period:

Estimated date of first patient randomized: Q1 2021

Estimated date of last patient completed: Q4 2025

Number of patients:

The study will plan to enroll approximately 1500 patients into surveillance and randomize approximately 284 MRD+ patients to treatment with durvalumab or placebo. The approximate number of enrolled patients is based on the anticipated emergence of MRD+ patients over the 96-week surveillance period based on previously published data (Abbosh et al 2017) and data internal to the Sponsor, combined with published historic data (see above). Eligible MRD+ patients will be randomized in a 1:1 ratio to receive durvalumab monotherapy or placebo. Patients will be stratified by PD-L1 status (TC <1% vs TC ≥1%), time from start of surveillance to emergence of MRD (≤6 months vs >6 months), and prior neoadjuvant immunotherapy (Yes vs No). It is required that 170 randomized patients will be PD-L1 TC≥1%. Therefore, once 114 PD-L1 TC<1% patients are randomized, the Sponsor will immediately withdraw all remaining PD-L1 TC<1% patients from surveillance and patients who are determined to be PD-L1 TC<1% during the first screening will not be allowed to enter surveillance.

In addition to the 284 MRD+ patients that will be treated with durvalumab or placebo, up to 142 MRD- patients who have no evidence of RECIST 1.1-defined disease recurrence will enter an observation period for exploratory purposes after completion of their 96-week surveillance period.

Treatments and treatment duration

Durvalumab 1500 mg or placebo by IV infusion once q4w starting at Week 0 for up to a maximum of 24 months of treatment (up to 26 doses/cycles).

(Please note, if a patient's weight falls to 30 kg or below [≤30 kg] during the treatment period, then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo q4w after consultation between Investigator and Study Physician, until the weight

improves to above 30 kg [>30 kg], at which point the patient should start receiving the fixed dosing of durvalumab or placebo 1500 mg q4w).

Duration of treatment

This study will use a 24-month treatment period (26 cycles of treatment). This study has selected a high-risk MRD+ population where prolonged adjuvant therapy is indicated. Treatment for 24 months is supported by early results from CheckMate 153, demonstrating that prolongation of nivolumab treatment beyond 12 months is beneficial in previously treated advanced NSCLC (Spigel et al 2017). In addition, 2 pembrolizumab studies (KEYNOTE-024 and -042) evaluated treatment over 24 months in the front-line setting (Mok et al 2019, Reck et al 2016). Targeted agents have also been developed using a 24-month treatment regimen in the adjuvant setting (Zhong et al 2018).

Unless specific treatment discontinuation criteria are met, patients will be treated q4w with durvalumab or placebo for a total of 24 months (26 cycles) or until RECIST 1.1-defined disease recurrence (whichever comes first).

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined disease recurrence may continue to receive study treatment at the discretion of the Investigator until the confirmatory, follow-up scan.

Post-treatment follow-up period

After completion of durvalumab or placebo treatment, patients will be followed for safety, MRD status, patient-reported outcomes (PROs), health economics, RECIST 1.1-defined disease recurrence, subsequent anticancer therapy, and survival status at specified intervals until the primary DFS analysis. Patients will be followed for safety and long-term survival until the end of the study.

Patients will not be eligible for retreatment at any time.

Follow-up of patients post discontinuation of investigational product

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy will be followed up with disease assessments until RECIST 1.1-defined disease recurrence plus an additional follow-up scan or until death (whichever comes first) and followed for survival until the end of the study. These patients are not eligible for retreatment at any time.

Survival assessments

All randomized patients and patients in observation should be followed up for survival until study completion. If OS data has not reached the required maturity per the timelines of the study, continued OS data collection and analysis may be performed in a roll-over study.

Disease assessments

Efficacy assessments of the primary endpoint of DFS will be derived using Investigator assessments according to RECIST 1.1 and pre-specified definitions of disease recurrence (ie, local or regional recurrence, distant recurrence, second primary NSCLC) and by survival assessments. All patients will be followed for disease recurrence until the primary DFS analysis and followed for survival until the completion of the study. PFS and OS are secondary endpoints of the study.

Tumor evaluations utilize images from CT (preferred) or MRI, each preferably with IV contrast of the chest and abdomen (including liver and adrenal glands) collected during screening, at the start of surveillance, and at selected timepoints during the study duration. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

Data Monitoring Committee

An independent data monitoring committee (IDMC) comprised of independent experts will meet approximately 12 months after the first patient has been dosed with IP or after approximately 50 patients have received at least 1 dose of IP (whichever occurs first) to assess the safety and tolerability of durvalumab. The IDMC will review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety findings. The timing of subsequent reviews will be determined by the IDMC but will not occur more frequently than every 6 months. The IDMC safety reviews will be conducted in an unblinded manner.

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

Statistical methods:

The primary objective of the study is to compare the efficacy of durvalumab to placebo in terms of DFS, defined as time from the date of randomization until the date of disease recurrence (using Investigator assessments according to RECIST 1.1) or date of death due to any cause (whichever occurs first) in the PD-L1 TC≥1% analysis set. DFS in the full analysis set (FAS) is a secondary endpoint.

The FAS will include all randomized patients. The PD-L1 TC≥1% analysis set will include all patients in the FAS who are PD-L1 TC≥1% at baseline.

DFS will be analyzed using a stratified log-rank test. The treatment effect will be estimated in terms of the hazard ratio (HR) together with the corresponding 95% confidence interval (CI) from the Cox proportional hazard model stratified by PD-L1 status (TC<1% vs TC ≥1%), time from the start of surveillance (ie, the date the plasma sample used to determine a patient's MRD status post-curative intent therapy is **collected**) to emergence of MRD (≤6 months vs

>6 months), and prior neoadjuvant immunotherapy (Yes vs No). For the primary analysis in the PD-L1 TC≥1% analysis set, the PD-L1 status (TC<1% vs TC ≥1%) stratification factor will not be included. The stratification factor covariates in the statistical modeling will be based on the values entered into interactive web response system (IWRS) at randomization, even if it is subsequently discovered that these values were incorrect. For the purpose of statistical analysis of the primary and relevant secondary endpoints, a plan for reducing the number of strata cells will be included in the statistical analysis plan (SAP) in case there are insufficient events in one level of any strata. Descriptive summaries and Kaplan-Meier curves and estimates will also be produced.

The study will plan to enroll approximately 1500 patients and randomize approximately 284 patients with stage II-III NSCLC and are MRD+, including at least 170 patients with PD-L1 TC≥1%. Patients will be randomized 1:1 to durvalumab or placebo. Randomization will be stratified by PD-L1 status (TC <1% vs TC≥1%), time from the start of surveillance to emergence of MRD (≤6 months vs >6 months), and prior neoadjuvant immunotherapy (Yes vs No).

The study is sized for the primary endpoint of DFS in the PD-L1 TC≥1% analysis set and for the secondary endpoint of DFS in the FAS.

The analysis of the primary endpoint (DFS) will occur when approximately 118 DFS events have occurred (69% maturity) in the PD-L1 TC≥1% analysis set. If the true DFS HR is 0.55 in the PD-L1 TC≥1% analysis set, the study will provide at least 90% power to demonstrate a statistically significant difference for DFS with overall 2-sided significance level of 5%; this translates to 3.2-month benefit in median DFS over 4 months on placebo, or 8.4% difference in 24-month DFS rate over 1.5% on placebo, if DFS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of 0.7.

The study is also sized to provide at least 90% power for the DFS endpoint in the FAS. The analysis will be performed at the same time as the primary analysis, when it is expected that approximately 197 DFS events have occurred (69% maturity) in the FAS. If the true DFS HR is 0.63 in this population, this will provide at least 90% power to demonstrate a statistically significant difference for DFS, assuming overall 5% 2-sided significance level; this translates to a 2.3-month benefit in median DFS over 4 months on placebo, or 5.6% difference in 24-month DFS rate over 1.5% on placebo, if DFS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of 0.76.

It is estimated that the primary analysis for DFS will occur approximately 38 months after the first patient has been randomized assuming a 34-month recruitment period and allowing for patients to have a minimum follow-up of 4 months.

In order to provide strong control of the type I error rate, α=5% (2-sided), a multiple testing procedure with gatekeeping strategy will be used across the primary endpoint of DFS in the PD-L1 TC≥1% analysis set and the secondary endpoint of DFS in the FAS, starting with testing the primary endpoint on the PD-L1 TC≥1% analysis set. The overall 5% alpha will be allocated to the analysis of DFS in the PD-L1 TC≥1% analysis set. If that analysis is significant, the 5% alpha will be recycled to the DFS endpoint in the FAS.

OS will be a secondary efficacy endpoint, 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. OS will analyzed at the time of the DFS analysis. In the PD-L1 TC≥1% analysis set if the true HR is 0.79 then it is anticipated that approximately 59 events (35% maturity) will have occurred. This translates to a 4.3 month benefit in median OS over 16 months on placebo. In the FAS if the true HR is 0.89 then it is anticipated that approximately 102 events (36% maturity) will have occurred. This translates to a 2 month benefit in median OS over 16 months on placebo. OS will be analyzed similarly to DFS.

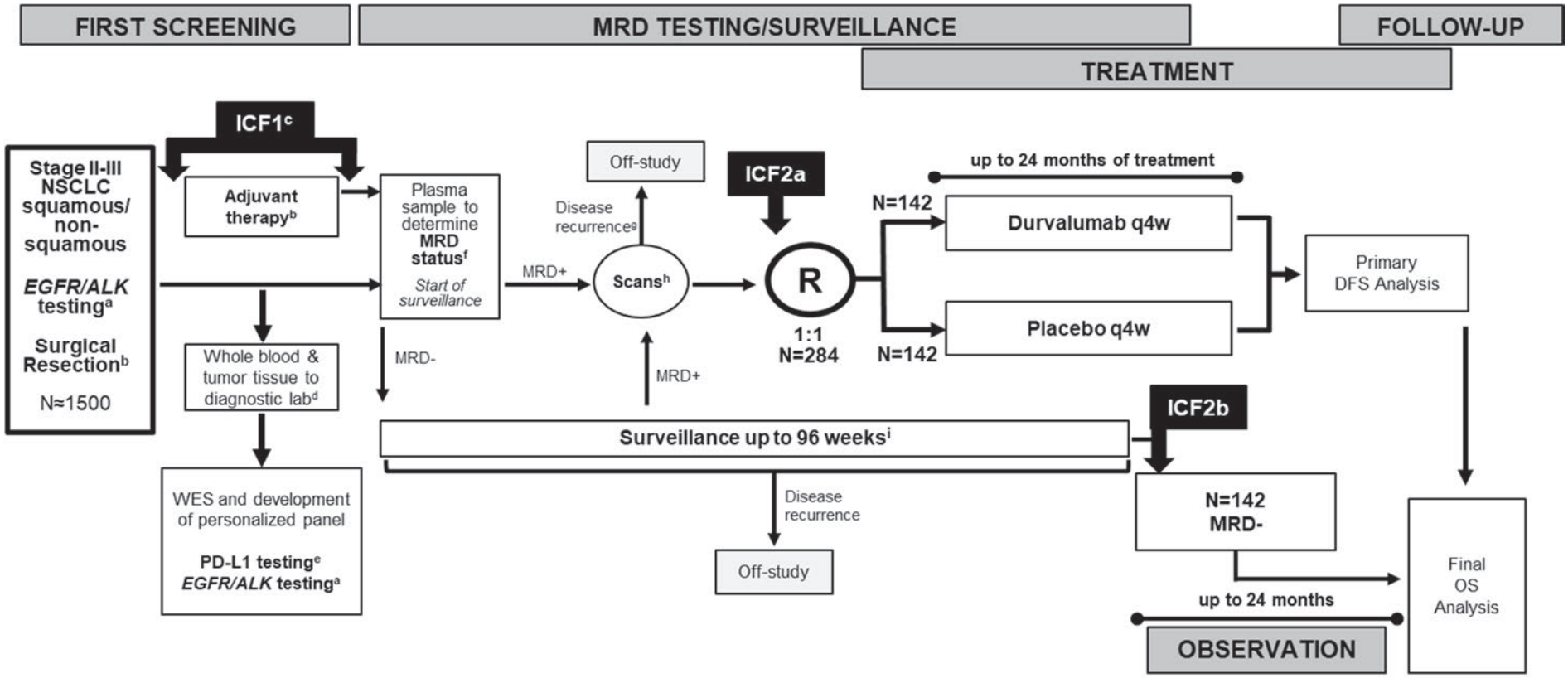
A further analysis of OS will be performed at approximately 127 events (75% maturity) in the PD-L1 TC≥1% analysis set. At this time there is also expected to be approximately 218 events (77% maturity) in the FAS. It is anticipated this analysis will occur approximately 60 months after first patient is randomized. If events are accruing slower than expected then the data cut-off (DCO) may occur 60 months after first patient is randomized regardless of number of events accrued.

Safety data will be summarized descriptively and will not be formally analyzed.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



[a] Results from local *EGFR/ALK* testing of either a pre-surgery biopsy or the resected tumor tissue performed as part of standard care may be used for this study, provided testing was performed using a well-validated, local regulatory-approved kit. *EGFR/ALK* status can also be assessed by the central laboratory using either a pre-surgical biopsy or on resected tumor tissue from surgery if local testing is not available. Patients whose tumors are positive for *EGFR* mutations and/or *ALK* translocations will be excluded from the study. Only patients with wild-type status should provide a plasma sample for MRD assessment at the start of surveillance (see footnote f).

[b] Patients will receive curative intent therapy (complete resection ± neoadjuvant and/or adjuvant therapy) as SoC within the clinics. Details of surgery and prior therapy will be captured in the appropriate section of the eCRF and will be included as a subgroup analysis. Please note that PORT can be included as part of adjuvant therapy and must be completed before starting surveillance. See Figure 2 for potential scenarios for permissible curative therapy in this study.

[c] ICF1 can be signed during or immediately following the completion of curative intent therapy and should be signed as soon as possible to allow the Sponsor access to the biosamples required for creation of the personalized panel for MRD detection (see footnote d) and for central testing of *EGFR/ALK* and/or PD-L1 (if required, see footnotes a and e).

[d] The whole blood and resected tumor tissue samples must be sent as soon as possible after ICF1 is signed but no later than 1-2 weeks after completion of adjuvant therapy or 3-5 weeks after surgery (if no adjuvant therapy is given) to enable creation of the personalized panel for MRD detection.

[e] PD-L1 status must be known prior to and is required for randomization.

[f] Surveillance is initiated once the first plasma sample used to determine MRD status is **collected** (approximately 8±1 weeks after completion of adjuvant therapy or up to 12±1 weeks post-surgery [if no adjuvant therapy is given; See Figure 2]).

[g] If scans conducted during the first screening or during surveillance demonstrates evidence of RECIST 1.1-defined disease recurrence and/or metastatic disease, the patient is considered a screen failure (section 5.5) and is no longer eligible to participate in the study

[h] Before an MRD+ patient can be randomized, a CT scan of the chest and abdomen (including liver and adrenal glands) and a brain MRI (preferred) or brain CT with IV contrast must be performed to confirm no evidence of disease recurrence and/or metastatic disease.

[i] During surveillance, patient visits will occur q6w±3d for plasma collection and q12w±1w for CT scans.

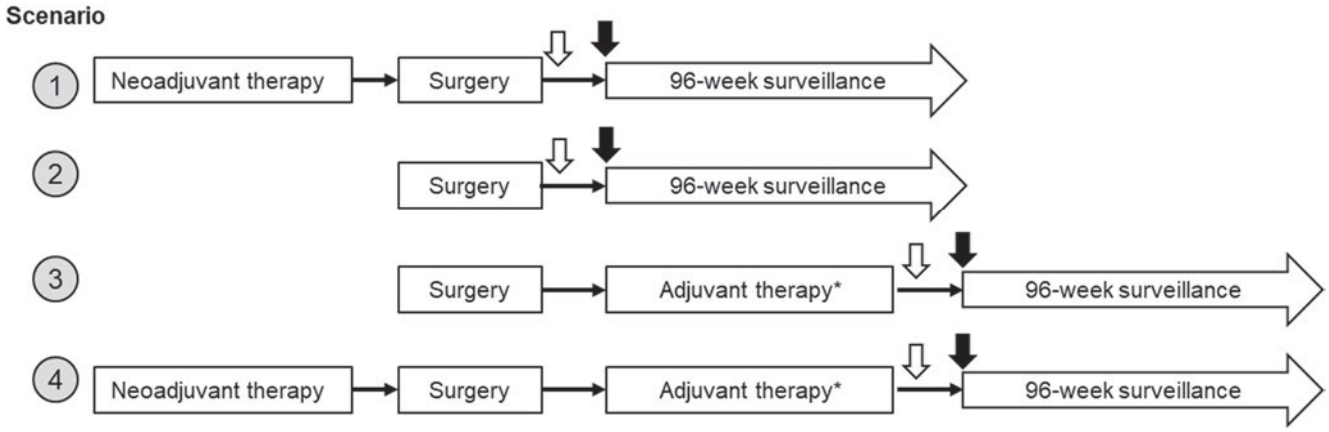
ALK Anaplastic lymphoma kinase; DFS Disease-free survival; EGFR Epidermal growth factor receptor; ICF Informed consent form; MRD Minimal residual disease; N number; NSCLC Non-small cell lung cancer; OS Overall survival; PD-L1 Programmed cell death ligand-1; q4w Every 4 weeks; R Randomization; WES whole exome sequencing.

Potential scenarios for permissible curative intent therapy are shown in Figure 2. Please note that only one course of standard of care (SoC) chemotherapy (eg, 4 cycles of platinum-based chemotherapy) is allowed in the adjuvant setting. In addition, adjuvant therapy may include post-operative radiotherapy (PORT).

All patients should be consented as soon as possible after surgery (Scenarios 1 and 2) but may be consented during adjuvant therapy (Scenarios 3 and 4) to ensure that the creation of the personalized panel for MRD detection and epidermal growth factor receptor *(EGFR)*, anaplastic lymphoma kinase *(ALK),* and PD-L1 testing are not rate-limiting and patients are able to enter surveillance within the appropriate timeframe.

The 96-week surveillance period must begin within 8 ± 1 weeks of completion of adjuvant therapy or within 12 ± 1 weeks post-surgery (if no adjuvant therapy is administered).

Figure 2 Potential scenarios for permissible curative intent therapy



*Adjuvant therapy may include post-operative radiotherapy (PORT).
The resected tumor tissue and whole blood samples should be sent to the diagnostic laboratory as soon as possible, as they are critical for the development of the personalized panel for MRD detection. The white arrow indicates latest time these samples can be sent to the diagnostic laboratory (ie, 3-5 weeks after surgery [Scenario 1 or 2] or 1-2 weeks after the completion of adjuvant therapy [Scenario 3 or 4]).
The black arrow indicates when the first surveillance plasma sample should be collected and marks the start of surveillance. Surveillance should start by 12 ± 1 weeks for Scenario 1 or 2 by 8 ± 1 weeks for Scenario 3 or 4.

Table 5 Inclusion criteria assessment relative to first and second screening periods

First screening (initiated by the signing of ICF1) (Section 5.1.1)	Second screening (initiated by MRD+ status and the signing of ICF2a) (Section 5.1.2)
Criteria for surgical planning Imaging of chest/abdomen and brain within 6 weeks prior to surgery **Criteria for curative intent therapy** • Complete resection • Undergone (or be undergoing) curative intent therapy (which may include neoadjuvant ± adjuvant therapy)[a] **Criteria for entering surveillance** • ICF1 signed prior to initiation of screening and surveillance activities • Age ≥18 years • Male and/or female • Diagnosis of histologically confirmed NSCLC with resectable (Stage IIA to select [ie, T3N2 or T4N2] Stage IIIB) disease[b] • Confirmation of resected tumor tissue and whole blood sample appropriate for WES for creation of the personalized panel required for the MRD assay[c] • Plasma sample marking start of surveillance collected 8±1w after completion of adjuvant therapy or 12±1w post-surgery for patients not receiving adjuvant therapy. Patient who is MRD- at start of surveillance and remains MRD- based on subsequent MRD tests continues in surveillance. Patient who is MRD+ at start of surveillance may be eligible to enter second screening (initiated by the signing of ICF2a). *If a patient has not received any adjuvant therapy (scenario 2,* Figure 2*), these patients are ideal candidates for the MERMAID-1 (D910LC00001) companion study. Investigators are asked to consider these patients for MERMAID-1. If the Investigator feels that the best course of action is to proceed with screening into MERMAID-2, the Investigator is asked to consult with the study physician on the study.* ▪ **Note:** Patient who received prior neoadjuvant immunotherapy **must** be MRD- based on analysis of the first plasma sample collected (which marks the start of surveillance) in order to continue in the study	**Criteria for randomization (must be met within 28 days ± 7 days prior to randomization)** • ICF2a signed after determination of MRD+ status but prior to final screening and randomization • Known PD-L1 status as determined by central laboratory[d] • No evidence of RECIST 1.1-defined disease recurrence confirmed by CT and/or MRI[e] • WHO/ECOG PS 0 or 1 • *If no adjuvant therapy administered:* Completed postoperative wound healing • *If adjuvant therapy administered:* Must have recovered from all acute, reversible toxic effects from chemotherapy that could potentially adversely impact further administration of durvalumab or placebo according to the Investigator's judgment • Adequate organ and marrow function based on specified criteria • Life expectancy >12 weeks • Body weight >30 kg

Table 5 Inclusion criteria assessment relative to first and second screening periods

First screening (initiated by the signing of ICF1) (Section 5.1.1)	Second screening (initiated by MRD+ status and the signing of ICF2a) (Section 5.1.2)
Patient who becomes MRD+ during any MRD test conducted during surveillance may be eligible to enter second screening (initiated by the signing of ICF2a) • No evidence of RECIST 1.1-defined disease recurrence confirmed by CT and/or MRI[c] • Consents to be accessible for q6w±3d plasma collection and for q12w±1w scans during the 96-week surveillance period	

[a] Patients who discontinue chemotherapy for toxicity prior to completion of all planned chemotherapy are eligible. Patients who have not received any neoadjuvant and/or adjuvant therapy, and meet all other eligibility criteria, may be eligible under protocol-specified circumstances (see Section 5.1.1).

[b] Select stage IIIB (ie, T3N2 or T4N2) patients will be eligible, provided they are upstaged to T3N2 or T4N2 based on confirmed pathology after surgery. Patients who are staged as T3N2 or T4N2 prior to surgery are not eligible.

[c] If a CT scan of the chest and abdomen (including liver and adrenal glands) conducted either prior to the start of surveillance or during surveillance shows evidence of RECIST 1.1-defined disease recurrence, the patient is a screen fail and is no longer eligible to participate in the study (see section 5.5).

[d] Patients entering MERMAID-2 (D910MC00001) after participating and subsequently screen-failing MERMAID-1 (D910LC00001) may be able to use their personalized panel for MRD detection and associated data as well as their previously determined PD-L1 status for this study. See section 5.4 for details.

[e] Before an MRD+ patient can be randomized, a contrast-enhanced CT scan of the chest and abdomen (including liver and adrenal glands) and a brain MRI (preferred) or brain CT with IV contrast must be performed to confirm no evidence of disease recurrence and/or metastasis. For a patient who is MRD+ at the start of surveillance scans do not need to be repeated during the second screening period if the post-curative intent therapy scans (ie, the scans conducted prior to the start of surveillance [Table 1]) was conducted within 28 days ± 7 days prior to randomization. If a patient becomes MRD+ during surveillance, a CT scan of the chest and abdomen conducted during surveillance may be used as the baseline scan, provided it was performed within 28 days ± 7 days prior to randomization. A brain MRI or brain CT with IV contrast must performed prior to randomization. If the previously performed scans fall outside of this window, additional scans of the chest, abdomen, and brain must be performed **before** the patient is randomized to confirm no evidence of disease recurrence and/or metastasis.

For details on each criterion, refer to the full list of inclusion criteria in Sections 5.1.1 (first screening) and 5.1.2 (second screening).

CT Computed tomography; d Day; ECOG Eastern Cooperative Oncology Group; ICF1 Informed consent form 1; ICF2a Informed consent form 2a; IV Intravenous; MRD Minimal residual disease; MRD+ MRD-positive; MRD- MRD-negative; MRI Magnetic resonance imaging; NSCLC Non-small cell lung cancer; PD-L1 Programmed cell death ligand 1; PS Performance status; q6w Every 6 weeks; q12w Every 12 weeks; RECIST Response Evaluation Criteria in Solid Tumors; WES Whole exome sequencing; w Week; WHO World Health Organization

Table 6 Exclusion criteria assessment relative to first and second screening periods

First screening	Second screening
• *EGFR* and/or *ALK* mutant on pre-surgical biopsy or resected tumor tissue[a] • Mixed small cell and NSCLC pathology • Require re-resection or are deemed to have unresectable NSCLC • History of allogeneic organ or bone marrow transplantation • Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection • Active or prior documented autoimmune or inflammatory disorders • Uncontrolled intercurrent illness • History of another primary malignancy (with specified exceptions) • Received any radiotherapy in the neoadjuvant setting • Received any IO therapy in adjuvant setting • Prior exposure to durvalumab • Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment • Previous IP assignment in the present study	• Active or prior documented autoimmune or inflammatory disorders • Baseline imaging demonstrating RECIST 1.1-defined disease recurrence or other evidence of clinical recurrence • Uncontrolled intercurrent illness • History of active, primary immunodeficiency • Active infection including tuberculosis, HBV, HCV, HIV • Brain metastases or spinal cord compression • Known allergy or hypersensitivity to any of the IPs • Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of IP • Receipt of live attenuated vaccine within 30 days prior to the first dose of IP • Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP • Current or prior use of immunosuppressive medication within 14 days before the first dose of IP • Previous IP assignment in the present study • Concurrent enrollment in another clinical study, unless observational (non-interventional) or follow-up period of an interventional study • Prior randomization/treatment in previous durvalumab clinical study regardless of treatment arm assignment • Female who is pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from second screening to 90 days after the last dose of IP • Judgment by Investigator that the patient should not participate in the study

[a] Patients entering MERMAID-2 (D910MC00001) after participating and subsequently screen-failing MERMAID-1 (D910LC00001) may be able to use the results from prior *EGFR/ALK* testing for this study. See section 5.4 for details.

For details, see the full list of exclusion criteria in Section 5.2. Some criteria must be checked during both screening periods and therefore appear twice in this table.

ALK Anaplastic lymphoma kinase; *EGFR* Epidermal growth factor receptor; HBV Hepatitis B virus; HCV Hepatitis C virus; HIV Human immunodeficiency virus; IO Immuno-oncologic; IP Investigational product; NSCLC Non-small cell lung cancer; RECIST Response Evaluation Criteria in Solid Tumors.

2 INTRODUCTION

2.1 Study rationale

Up to 30% of patients with NSCLC present with surgically resectable disease (Molina et al 2008). For patients with stage II-III disease, surgery and adjuvant SoC chemotherapy results in 5-year DFS rates of only ~40% (Wakelee et al 2017). Adjuvant chemotherapy following resection of NSCLC is standard practice to reduce risk of disease recurrence. Further benefit has been obtained with immune-oncologic (IO) therapy, including durvalumab (Antonia et al 2018). However, even with these improvements, most patients will experience disease recurrence and ultimately die. There is evidence that detection of MRD by measurement of ctDNA post-surgery can accurately predict disease recurrence (Abbosh et al 2017, Chaudhuri et al 2017). Determination of MRD in lung cancer through ctDNA detection has been investigated in 2 studies. In TRACERx, the presence or absence of ctDNA was evaluated in plasma samples taken from patients who had undergone surgical resection for stage I-III NSCLC. In 13 of 14 patients who experienced disease recurrence following surgical resection, MRD was detected using ctDNA before or at clinical detection of disease recurrence diagnosed through follow-up assessments (Abbosh et al 2017). An additional study of lung cancer patients (the majority of whom had undergone curative intent therapy including a complete resection) post-intervention ctDNA was detectable in 20 of 37 patients; all 20 patients ultimately recurred and MRD was detectable earlier using ctDNA than when using SoC radiological imaging (Chaudhuri et al 2017).

Durvalumab can be effective in situations of residual cancer as evidenced by improved PFS and OS observed with durvalumab versus placebo following definitive concurrent chemoradiation in the PACIFIC study (Antonia et al 2018, Gray et al 2019). Moreover, intervention with combination chemotherapy and immunotherapy versus chemotherapy alone improves PFS and OS in advanced NSCLC (Gandhi et al 2018, Gadgeel et al 2019, Paz-Ares et al 2018). These data suggest that earlier intervention with immunotherapy as adjuvant therapy following curative intent treatment could improve outcomes in early-stage NSCLC, prevent progression, and circumvent the need to expose patients to potentially more toxic chemotherapy regimens in the metastatic setting.

This study is designed to assess whether detection of MRD via ctDNA isolation after complete resection ± neoadjuvant and/or adjuvant therapy (Figure 2) for stage II-III NSCLC identifies a high risk patient population that would receive benefit from additional adjuvant therapy. In addition, this study tests the research hypothesis that adjuvant durvalumab monotherapy will be more effective than placebo in treating this patient population.

From CSP v2.0 implementation at site, please use Section 10 as a reference point for the study. This study has closed enrolment early and patients will either start durvalumab (as open-label treatment) or be discontinued from the study.

2.2 Background

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

2.2.1 Immunotherapies

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

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

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

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

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of pre-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance 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,

Zhong et al 2018, Zhang et al 2008) 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 a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and PD-L1 has promising clinical activity. Ipilimumab was first granted United States (US) FDA approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell NSCLC, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of 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) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca. 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 IFN-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell dependent 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 CCI patients as part of completed and ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.2.1 and Section 8.3.12. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

2.2.3 Non-small cell lung cancer and unmet need

Lung cancer is the most common cancer and the most common cause of death from cancer in the world, with an estimated 2.1 million new cases (11.6% of all new cancers) and 1.8 million deaths (18.4% of cancer deaths) in 2018 (GLOBOCAN 2018). NSCLC represents 80% to 85% of all lung cancers (Pisters and LeChevalier 2005) and up to 30% of these patients present with surgically resectable disease (Molina et al 2008).

Despite presentation with resectable disease, surgery and adjuvant SoC chemotherapy results in a 5-year DFS rate of only ~40% in stage II and III NSCLC (Wakelee et al 2017). Following disease recurrence, long-term survivorship is rare, ranging from 2% to 13% at 5 years (Wong et al 2016, Sekihara et al 2017, McMurry et al 2018). Adjuvant chemotherapy following resection of NSCLC is standard practice to reduce risk of disease recurrence. In stage III disease, a 5-year OS benefit of up to 15% has been observed with adjuvant cisplatin and vinorelbine (Pignon et al 2008). Additional adjuvant chemotherapy regimens have shown similar benefits, as reflected in national guidelines (NCCN 2019). However, although adjuvant chemotherapy following resection of NSCLC provides important benefits, most patients will experience disease recurrence and ultimately die. Identifying patients who would benefit from additional treatment in the adjuvant setting represents an important unmet need.

2.2.3.1 Value of anti-PD-1 and anti-PD-L1 monotherapy in NSCLC

Immunotherapy has changed the landscape of advanced NSCLC treatment (Martinez et al 2019). Randomized controlled studies of mAbs targeting PD-1 first demonstrated benefit in second or later line metastatic NSCLC setting in 2015, with nivolumab improving survival versus docetaxel in patients with both squamous and non-squamous NSCLC (Brahmer et al 2015, Borghaei et al 2015, Horn et al 2017). Subsequent clinical trials reported that first-line treatment of metastatic NSCLC with anti-PD-1 monotherapy demonstrated an OS benefit compared with chemotherapy alone in patients whose tumors expressed PD-L1 (Spigel et al 2019, Mok et al 2019, Reck et al 2016, Reck et al 2019). However, CheckMate 026 did not demonstrate a benefit of nivolumab versus platinum-based chemotherapy in patients with advanced untreated NSCLC and PD-L1 tumor proportion score (TPS)≥1%, analyses in PD-L1 TPS>5% and TPS>50% populations also failed to show a benefit of intervention with nivolumab over platinum-based chemotherapy (Carbone et al 2017).

The PACIFIC study randomized unresectable stage III patients to receive durvalumab or placebo following definitive radiotherapy, irrespective of primary tumor PD-L1 status (Antonia et al 2018). Patients randomized to durvalumab consolidation therapy experienced improved PFS (HR 0.52 [95% CI 0.42, 0.65], p<0.001, 16.8 months versus 5.8 months) and OS (HR 0.68 [95% CI 0.53, 0.87], p=0.00251 (Antonia et al 2018). Updated analyses revealed that 3-year OS rate in the durvalumab-treated patients was 57% versus 43.5% in the placebo group (Gray et al 2019). The results from PACIFIC provide a rationale for anti-PD-L1 as a consolidation therapy following definitive treatment of NSCLC capable of improving long-term OS outcomes by effectively treating patients with low tumor burden. Moreover, anti-PD-(L)1 agents have demonstrated clinically meaningful responses in metastatic NSCLC, with some patients exhibiting durable responses even after discontinuing therapy (Martinez et al 2019). Ongoing studies are assessing the efficacy of adjuvant immunotherapy in NSCLC (eg, IMpower-10, KEYNOTE-091, BR.31, ANVIL, and MERMAID-1 [D910LC00001]).

2.2.3.2 Minimal residual disease detection in NSCLC

Detection of MRD, as indicated by the presence of ctDNA, may reveal the existence of clinically indiscernible residual tumor following curative intent therapy (completed resection ± neoadjuvant and/or adjuvant therapy). Detection of MRD at a time when there is no radiologic evidence of disease provides an opportunity for earlier therapeutic intervention (Abbosh et al 2018). MRD+ patients experience inferior recurrence-free survival compared to MRD- patients. Therefore, MRD+ patients may benefit from earlier intervention and escalation of treatment, including immunotherapy alone or in combination with chemotherapy; furthermore, MRD- patients (the majority of whom are cured by surgery alone) could be spared from more intensive therapy and the resulting unnecessary toxicity. This MRD-driven treatment hypothesis is currently under investigation in MERMAID-1 (D910LC00001) in stage II-III NSCLC patients who are determined to be MRD+ post-surgery (landmark MRD+).

MRD detection in lung cancer via isolation of ctDNA has been investigated in 2 studies. In the TRACERx study, the presence or absence of ctDNA was evaluated in plasma samples taken from patients who had undergone surgery for stage I-III NSCLC. In 13 of 14 patients who underwent surgical resection of their tumors and subsequently suffered post-operative relapse of their disease, MRD was detected either before or at the point of clinically evident disease recurrence (through SoC imaging or presentation of symptoms). In all 12 patients who did not experience post-operative disease recurrence, MRD was not detected following surgery (Abbosh et al 2017). In the other study, MRD was detectable in 20 of 37 lung cancer patients, the majority of whom had undergone curative intent therapy with chemotherapy and/or radiotherapy. All 20 MRD+ patients ultimately recurred, whereas the 17 MRD- patients did not experience a progression event (Chaudhuri et al 2017). Detection of MRD preceded radiographic progression in 72% of patients by a median of 5.2 months (Chaudhuri et al 2017). These studies demonstrate the potential utility of MRD detection for identifying patients who are at high risk of experiencing disease recurrence.

Technically, MRD detection is challenging due to the ultra-low frequency of ctDNA molecules in cell-free DNA (Abbosh et al 2018). In this study, the Sponsor will leverage an advanced, sensitive, personalized assay predicated on sequencing excised primary tumor alongside a whole blood sample to derive a patient-specific MRD signature. This approach will lead to optimal capture of MRD+ patients during surveillance after SoC curative intent therapy.

2.2.3.3 Rationale for early interception studies predicated on MRD

Long-term survival can be improved through administration of chemotherapy in the immediate post-operative setting (Pignon et al 2008), yet chemotherapy in the first-line metastatic setting results in no long-term survival benefit and PFS benefits of only a small number of months (Cochrane Review 2000). Intervention with consolidation durvalumab following definitive chemoradiation in unresectable stage III NSCLC resulted in improved OS outcomes in an all-comers PD-L1 TPS population (Antonia et al 2018). Together, these

data highlight that the residual disease left after curative intent therapy is vulnerable to additional adjuvant therapy and thereby provide rationale to escalate this consolidation therapy in these patients in order to intercept relapsing NSCLC when tumor burden is low.

In metastatic NSCLC, the combination of chemotherapy and IO therapy is an established treatment option, particularly in patients whose tumors exhibit PD-L1 TPS <50% and who lack targetable driver mutations (Gandhi et al 2018, Paz-Ares et al 2018). However, this combination leads to an increased rate of treatment discontinuation due to toxicity. For example, in KEYNOTE-407 study, 13.3% of patients treated with chemotherapy and IO therapy discontinued treatment due to toxicity, compared to only 6.4% in the chemotherapy-only arm (Paz-Ares et al 2018). Interception of relapsing NSCLC with maintenance anti-PD-(L)1 monotherapy could improve DFS while sparing patients the toxicity associated with combination treatment for recurrent disease. MRD detection provides a solution to these challenges by facilitating adjuvant studies in smaller, more relevant MRD+ patient populations where adjuvant treatment can be escalated due to the high probability of disease recurrence. Two studies conducted in patients with either NSCLC or urothelial cancer showed that patients treated with durvalumab had a reduction in ctDNA at 6 weeks that was associated with tumor shrinkage and improved PFS and OS (Raja et al 2018). Similar correlation between ctDNA and outcomes have been reported in other studies of agents that target EGFR (Friends of Cancer Research White Paper 2018). These findings suggest that on-treatment ctDNA clearance could be established as a surrogate endpoint of therapeutic response to adjuvant intervention, thereby facilitating accelerated clinical adoption of novel treatment options that prove to be efficacious in this setting.

2.2.3.4 MRD monitoring following surgery and other curative therapy

In this study, patients will be monitored for MRD over a 96-week surveillance period beginning post-surgery and completion of other curative therapy (complete resection ± neoadjuvant and/or adjuvant therapy). Historic NSCLC adjuvant trials demonstrate that ~75% of the total number of 5-year DFS events occur within the first 2 years following surgery (Wakelee et al 2017, Douillard et al 2006, Waller et al 2004, Arriagada et al 2004). This provides a rationale for 96-week MRD surveillance which should theoretically capture the majority of NSCLC recurrence events.

Tumor doubling times in metastatic solid tumors can be as low as 47 days (reported in colorectal liver metastases) (Wiggans et al 2016). A study of NSCLC brain metastases demonstrated tumor doubling times of 58.5 days (Yoo et al 2008). Since NSCLC tumor burden correlates with concentration of ctDNA in blood (Abbosh et al 2017), it was determined that tumor burden and consequently ctDNA could rise quickly in a relapse setting. Therefore, in order to capture disease recurrence at the lowest possible tumor volume to intervene with durvalumab adjuvant therapy, q6w monitoring using the Sponsor-approved panel for MRD detection will be used.

2.3 Benefit/risk assessment

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

See Section 9.6.1 and Appendix A for information regarding the IDMC.

2.3.1 Potential benefits of durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first-in-human, single-agent study CCI in patients with advanced solid tumors, the study of durvalumab monotherapy in NSCLC CCI, CCI, CCI and the study of durvalumab monotherapy in NSCLC following completion of platinum-based chemotherapy concurrent with radiation therapy CCI. Data from these studies have demonstrated clinical activity of durvalumab therapy in patients with NSCLC. Details pertaining to these studies are provided in the durvalumab IB. Additionally, recent data from D419MC00004 (POSEIDON) show a benefit of durvalumab plus platinum-based chemotherapy in metastatic NSCLC when administered in the first-line setting (AstraZeneca press release 2019; Johnson et al 2021).

2.3.2 Overall risks

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

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

2.3.2.1 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus, and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, 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 monotherapy clinical studies, including a study in unresectable NSCLC in which patients received durvalumab following concurrent SoC platinum-based chemoradiotherapy (PACIFIC), AEs at an incidence of ≥20% include events such as fatigue, cough, decreased appetite, dyspnea, and nausea. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs), and Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 5 events reported across the durvalumab program.

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

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

2.3.3 Overall benefit/risk

Recent progress in immunotherapy for NSCLC has been a substantive advance, although further improvement is needed. However, up to 60% of patients will still experience disease recurrence. Novel treatment approaches are needed to improve the long-term prognosis for patients with early-stage NSCLC. Identification of patients who will benefit from immunotherapy in the adjuvant setting following curative intent therapy could lead to improved outcomes. Early studies of immunotherapy in the neoadjuvant setting in patients with resected NSCLC have shown promising clinical activity as well as acceptable safety profiles (Forde et al 2018; Shu et al 2018). Data from PACIFIC demonstrated the efficacy and tolerability of durvalumab administered after completion of platinum-based adjuvant chemotherapy (Antonia et al 2018). Therefore, in this Phase III study, the administration of durvalumab monotherapy compared to placebo will be investigated in patients with stage II-III NSCLC who are or become MRD+ following curative intent therapy.

The study design aims to minimize potential risks. For example, a safety evaluation by an IDMC will take place to assess whether durvalumab may adversely impact post-operative or post-treatment outcomes; the IDMC will report back to the Sponsor.

Therefore, based upon the available nonclinical and clinical safety data and the mitigations designed for this study, the investigation of the potential therapeutic efficacy and safety of durvalumab monotherapy following completion of curative intent therapy is acceptable in patients with completely resected NSCLC and the overall benefit/risk assessment supports the proposed study design.

Note for CSP v2.0: There is no change to the overall benefit/risk assessment of the study.

3 OBJECTIVES AND ENDPOINTS

From CSP v2.0 implementation at site, please use Section 10 as a reference point for the study. This study has closed enrolment early and patients will either start open-label durvalumab or be discontinued from the study.

The objectives and endpoints have been updated for CSP v2.0. All analyses of the objectives and endpoints will be descriptive only and considered exploratory. Please see Section 10.4 for additional information.

Table 7 Study objectives and endpoints/variables

Primary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab compared to placebo as measured by DFS in all randomized patients	DFS in FAS (using Investigator assessments according to RECIST 1.1)
Secondary/safety objective:	**Endpoint/variable:**
To assess the safety and tolerability profile of durvalumab monotherapy compared with placebo	AEs, physical examinations, vital signs, and laboratory findings
Exploratory objectives:	**Endpoint/variable:**
To assess the efficacy of durvalumab compared to placebo as measured by DFS in the PD-L1 TC≥1% analysis set	DFS in PD-L1 TC≥1% (using Investigator assessments according to RECIST 1.1)
To assess the efficacy of durvalumab compared to placebo on post-recurrence outcomes	PFS (using local standard practice) CCI [redacted] CCI [redacted]
To assess the efficacy of durvalumab compared to placebo as measured by OS in the PD-L1 TC≥1% analysis set and in all randomized patients	OS in PD-L1 TC≥1% and in FAS
To assess patient-reported symptoms, functioning, and HRQoL in patients treated with durvalumab compared to placebo	Change from baseline and time to deterioration in EORTC QLQ-C30 and EORTC QLQ-LC13
To investigate the relationship between a patient's baseline PD-L1 TC expression and efficacy of study treatments	IHC analysis of PD-L1 TC expression and spatial distribution within the tumor microenvironment relative to efficacy outcomes (ie, DFS, OS)
To assess the efficacy of durvalumab monotherapy to clear ctDNA compared to placebo	ctDNA endpoints, as defined by: • Best overall clearance rate (number converted at any time) • Best confirmed clearance rate (as above but confirmed at subsequent visit) • Time to ctDNA clearance • Duration of ctDNA clearance • Time to ctDNA recurrence • Time to confirmed ctDNA recurrence • Changes in variant allele frequencies (VAF) following treatment
To assess the relationship between treatment effect on DFS and treatment effect on ctDNA endpoints	ctDNA endpoints (as defined above) and DFS

Table 7 Study objectives and endpoints/variables

To assess the association of TMB with efficacy of durvalumab compared with placebo, and other biomarker subpopulations	DFS, OS, and other efficacy endpoints in patients according to TMB in subpopulations including, but not limited to, PD-L1 TC≥1%, ctDNA endpoints, etc.
To investigate biomarkers in tumor and periphery at baseline, on treatment, post-treatment and/or at recurrence wherever feasible to identify markers related to disease, mechanism of action of the drug and/or their associations with response and clinical endpoints.	Exploratory markers, which may include, but are not limited to: tumor, immune, and/or stromal cell gene and protein expression profiles within the peripheral and tumoral compartments. TMB and somatic mutations in tissue and/or blood/plasma. Changes in RNA, DNA or protein Attributes of tumor microenvironment that could be assessed using various methods which may include, but not limited to, high content imaging, multiplex RNA/DNA/protein analysis with spatial resolution such as Mass Spec or other technologies.
To evaluate patient-reported treatment-related symptoms using PRO-CTCAE To assess the patient´s global impression of symptoms severity, and global treatment tolerability	Pre-specified items on the PRO-CTCAE Patient global assessments
To explore the impact of treatment and disease	CCI , descriptor, and VAS
To assess alternative methodologies for determining MRD	MRD determinations in screened patients
To assess prognostic value of ctDNA quantification at baseline	ctDNA quantification vs binary MRD classification (+/-) to DFS and other efficacy endpoints
To assess prognostic value of MRD classification by comparing outcomes of randomized (MRD+) placebo-treated patients to those of patients in surveillance and/or observation	• MRD status as determined at screening and various timepoints post-surgery/curative intent therapy • DFS and other efficacy endpoints • Time from surgery to DFS • Site of relapse • Second primary NSCLC

AE Adverse event; ctDNA Circulating tumor DNA; DFS Disease-free survival; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; EORTC QLQ-LC13 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items; CCI , 5 Level health state utility index; FAS Full analysis set; HRQoL Health-related quality of life; ICU Intensive care unit; MRD Minimal residual disease; NSCLC Non-small cell lung cancer; OS Overall survival; PD-L1 Programmed cell death ligand 1; PD-L1 TC≥1% Expression of PD-L1 on tumor cell membrane, at any intensity, in ≥1% of tumor cells; PFS Progression-free survival; PRO-CTCAE Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; RECIST Response Evaluation Criteria in Solid Tumors; RNA Ribonucleic acid; TC Tumor cells; CCI ; TMB Tumor mutational burden; CCI ; VAS Visual analog scale.

4 STUDY DESIGN

From CSP v2.0 implementation at site, please use Section 10 as a reference point for the study. This study has closed enrolment early (with a total of 416 patients having signed informed consent) and patients will either start open-label durvalumab or be discontinued from the study.

The section below refers to the original study design. Microbiome analysis has been removed and the end of study definition section has been amended. Refer to Section 10.1 for the rationale for changes under CSP v2.0.

4.1 Overall design

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 Objectives and Endpoints.

This is a Phase III, randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and safety of durvalumab adjuvant therapy compared to placebo in patients with stage II-III NSCLC who have undergone curative intent therapy (complete resection ± neoadjuvant and/or adjuvant therapy), who have no evidence of RECIST 1.1-defined disease recurrence, and who become MRD+ during a 96-week surveillance period.

The study will screen approximately 1500 patients and randomize approximately 284 MRD+ patients with stage II-III NSCLC (according to IASLC Staging Manual in Thoracic Oncology v8.0) (select Stage IIIB [T3N2 or T4N2] patients) whose tumors are *EGFR* and *ALK* wild type, and who have completed curative intent therapy. The study will be conducted in approximately 250 centers globally.

This study requires mandatory genetic testing. During the first screening, WES is performed on the patient's resected tumor tissue and derived tumor-specific DNA variants are identified by removing background germline variants, determined by WES of the patient's whole blood sample. A personalized panel is then created, comprised of up to 50 of the patient's tumor variants present at a high frequency. This panel is then used to identify the presence of these tumor-specific variants on DNA extracted from the patient's plasma. The patient is considered MRD+ if the panel detects patient-specific tumor variants.

Resected tumor tissue collected during the first screening will be evaluated for *EGFR/ALK* and programmed death ligand-1 (PD-L1) expression by a central reference laboratory. Patients whose tumor tissue tests positive for *EGFR* mutations and/or *ALK* translocations will be excluded from the study. In addition, PD-L1 status must be known prior to, and is required for, randomization.

- ***Note**:* Results from local *EGFR/ALK* testing of either a pre-surgery biopsy or the resected tumor tissue performed as part of SoC may be used for this study, provided testing was performed using a well-validated, local regulatory-approved kit.

Eligible patients will be enrolled in a 96-week surveillance period during which they will be monitored for the emergence of MRD. During surveillance, the patient will be assessed for MRD by plasma sampling every 6 weeks (q6w±3d) and will receive CT scans every 12 weeks (q12w±1w) for up to 96 weeks.

Patients with evidence of RECIST 1.1-defined disease recurrence using Investigator assessments during the surveillance period will not be eligible for randomization and will no longer be followed as part of the study; however, data pertaining to their recurrence must be captured.

Patients who become MRD+ during surveillance (including cases where analysis of the first plasma sample collected [marking the start of surveillance] returns an MRD+ status) will undergo a second screening period, initiated by the signing of ICF2a (Table 2). **Note:** Patients who received prior neoadjuvant immunotherapy **must** be MRD- based on analysis of the first plasma sample collected (which marks the start of surveillance).

Patients should sign ICF2a as soon as their MRD+ result is available and immediately enter the second screening period. To ensure the duration of the second screening period is as short as possible, and to prevent any unforeseen delays in scheduling necessary scans, the Investigator should proactively schedule CT and/or MRI scans of the chest/abdomen and brain within 2 weeks following each q6w plasma collection. Thus, the baseline scans necessary to confirm eligibility will already be scheduled if testing of the plasma sample returns an MRD+ status.

Once all additional inclusion and none of the exclusion criteria are met, patients will be eligible for randomization. Patients must be randomized as soon as possible after eligibility criteria are confirmed, and treatment **must** begin within 3 days of randomization (Table 2).

Approximately 284 MRD+ patients will be randomized 1:1 to treatment with durvalumab monotherapy 1500 mg or placebo every 4 weeks (q4w) intravenously (IV). Patients will be treated for up to a total of 24 months (26 cycles), until disease recurrence, or until other specific treatment discontinuation criteria are met (whichever comes first). This study will be fully blinded.

Based on internal Sponsor data from stage II-III resected patients, it is estimated that CCI of randomized patients will be PD-L1 TC≥1%. To ensure that the target of CCI PD-L1 TC≥1% patients are randomized in the study, enrollment of PD-L1 TC<1% patients into surveillance will end once CCI PD-L1 TC<1% patients have been randomized. The remaining PD-L1 TC<1% patients will be immediately withdrawn from surveillance. Additional data will not be collected on these patients. Patients who are determined to be PD-L1 TC<1% during the first screening will not be eligible to continue to surveillance

and will be considered screen failures (see Section 5.5). Please note that any PD-L1 TC <1% patient who is already in the observation arm will remain in the study.

Similarly, enrollment into the study will end once 284 MRD+ patients are randomized. Patients in surveillance will be immediately withdrawn from the study and additional data will not be collected on these patients. Please note that patients already in the observation arm will remain in the study.

Note: In the event the Sponsor withdraws patients from surveillance because the applicable cohort(s) have been filled, these patients may continue to receive CT scans every 12 weeks until 96 weeks have elapsed (relative to the start of surveillance) to honor the patient's consent to q12w scans or until disease recurrence or primary DFS analysis (whichever occurs first). No additional data will be collected on these patients.

Up to 142 of the patients who complete their 96-week surveillance period, remain MRD-, and have no evidence of RECIST 1.1-defined disease recurrence may be eligible for entry into an observation period initiated by the signing of a separate informed consent (ICF2b; Table 4). These patients will be followed for SAEs, DFS, OS, subsequent anticancer therapy, and MRD assessments for 24 months or until completion of the study (whichever occurs first). Patients who complete 24 months of observation will be followed for OS until the end of the study. Data from this cohort of patients will be compared to the patients randomized to placebo to support the hypothesis that MRD can be used as a prognostic biomarker to identify patients at high risk of disease recurrence prior to radiologic evidence of disease.

Efficacy assessments of the primary endpoint of DFS will be derived using Investigator assessments according to RECIST 1.1 and pre-specified definitions of disease recurrence (ie, local or regional recurrence, distant recurrence, second primary NSCLC) and by survival assessments. All randomized patients and patients in the observation arm will be followed for disease recurrence until the primary DFS analysis and followed for safety and survival until the completion of the study. Disease evaluations utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including liver and adrenal glands) collected during screening/baseline and at selected timepoints during the study duration. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients

An IDMC comprised of independent experts will meet approximately 12 months after the first patient has been dosed with IP or after approximately 50 patients have received at least 1 dose of IP (whichever occurs first) to assess the safety and tolerability of durvalumab, and will report back to the Sponsor. The timing of subsequent reviews will be determined by the IDMC but will not occur more frequently than every 6 months. Full details of the IDMC procedures will be specified within the IDMC Charter. The IDMC safety reviews will be conducted in an unblinded manner. Scientific rationale for study design

4.1.1 Overall rationale and study population

For patients with stage II-III disease, surgery and adjuvant SoC chemotherapy per National Comprehensive Cancer Network and European Society for Medical Oncology guidelines results in 5-year DFS rates of only ~40% (Wakelee et al 2017). Improvement in clinical outcomes may be achieved through the early identification of patients at high risk for recurrence and combined treatment of immunotherapy and SoC chemotherapy. Identification of high-risk patients may be achieved by monitoring patients for MRD for 96 weeks after completion of curative intent therapy.

The 96-week surveillance period was selected based on 5-year DFS data across historic adjuvant studies (ANITA [Douillard et al 2006], BLT [Waller et al 2004], E1505 [Wakelee et al 2017], IALT [Arriagada et al 2004], JBR.10 [Winton et al 2005]) in which DFS events were observed to be highest in years 1 and 2 and then plateaued. Data available to the Sponsor estimates a lead-time of CCI days from MRD detection to measurable disease in an untreated patient population (CCI unpublished data). Taken together, these data suggest a 96-week surveillance strategy would be expected to capture ~82% of patients who suffer NSCLC recurrence post-operatively. Based on an estimated CCI tumor doubling time at NSCLC recurrence, q6w plasma sampling for MRD assessments should capture approximately CCI of tumors at a volume of CCI, the approximate volume limit-of-detection associated with the personalized MRD assay being leveraged in this study.

The stratification factors of PD-L1 status (TC <1% vs TC ≥1%), time from start of surveillance to emergence of MRD (≤6 months vs >6 months), and prior neoadjuvant immunotherapy (Yes vs No) were chosen to mitigate the risk of imbalance of known or potential prognostic factors across treatment arms. PD-L1 status was chosen based on the established prognostic differences of PD-L1 expression with IO monotherapy agents (Spigel et al 2019, Mok et al 2019, Reck et al 2016, Reck et al 2019). A previous study in NSCLC demonstrated that PFS was significantly improved for patients treated continuously with immunotherapy versus those whose treatment was interrupted and re-started (Spigel et al 2017). Therefore, prior neoadjuvant immunotherapy was selected as a stratification factor as patients who receive neoadjuvant immunotherapy may be less likely to respond to additional immunotherapy in the adjuvant setting. Data internally available to the Sponsor suggest that emergence of MRD following curative therapy follows an exponential distribution. Assuming an exponential distribution, the median time from surgery to becoming MRD+ would be approximately CCI. Based on these data and taking into account the typical 3-month duration of adjuvant therapy, the length of time from the start of the surveillance period to becoming MRD+ will be stratified using a ≤6 months vs >6 months cut-off. Phenotypic differences may also be elucidated between patients who become MRD+ shortly after completing curative intent therapy (ie, those with residual disease refractory to SoC curative therapy) compared to patients who become MRD+ many months after (ie, those who initially responded to SoC curative therapy and then develop recurrent disease).

4.1.2 Study design

In order to avoid bias, the study will be randomized and double-blind.

4.1.3 Primary and secondary outcome measures

The primary efficacy endpoint of this study is DFS in the PD-L1 TC≥1% analysis set. DFS (see Section 9.4.1.1 for full definition), which represents a direct measure of the IP's efficacy. Historical data have shown that the DFS benefit seen with the use of adjuvant chemotherapy in this disease setting was consistent with an improvement in the OS outcome, which suggests an association between these 2 endpoints in this setting (Mauguen et al 2013). DFS has been the primary basis of approval for adjuvant breast cancer hormonal therapy, adjuvant colon cancer therapy, and adjuvant cytotoxic breast cancer therapy. The study is sized for the PD-L1 TC≥1% population, as PD-L1 is the most established predictive biomarker for immune checkpoint inhibitors (see Section 2.2.3.1). However, DFS in all patients will be evaluated as a secondary outcome.

OS, which also represents a direct measure of efficacy, is routinely used on oncology trials and will also be evaluated as a non-powered, secondary outcome.

The secondary objective of disease-related symptoms and overall health-related quality of life (HRQoL), assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30), version 3 (QLQ-C30 v3), and the complementary 13-item Lung Cancer Quality of Life Questionnaire (QLQ-LC13). These PRO questionnaires are well established instruments that have been previously included in cancer clinical studies.

The safety and tolerability of each study treatment will be assessed by the standard safety endpoints including AEs, SAEs, laboratory abnormalities, and vital signs.

4.1.3.1 Rationale for exploratory endpoints

Biomarkers to be assessed are justified on the basis that they may identify subpopulations most likely to derive clinical benefit from therapy (predictive biomarkers); to rapidly identify subjects most likely to experience clinical benefit after treatment has started (early efficacy biomarkers); and to assess target engagement and/or mechanism of action (pharmacodynamic biomarkers) to support dosing, understanding of the therapeutic index, and/or potential future combination therapies. Biomarkers may include, but are not limited to, PD-L1 TC expression; tumor, immune, and stromal cell gene and protein expression profiles; and genomic analyses such as tumor mutational burden (TMB).

Although ctDNA is an emerging biomarker, the endpoint has significant capability for diagnosis and has already demonstrated utility at various levels of disease staging and management (De Rubis et al 2018, Wills et al 2018). Limitations in using ctDNA as an endpoint include detection sensitivity in early cancers, predictability in diseased individuals versus healthy individuals, and quality aspects due to processing time (De Rubis et al 2018). However, given the supporting literature and regulatory landscape, the

proposed primary and secondary endpoints are aligned with existing clinical trials and justified by the expected clinical benefits, and ctDNA clearance will be assessed as an exploratory outcome.

CCI

Patients who remain MRD- through their 96-week surveillance period and have no evidence of RECIST 1.1-defined disease recurrence may be eligible for entry into an observation period initiated by the signing of a separate informed consent (ICF2b; Table 4). Data from this observation cohort will be compared to data from randomized placebo-treated patients to support the hypothesis that MRD can be used as a prognostic biomarker to identify patients at high risk of disease recurrence prior to radiologic evidence of disease.

4.2 Justification for durvalumab dose

4.2.1 Durvalumab monotherapy dose

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).

4.2.1.1 PK/Pharmacodynamic data

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

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUCss (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be

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

Given the similar area under the serum drug concentration-time curve and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w. This dose has been used in multiple studies previously with no safety concern.

4.2.1.2 Clinical data

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

4.2.1.3 Rationale for fixed dosing

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

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

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

4.3 End of study definition

From CSP v2.0 implementation at site, please use Section 10 as the reference point for the study. Refer to Section 10.3.3 for the updated end of study definition for CSP v2.0.

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 or for any other reason.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, randomized patients (including those currently receiving treatment with durvalumab and those in follow-up) 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 and/or follow-up 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 form.

See Sections 8.3.13 and 10.3 for details regarding data collection on randomized patients.

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

5 STUDY POPULATION

Note for CSP v2.0: Enrolment is closed as of 25May2022 and no patients will be randomized following implementation of this amendment at site.

Section 5.3 remains in effect for the patients who receive durvalumab during open-label or double-blind treatment and up to 90 days after the last dose.

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

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to Section 5.5.

In this protocol:

- "**Enrolled**" patients are defined as those who sign ICF1.
- **"Patients in surveillance"** are defined as those who have successfully completed the first screening and have had at least one plasma sample collected for MRD testing but are not randomized nor in observation.
- "**Randomized**" patients are defined as those who sign ICF2a, complete the second screening period, undergo randomization, and receive a randomization number.

- "**Patients in observation**" are MRD- patients who remain MRD- during their 96-week surveillance period and who have no evidence of RECIST 1.1-defined disease recurrence. These patients have signed ICF2b and entered the observation cohort.

For procedures for withdrawal of incorrectly enrolled subjects see Section 6.2.2 and Section 7.3.

5.1 Inclusion criteria

This study will employ a tiered informed consent and screening process.

Table 1 summarizes the study procedures and assessment during the first screening period and surveillance. Sites should review the appropriate inclusion and exclusion criteria summarized in Table 5 and Table 6 to confirm the patient's eligibility prior to signing ICF1 and entering surveillance.

Patients who are MRD+ at the start of surveillance or become MRD+ during their 96-week surveillance period may be eligible to enter the second screening period. If all additional inclusion and none of the exclusion criteria are met, these MRD+ patients may be randomized to treatment with IP. Table 2 includes the study procedures and assessment during the second screening period and randomization, and Table 5 and Table 6 summarize the inclusion and exclusion criteria, respectively, that are applicable to this period.

Up to 142 of the patients who remain MRD- during their 96-week surveillance period and have no evidence of RECIST 1.1-defined disease recurrence may be eligible to sign a separate ICF (ICF2b) and enter an observation period. Table 4 outlines the assessments during observation.

Some criteria will need to be checked during both screening periods and/or prior to entering observation. Subjects are eligible to be included in the study only if all of the following inclusion criteria at the indicated times and none of the exclusion criteria apply:

Informed consent

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

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

ICF1 must be signed and dated prior to initiation of the first screening and surveillance activities outlined in Table 1.

ICF2a must be signed and dated prior to initiation of the second screening activities and randomization outlined in Table 2.

ICF2b must be signed and dated prior to initiation of the study-specific observation period and procedures outlined in Table 4.

3 Provision of signed and dated written **optional** genetic informed consent prior to collection of the optional sample for genetic analysis. This consent should be signed at the time of second screening. This optional sample and analyses are separate from the mandatory genetic testing consent included in ICF1.

The ICF process is described in Appendix A 3.

5.1.1 Inclusion criteria assessed during the first screening period

The following criteria must have been met at the time of surgery or at the time of the curative intent therapy (first screening):

Age

4 Age ≥18 years at the time of screening (ICF1).

Sex

5 Male and/or female.

Type of subject and disease characteristics

6 Histologically confirmed NSCLC with resectable stage II-III disease (according to IASLC Staging Manual in Thoracic Oncology v8.0) who have undergone curative intent therapy (complete resection of the primary tumor ± neoadjuvant and/or adjuvant therapy) per SoC.

Select stage IIIB (ie, T3N2 or T4N2) patients will be eligible, provided they are upstaged to T3N2 or T4N2 based on confirmed pathology after surgery. Patients who are staged as T3N2 or T4N2 prior to surgery are not eligible.

7 A contrast-enhanced CT/MRI scan of the chest and abdomen (including liver and adrenal glands) along with brain MRI (preferred) or brain CT with IV contrast must have been done for surgical planning prior to surgery. It is recommended that patients undergo combined FDG-PET (^{18}F-Fluoro-deoxyglucose positron emission tomography) and CT scan (computerized tomography) within the 6 weeks prior to surgery in order to rule out detectable extrathoracic, extracranial metastasis and to assess for potential mediastinal lymph node involvement prior to surgery. If the positron emission tomography (PET) scan was not performed, or data from a PET is not available, patients may still be enrolled into the study provided appropriate imaging (CT/MRI) is performed prior to randomization.

8 Complete resection of the primary NSCLC is mandatory. Invasive (pre-operative or intra-operative) exploration of hilar and mediastinal lymph nodes must have been performed to confirm primary tumor nodal status (prior to or after surgery). Surgical resection of the primary NSCLC can occur by open thoracotomy or by video-assisted thoracic surgery (VATs) and resection can be achieved by segmentectomy, lobectomy, sleeve resection, bilobectomy or pneumonectomy. Patients undergoing wedge resection are not eligible for this study.

Note: Where a resection has been extended by means of a wedge resection of an adjacent lobe to ensure complete resection of a tumor at or crossing a fissure between lobes, this is acceptable if surgical margins are clear of disease. Where the resection of a second tumor nodule (eg, a T4 lesion) is undertaken by means of a wedge resection of a separate lobe, then the patient is not eligible.

Note: Carcinoma-in-situ can be present at the bronchial margin.

Criteria for prior systemic chemotherapy/radiotherapy:

9 Patients should have completed (or be undergoing) curative intent therapy (surgery ± neoadjuvant and/or adjuvant therapy; adjuvant therapy can include PORT) with exceptions noted below:

Patients who discontinue chemotherapy and/or PORT for toxicity prior to completion of all planned therapy are eligible.

Patients who have not received any neoadjuvant and/or adjuvant chemotherapy, and meet all other eligibility criteria, may be eligible under the following circumstances:

- All patients who are eligible for adjuvant chemotherapy MUST be offered adjuvant chemotherapy.
- The patient has declined adjuvant chemotherapy, and in the opinion of the Investigator, this is the patient's final decision after receiving appropriate information and adequate time to make the decision. The patient's refusal of adjuvant chemotherapy must be documented**.**
- If in the view of the Investigator, adjuvant chemotherapy is contraindicated due to an underlying intercurrent illness/laboratory abnormality, which is not considered reversible within a reasonable timeframe for the patient to be eligible for adjuvant therapy, which must be documented.

Criteria assessed prior to and at the start of surveillance:

10 Confirmation of suitable biosamples for WES and central PD-L1 testing. Resected tumor tissue and whole blood samples must be provided to the diagnostic laboratory for WES of tumor and germline DNA, respectively as soon as possible following pathology confirmation. Samples must be sent no later than 1-2 weeks after completion of adjuvant therapy or 3-5 weeks after surgery (if no adjuvant therapy is given) for development of the Sponsor-approved personalized panel for MRD detection at a central reference laboratory. Germline sequencing of whole blood is **mandatory**. Resected tumor tissue must also be provided for PD-L1 testing at a central reference laboratory (see inclusion criteria 15).

11 Post-adjuvant therapy or post-surgery (if no adjuvant therapy is given) CT scan of the chest and abdomen (including liver and adrenal glands) and brain MRI [preferred] or brain CT with IV contrast should be available to confirm no evidence of metastasis. If

scans were not performed post-curative intent therapy, additional scans must be done prior to start of surveillance.

12 Consents to be accessible for q6w±3d plasma sample collection for MRD evaluation and for q12w±1w CT scans during the 96-week surveillance period.

13 The plasma sample that marks the start of surveillance must be collected 8±1 weeks after completion of adjuvant therapy (if administered) or 12±1 weeks after surgery (where adjuvant therapy is not given).

- A patient who is determined to be MRD- based on analysis of this plasma sample (ie, MRD- at the start of surveillance) may continue in surveillance provided all other eligibility criteria are met.
- A patient who is determined to be MRD+ based on analysis of this plasma sample (ie, MRD+ at the start of surveillance) may be eligible for immediate randomization provided all other eligibility criteria are met.
    - **Note:** In order for a patient who received prior neoadjuvant IO immunotherapy to continue in the study, they **must** be MRD- based on analysis of this plasma sample (ie, **must** be MRD- at the start of surveillance).

A patient who becomes MRD+ *during* surveillance is eligible to enter the second screening period and may be randomized in the study if all other eligibility criteria are met.

5.1.2 Inclusion criteria assessed during the second screening period

Criteria for second screening prior to randomization to treatment:

14 CT scan of the chest and abdomen (including liver and adrenal glands) and brain MRI [preferred] or brain CT with IV contrast performed within the 28 days ± 7 days **prior to randomization** to confirm no evidence of RECIST 1.1-defined disease recurrence and/or metastasis.

15 Known tumor PD-L1 status determined at a central reference laboratory testing service using a validated Ventana SP263 PD-L1 immunohistochemistry (IHC) assay prior randomization. Patients with unknown PD-L1 status are not eligible for the study.

16 WHO/Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.

17 Complete post-operative wound healing must have occurred prior to randomization; patients must have recovered from all acute, reversible toxic effects from prior treatments (excluding alopecia) that could potentially adversely impact further administration of durvalumab/placebo according to the Investigator's judgment.

18 Must have recovered from all acute, reversible toxic effects from chemotherapy that could potentially adversely impact further administration of durvalumab or placebo according to the Investigator's judgment

19 Adequate organ and marrow function 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 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.

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

Measured creatinine clearance (CL) ≥30 mL/min or Calculated CL >30 mL/min as determined by Cockcroft-Gault (using actual body weight)

Males:

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

Females:

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

20 Must have a life expectancy of at least 12 weeks

Weight

21 Body weight >30 kg

5.1.3 Inclusion criteria assessed prior to entering the observation period

22 No evidence of RECIST 1.1-defined disease recurrence or metastasis confirmed by CT scan of the chest and abdomen (including liver and adrenal glands) and a brain MRI (preferred) or brain CT with IV contrast.

23 MRD- status, as determined by testing the last plasma sample collected during the 96-week surveillance period.

5.2 Exclusion criteria

These exclusion criteria must be checked during first and/or second screening periods, as summarized in Table 6. If a patient meets an exclusion criterion at one of these timepoints, the patient is ineligible to continue in the study.

Diagnostic assessments

1 *EGFR* and/or *ALK* mutant as assessed either from the tumor biopsy taken prior to surgery or the resected tumor tissue. Testing must be performed using a well-validated, local regulatory-approved test. *EGFR/ALK* may be tested centrally if local testing is unavailable.

2 Mixed small cell and NSCLC histology.

3 Require re-resection or are deemed to have unresectable NSCLC by a multidisciplinary evaluation that must include a thoracic surgeon who performs lung cancer surgery as a significant part of their practice.

4 Baseline imaging demonstrating unequivocal evidence of RECIST 1.1-defined disease recurrence or evidence of clinical recurrence outside of imaging prior to randomization. In the event of lymphadenopathy on imaging that would lead to exclusion, histopathological confirmation of lymph node metastasis should be obtained prior to excluding a patient from the study. If pathological confirmation of lymph node metastasis is not technically feasible and imaging appearance are deemed unequivocal for relapse, the patient will be excluded.

Medical conditions

5 History of allogeneic organ or bone marrow transplantation.

6 Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection

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

Patients with vitiligo or alopecia

Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement

Any chronic skin condition that does not require systemic therapy

Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician

Patients with celiac disease controlled by diet alone

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

9 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

Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

Adequately treated carcinoma in-situ without evidence of disease

10 History of active primary immunodeficiency

11 Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B virus (HBV)** (known positive HBV surface antigen (HBsAg) result), **hepatitis C virus (HCV)**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

12 Known allergy or hypersensitivity to any of the IPs or any of the IP excipients

Prior/concomitant therapy

13 Received any IO therapy in the adjuvant setting or any prior exposure to durvalumab.

14 Received any radiotherapy in the neoadjuvant setting.

15 Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

16 Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of IP.

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

18 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP.

19 Current or prior use of immunosuppressive medication within 14 days 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

20 Previous IP assignment in the present study

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

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

Other exclusions

23 Female patients who are pregnant or breastfeeding.

- Female patients who become pregnant during the study will be withdrawn from surveillance and are not eligible for randomization.

24 Male or female patients of reproductive potential who are not willing to employ effective birth control at the time of entry into second screening (initiated with the signing of ICF2a) until 90 days after the last dose of IP (See Appendix H).

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

5.3 Lifestyle restrictions (to be observed up to 90 days after last dose of durvalumab)

Note for CSP v2.0: these restrictions remain for patients who start or continue durvalumab treatment.

The following restrictions apply while the patient is receiving IP and for the specified times before and after. **These restrictions do not apply to patients during the surveillance or observation periods.**

1 Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly.) Women of childbearing potential must agree to use one highly effective method of birth control. They should have been stable on their chosen method of birth control for a minimum of 3 months before randomization to 90 days the last dose (see Appendix H for complete list of highly effective birth control methods). Non-sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period.

2 Non-sterilized male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Appendix H) from the time of screening throughout the total duration of the study and the drug washout period (90 days after the last dose of study intervention) to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period.

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

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

5.4 Information regarding patients previously enrolled in MERMAID-1 (D910LC00001)

Patients may be entering this study (MERMAID-2; D910MC00001) after they were screen failed for another durvalumab study (ie, MERMAID-1; D910LC00001). These patients may have received chemotherapy in the time between screen-failing MERMAID-1 and enrolling in MERMAID-2.

Samples and data collected during the first screening for MERMAID-1 may be used for MERMAID-2 if the patient provides consent.

If a patient's personalized panel for MRD detection has already been created during screening for MERMAID-1, it may be possible for that panel to be used for this study. A patient with an existing Sponsor-approved personalized panel for MRD detection must sign ICF1 for MERMAID-2 (D910MC00001) prior to the use of their panel and associated MRD data in this study.

If a patient's *EGFR/ALK* status was determined during screening for MERMAID-1, those results may be used for this study provided a well-validated, local regulatory-approved kit was used. Similarly, if a patient's PD-L1 status was previously determined at a central reference laboratory during screening for MERMAID-1, that test does not need to be repeated, provided a validated SP263 assay was used. Patients must sign ICF1 for MERMAID-2 to allow the Sponsor retrospective access to these results.

5.5 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not enter the surveillance period (if eligibility during the first screening is not met) or must not be randomized (if eligibility during the second screening is not met). 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 may not be rescreened or re-randomized in this study. The reason for screen failures will be captured in the appropriate section of the electronic case report form (eCRF).

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. In addition, surgical history, scans and imaging data, and the date of disease recurrence will also be collected on screen failed patients.

See Table 1 in the SoAs and Section 8.2.2 for additional details on information that should be collected for patients who participate in the first screening period and surveillance of this study (initiated by signing ICF1).

6 STUDY TREATMENTS

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to durvalumab (supplied as either double-blind or open-label) or placebo.

Note for CSP v2.0: Placebo will no longer be administered to patients following implementation of this amendment at the study site.

From implementation of CSP v2.0 at site, preparation, storage, and administration of open-label durvalumab should occur as per durvalumab instructions in Sections 6.1, 6.3, and 6.4 (unless otherwise indicated in Section 10). Refer to Section 10 regarding the eligibility and duration of open-label durvalumab treatment, as well as required assessments during the treatment.

6.1 Treatments administered

6.1.1 Investigational products

From implementation of CSP v2.0 at site, AstraZeneca will supply open-label durvalumab only.

The original study treatments are described in Table 8.

Table 8 Study treatments

Study treatment name:	Durvalumab	Placebo
Dosage formulation:	500 mg vial solution for infusion after dilution, 50 mg/mL	Vial solution for infusion after dilution
Route of administration	IV	IV
Dosing instructions:	1500 mg infusion over 60 min q4w.[a,b] See Section 6.1.1 for specific instructions for preparing and storing IP.	Infusion over 60 min q4w.[a,b] See Section 6.1.1 for specific instructions for preparing IP.
Packaging and labeling	Study treatment will be provided in 500 mg vials. Each 500 mg vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.[c]	Study treatment will be provided in vials. Each vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.
Provider	AstraZeneca	AstraZeneca

[a] If a patient's weight falls to 30 kg or below while on treatment, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo q4w after consultation between Investigator and Study Physician until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab or placebo 1500 mg q4w.
[b] See Section 6.1.1 for specific instructions for preparing and storing durvalumab and placebo
[c] Label text prepared for durvalumab (MEDI4736) 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.
GMP Good Manufacturing Practice; IP Investigational product; IV Intravenous; q4w Every 4 weeks.

Durvalumab and placebo will be supplied by AstraZeneca as vial solutions for infusion after dilution. Durvalumab will be supplied as a 500 mg vial containing 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL.

Placebo will be supplied as a vial containing CCI histidine/histidine hydrochloride, CCI trehalose dihydrate, and CCI polysorbate 80; it has a pH of 6.0. The nominal fill volume for durvalumab and placebo is 10.0 mL.

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

Durvalumab and placebo vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab and placebo should be kept in original packaging until use to prevent prolonged light exposure.

Preparation of investigational product doses for administration with an IV bag

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

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature
- If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

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

If participant weight falls to ≤30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag size selected such that the final concentration is within 1 to 15 mg/mL.

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

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

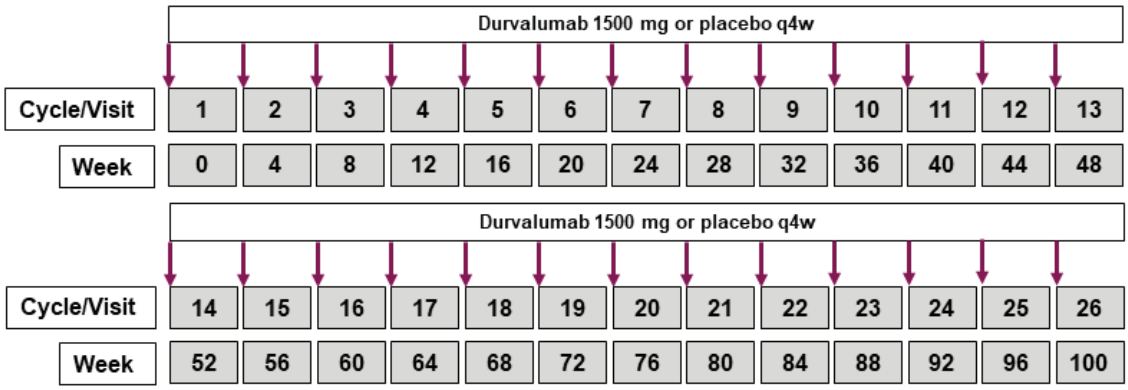
The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

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

6.1.2 Dosage and treatment regimens

The full dosing scheme by treatment arm throughout the 24-month treatment period is shown in Figure 3 and described in the following sections.

Figure 3 Dosing scheme



q4w Every 4 weeks.

6.1.2.1 Durvalumab or placebo

Patients will receive 1500 mg durvalumab or placebo via IV infusion q4w unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Figure 3. (Please note, if a patient's weight falls to 30 kg or below (≤30 kg) during the treatment period the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo q4w after consultation between Investigator and Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab or placebo 1500 mg q4w).

6.1.3 Duration of treatment

Note for CSP v2.0: See Section 10.3.1 for the duration of open-label durvalumab treatment.

All treatment will be administered beginning on Day 1 for up to 26 cycles (up to a total of 24 months) of durvalumab or placebo q4w, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Treatment will be stopped when a patient has received a total of 24 months of therapy (26 cycles of treatment) or upon evidence of RECIST 1.1-defined disease recurrence using Investigator's assessments, whichever occurs first.

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined disease recurrence may continue to receive study treatment at the discretion of the Investigator until the follow-up scan.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due

to tumor compression, or spinal cord compression) will not be eligible for continuing durvalumab or placebo.

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

Patients may not receive retreatment in this study.

Post data cut-off

This section is no longer applicable following implementation of CSP v2.0 at site.

After the primary DFS analysis, the study will be unblinded and AstraZeneca will continue to supply open-label drug to patients receiving durvalumab monotherapy up to completion of a patient's 24-month treatment period (26 cycles of treatment). Investigators should continue to monitor and document data for all study patients in the database after scheduled DCO and database lock (DBL) for the primary DFS analysis. Scheduled visits as described in Table 2, Table 3, and Table 4 should be followed and data will be collected on all randomized patients (including patients in follow-up) and patients in observation until final DCO. Depending on the analysis results, a decision may be made to continue further data collection for a longer period with intent to analyze long-term DFS and safety data to fulfill any other potential Health Authority requirements.

Following DBL for primary DFS analysis, efficacy scans will be collected in accordance with local practice.

In the event that a roll-over or safety extension study is available at the time of the DCO for primary DFS analysis, randomized patients (including those currently receiving treatment with durvalumab and those in follow-up) and patients in observation 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 and/or follow-up 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 form.

Safety, subsequent therapy, and survival data will continue to be collected after the final DCO until any of following conditions are met:

- Remaining patients have been transferred into a roll-over study OR
- All patients receiving durvalumab monotherapy have completed their 24-month treatment period (26 cycles of treatment).

6.1.4 Storage

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

6.2 Measures to minimize bias: randomization and blinding

This section is not applicable following implementation of CSP v2.0 at site. Refer to Section 10 for updated unblinding instructions for CSP v2.0.

6.2.1 Patient enrollment and randomization

All patients will be centrally assigned to randomized study treatment using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

If a patient withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

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

This study will use a tiered consent process. The signing of ICF1 will initiate the first screening, which includes mandatory genetic testing and development of the personalized panel for MRD detection, as well as procedures conducted during the surveillance period (Table 1). The signing of ICF2a will initiate the second screening procedures (which includes confirmation of final eligibility) followed by the treatment and follow-up periods (Table 2). ICF2b will cover the observation period for patients who remain MRD-throughout their 96-week surveillance period; study procedures and assessments for the observation period are outlined in Table 4.

- ***Note:*** The time between signing ICF1 and ***either*** ICF2a or ICF2b may be up to 96 weeks.

At the first screening period and prior to start of surveillance, the Investigators or suitably trained delegate will:

- Obtain signed ICF1 before any study-specific procedures (outlined in Table 1) are performed.
- Obtain a unique 7-digit enrollment number (E-code), through the IWRS in the following format (ECCNNXXX: CC being the country code, NN being the center

number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the eCRFs.

- Determine patient eligibility for entry into the surveillance period based on the criteria outlines in Table 1, Table 5, and Table 6 and Sections 5.1 and 5.2.

  NOTE: Surgery and any neoadjuvant and/or adjuvant therapy will not be considered study-specific procedures. However, patients will need to sign ICF1 to give the Sponsor access to all information related to prior therapy (including surgery) and to obtain resected tumor tissue for this study.

If a patient is determined to be MRD+ at the start of surveillance (Refer to inclusion criterion 13 [Section 5.1.1]) or during the surveillance period, they may enter the second screening period (Days -28 to -1 relative to randomization). During this second screening period, the Investigator or suitably trained delegate will:

- Obtain signed ICF2a before any study-specific procedures (outlined in Table 2) are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all second screening laboratory and imaging results required for final eligibility (specified in Table 2) must have been obtained within 28 days ± 7 days **prior to** randomization.
- Determine patient eligibility for randomization based on the criteria outlines in Table 2, Table 5, and Table 6, and Sections 5.1 and 5.2.
- Obtain signed informed consent for the **optional** genetic research study (optional).

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

- Randomize the patient in IWRS. Numbers will be assigned strictly sequentially by IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 2 treatment groups.

If the patient is ineligible and not randomized, the IWRS should be contacted to terminate the patient in the system.

Patients will begin treatment on Day 1. Treatment should start no more than 3 days after being randomized. Patients must not be randomized and treated unless all eligibility criteria have been met.

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

For details regarding MRD- patients who are withdrawn from surveillance once the study is fully randomized, refer to section 7.3.2.

6.2.2 Procedures for handling incorrectly enrolled or randomized patients

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

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

6.2.3 Methods for assigning treatment groups

The actual treatment given to patients will be determined by the randomization scheme in the 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 group.

Patients will be identified to the IWRS per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The IWRS will provide the kit identification number to be allocated to the patient at the randomization visit and subsequent treatment visits.

6.2.4 Methods for ensuring blinding

The study is being conducted in a double-blind fashion. Investigator and all study staff, study team, and Sponsor will be fully blinded to all treatment.

The IWRS will provide to the Investigator(s) or pharmacists (or a trained delegate) the kit identification number to be allocated to the patient at the dispensing visit.

Routines for this will be described in the IWRS user manual that will be provided to each center.

The randomization code should not be broken except in medical emergencies and/or when the appropriate management of the subject requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject 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. Randomization codes will not be broken for the planned analyses of

data until all decisions on the evaluability of the data from each individual subject have been made and documented.

The IWRS will provide to the Investigator and pharmacists or a trained delegate the kit identification number to be allocated to the patient at the dispensing visit. Blinded access and notifications will be controlled using the IWRS. Investigators will remain blinded to each subject's assigned study treatment throughout the course of the study.

In the event that the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study patients, or needs to be known to treat an individual patient for an AE, the Sponsor must be notified promptly by the Investigator and if possible, before unblinding.

6.2.5 Methods for unblinding the study

The IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the Investigator, it is in the patient's best interest for the Investigator to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (eg, antidote available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF. Study unblinding should not occur until DBL and all decisions on the evaluability of the data from each individual patient have been made and documented.

If the blind is broken, a patient should continue to be followed up per the SoAs outlined in Table 3.

6.3 Treatment compliance

The administration of IP should be recorded in patient source documents.

Any change from the dosing schedule, dose delays/interruptions, and dose discontinuations should be recorded in patient source documents.

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

The Investigational Product Storage Manager 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.

6.4 Concomitant therapy

6.4.1 Restrictions for patients during the first screening and surveillance periods

This section will no longer apply following CSP v2.0 implementation; patients who are in first screening and surveillance will be discontinued from the study.

Patients who have signed ICF1 and have initiated the surveillance period are prohibited from taking any anti-cancer medication.

The Investigator must be informed as soon as possible about any anti-cancer therapy taken from the time of the first screening and during the surveillance period (see Table 9).

6.4.2 Restrictions for patients during the second screening and treatment

The Investigator must be informed as soon as possible about any medication taken from the time of the second screening through 90 days following the last dose of study treatment (either blinded study treatment or open-label durvalumab) or (if the patient will not receive open-label durvalumab) until patient discontinuation from study.

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the patient is receiving at the time of enrollment or receives during the study (including treatment with open-label durvalumab and associated 90-day follow-up period) must be recorded in patient source documents along with:

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

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

Restricted, prohibited, and permitted concomitant medications are described in Table 9 and Table 10. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

Table 9 Prohibited concomitant medications

Medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment (second screening and randomization [initiated with the signing of ICF2a])
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment

Table 9 Prohibited concomitant medications

Medication/class of drug:	Usage:
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 on study treatment (second screening and randomization; initiated with the signing of ICF2a). Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable at any time in the study.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP
Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent methotrexate, azathioprine, and tumor necrosis factor –alpha blockers	Should not be given concomitantly or used for premedication prior to the IO infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 30 days after the last dose of IP
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

AE Adverse event; CTLA-4 cytotoxic T-lymphocyte-associated antigen-4; ICF Informed consent form; IO Immuno-oncologic therapy; IP Investigational Product; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1.

Table 10 Supportive medications

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

6.4.3 Other concomitant treatment

Medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the patient source notes.

For the first screening, surveillance, and exploratory observation periods, any anti-cancer medication given must be recorded in the appropriate section of the eCRF prior to patient discontinuation from the study.

For the second screening, randomization and study treatment, and follow-up periods, any concomitant medications must be reported in the appropriate section of the eCRF or (if patient has started open-label durvalumab or has discontinued the study) in patient source notes.

In the event that an SAE occurs during either the first or second screening period, the concomitant medications given for that SAE must be reported in the appropriate section of the eCRF.

6.4.4 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 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 PK 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 Dose modification

This section is not applicable following implementation of CSP v2.0 at site. Refer to Dosing Modification and Toxicity Management guidelines (Section 8.4.5).

Dose delays are permitted for IO therapy (see Dosing Modification and Toxicity Management Guidelines) (See Section 8.4.5).

The patient should receive up to 26 cycles of durvalumab or placebo, even if a dose delay causes the treatment period to extend beyond 24 months.

However, **dose reduction is not permitted**.

6.6 Treatment after the primary DFS analysis

This section is not applicable following implementation of CSP v2.0 at site.

After the primary DFS analysis, the study will be unblinded and AstraZeneca will continue to supply open-label drug to patients receiving durvalumab up to completion of a patient's 24-month treatment period (26 cycles of treatment) or the time that they discontinue the treatment for whatever reason (including roll-over to another study) (see Section 6.1.3 and 7.3).

Patients who are still receiving durvalumab at the time of primary DFS analysis should follow the scheduled visits as described in Table 2. Safety data, including safety labs, and OS should be reported and entered into the database until final DCO. Efficacy scans will be collected in accordance with local clinical practice.

Subsequent therapy and OS data will continue to be collected following the DBL for primary DFS analysis on all patients in follow-up and in observation until final DCO.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients receiving durvalumab

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

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5)
- 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
- Documented recurrence of disease (Section 8.1.1 and Appendix G text is retained in this protocol version as guidance for Investigators) or Investigator determination that the patient is no longer benefiting from treatment with IP.
- Completion of study treatment (see Section 10.3.1 for updated treatment duration details applicable following implementation of the amendment at site).

7.1.1 Procedures for discontinuation of study treatment

This section is not applicable following implementation of CSP v2.0 at site.

Randomized patients only

This section is applicable only to randomized patients who have initiated treatment with IP (ie, it is not applicable to patients in the surveillance or observation periods of the study).

At any time, patients are free to discontinue treatment without prejudice to further treatment.

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

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see the SoAs Table 3).

Patients who prematurely permanently discontinue IP prior to completing 24 months (26 cycles) of treatment for reasons other than RECIST 1.1-defined disease recurrence should continue to have scans performed q12w ±1w (relative to the date of randomization) until completion of the study or until RECIST 1.1-defined disease recurrence plus an additional follow-up scan or death (whichever comes first) as defined in the SoAs (Table 3).

If a patient is discontinued for RECIST 1.1-defined disease recurrence, then the patient should have 1 additional follow-up scan performed between 4-8 weeks after the prior assessment of disease recurrence.

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 IWRS.

7.2 Lost to follow-up

From CSP v2.0 implementation at site, please refer to Section 10 for lost to follow-up definitions for patients who receive open-label durvalumab.

All enrolled patients

The procedures in this subsection apply to all patients who participate in either the surveillance and/or observation periods of this study or who are randomized to treatment with IP.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.3), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support the secondary endpoint of OS, the survival status of all patients in the FAS and the safety analysis set (SAS) should be re-checked; this includes those patients who withdrew consent or are classified as "lost to follow-up." The survival status of all patients in the observation period should also be re-checked, including those who withdrew consent or are classified as "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.

7.3 Withdrawal from the study

7.3.1 All patients

This section remains in effect following implementation of CSP v2.0 at site.

The procedures in this subsection apply to all patients who participate in either the surveillance and/or observation periods of this study or who are randomized to treatment with IP.

Patients are free to withdraw from the study at any time (IP and/or 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, the site should review the withdraw consent checklist and specifically ask the patient if they are also withdrawing consent to the use of any already collected/donated samples (see Section 8.7.3).

7.3.2 MRD- patients who are withdrawn from surveillance by the Sponsor

This section is no longer applicable following implementation of CSP v2.0 at site.

Based on internal Sponsor data, it is estimated that CCI of randomized patients will be PD-L1 TC≥1%. To ensure that the target of CCI PD-L1 TC≥1% patients are randomized in the study, enrollment of PD-L1 TC<1% patients into surveillance will end after CCI PD-L1 TC<1% patients have been randomized to treatment. The remaining PD-L1 TC<1% patients in surveillance will no longer be tested for MRD nor included in subsequent analyses of the study.

Similarly, enrollment into the study will end once 284 MRD+ patients are randomized to treatment. The remaining MRD- patients still in surveillance will no longer be tested for MRD nor included in subsequent analyses of the study.

In both cases, patients may choose to continue to have CT scans every 12 weeks as part of the study until 96 weeks have elapsed (relative to the start of their surveillance), until evidence of RECIST 1.1-defined disease recurrence, or until the end of the study (whichever occurs first), after which they will receive SoC per local clinical practice. No

data, including OS data, will be collected on these patients after they are withdrawn from surveillance.

8 STUDY ASSESSMENTS AND PROCEDURES

From CSP v2.0 implementation at site, please use Section 10 as a reference point for the study. This study has closed enrolment early and patients will either start open-label durvalumab or be discontinued from the study.

Study assessments are clearly indicated in Section 10. Assessments and reporting of adverse events (Sections 8.3and 8.4) have been retained; these sections must be followed for AE assessments and reporting prior to patient starting open-label durvalumab treatment or discontinuing the study. Sections 8.6 and 8.7 have been retained as a reference for samples collected prior to CSP v2.0 implementation at site; please note that no additional samples will be collected from patients once they have discontinued the study or have started to receive open-label durvalumab. Sections 8.1, 8.2, and 8.5 below refer to the original study assessments and procedures; these sections are not applicable following implementation of CSP v2.0 but are included below for reference and data completion.

Study procedures and their timing are summarized in the SoAs (Table 1, Table 2, Table 3, and Table 4).

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

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

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject 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 subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of ICF1 and/or ICF2a may be

utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoAs.

8.1 Efficacy assessments

This study will evaluate the primary endpoint of DFS in the PD-L1 TC ≥1% analysis set, using Investigator assessments according to RECIST 1.1. See Section 8.1.1 for details on the assessment of DFS.

Secondary efficacy endpoints will include DFS in all patients (FAS), also using Investigator assessment according to RECIST 1.1; DFS in both the PD-L1 TC≥1% patients and the FAS using Blinded Independent Central Review (BICR) assessments according to RECIST 1.1; and PFS, CCI [redacted], CCI [redacted], and OS in both PD-L1 TC ≥1% analysis set and the FAS.

Radiological assessment of scans will be according to RECIST 1.1 guidelines (Appendix G).

A "baseline" scan of MRD+ patients must be performed within 28 days ± 7 days **prior to randomization** (Table 2). Subsequent scans are to be performed every 8 weeks (q8w±1w) from week 8-48, and then every 12 weeks (q12w±1w) until RECIST 1.1-defined disease recurrence is recorded. If an unscheduled assessment is performed and the patient has not shown evidence of disease recurrence, every attempt should be made to resume subsequent assessments according to the original imaging visit schedule. For patients who discontinue treatment due to toxicity or other reasons in the absence of RECIST 1.1-defined radiological disease recurrence, disease assessments should continue according to the schedule of assessments.

- ***Note:*** MRD- patients in surveillance will have CT scans q12w±1w for up to 96 weeks of surveillance, until they become MRD+ (and thus eligible for randomization), or until RECIST 1.1-defined disease recurrence is recorded.
- ***Note:*** For MRD- patients who enter the observation arm, scans will be performed q12w±1w for 24 months (up to 8 additional visits) or until RECIST 1.1-defined disease recurrence is recorded.

8.1.1 Disease-free survival

Disease-free survival is the primary endpoint in this study and is defined as the time from the date of randomization until any one of the following events:

- Disease recurrence
  Local, regional or distant disease recurrence
  Diagnosis of a second primary NSCLC
  OR
- Death from any cause

As DFS is the primary endpoint in this study, it is vital that it be adequately and precisely documented.

The imaging modalities used for radiological assessments will be CT scans of the chest and abdomen (including liver and adrenal glands) with contrast. In the rare case where a patient is contrast intolerant, the preferred imaging would be CT chest without contrast and MRI abdomen with contrast; however, a non-contrast abdominal CT will also be accepted. The methods used at baseline (CT or MRI) must be used at each subsequent follow-up assessments.

The "baseline" scan of MRD+ patients must be performed within 28 days ± 7 days **prior to randomization** (Table 2). Subsequent assessments are to be performed every 8 weeks (q8w±1w) until Week 48, and then every 12 weeks (q12w±1w) until RECIST 1.1-defined disease recurrence is recorded. If a patient discontinues treatment prior to disease recurrence or receives other anti-cancer treatment, patient should continue to be imaged in accordance with this schedule until disease recurrence is noted. It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit (± 7 days window interval; unscheduled assessment) and the patient has not recurred, every attempt should be made to perform the subsequent scans at their scheduled timepoints. Any other sites at which a new disease is suspected should also be appropriately imaged during the study.

8.1.1.1 Evidence of disease recurrence

Disease recurrence is defined as evidence of RECIST 1.1-defined disease recurrence on CT or MRI scan and/or pathological disease on biopsy by investigational site assessment

NOTES:

1 The finding of a new lesion should be unequivocal. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans (4-8 weeks later) definitively confirm there is a new lesion, then recurrence should be declared using the date of the initial scan where the equivocal new lesion was first identified.

2 For all patients, upon detection of definitive recurrent disease, an additional follow-up scan should be performed 4-8 weeks later. Additional scans to be completed per standard practice post progression.

3 Please refer to Appendix G for measurability and criteria for new lesions according to RECIST 1.1, and further guidance on defining disease recurrence.

4 Invasive biopsy is recommended for all cases of disease recurrence.

Recurrence will be categorized as local/regional, distant, or second primary NSCLC. When recurrence is first documented at any site, complete restaging is required to identify all sites of recurrence.

Local or regional recurrence

Local or regional recurrence is defined as recurrence in the area of the tumor bed, hilum or mediastinal lymph nodes. Loco-regional recurrence of the disease should be cytologically/histologically confirmed.

Distant recurrence

Distant recurrence is defined as spread of disease beyond the area of the tumor bed, hilum or mediastinal lymph nodes and can describe extrathoracic disease, metastasis to the contralateral lung, pleural metastasis, pleural effusion, or pericardial effusion. Distant recurrence should be diagnosed by radiological examination and/or histopathological confirmation when the metastatic lesion is easily accessible for biopsy.

Second primary NSCLC

Second primary NSCLC is defined as diagnosis of a new primary invasive NSCLC and should be pathologically or molecularly defined. A new cancer other than NSCLC is defined as diagnosis of a new malignancy excluding second primary NSCLC or recurrent NSCLC and should be pathologically defined as well.

If the site staff is unsure whether a new lesion represents NSCLC recurrence, a second primary NSCLC, or a new malignancy, a tissue biopsy should be performed to characterize the nature of the new lesion. If a new lesion cannot be unequivocally confirmed as a second primary NSCLC or a new malignancy other than NSCLC by tissue analysis, the new lesion should be considered a NSCLC recurrence and documented as such.

The development of a new cancer other than NSCLC should be regarded as an SAE (see Section 8.3.10).

8.1.1.2 Dating of recurrence

Dating of recurrence should always be based on the first onset of a sign but never on the onset of a symptom. The date of first detection of a palpable lesion is acceptable only when the diagnosis of tumor involvement is subsequently established. The diagnosis of recurrent disease by radiographs or scans should be dated from the date of the first positive record, even if this is determined in retrospect, or tissue confirmation occurs subsequent to the initial appearance of a suspicious area/lesion on a scan.

If there is equivocal progression and the site staff is unsure whether to consider this a DFS event, the medical monitor/study physician should be contacted.

8.1.1.3 Post-recurrence

Following recurrence, patient management is at the discretion of the Investigator, and tumor assessments will be in accordance with local policy. First PFS 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. Date of PFS as indicated in the SoAs (Table 2 and Table 3) will be collected per local practice and entered into the database

8.1.2 Computed tomography and magnetic resonance imaging

Efficacy evaluation of DFS will be derived using Investigator assessments according to RECIST 1.1. The management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator.

8.1.2.1 Central reading of scans

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization (CRO) for Quality Control and storage for BICR. Guidelines for image acquisition, de-identification, storage of digital copies at the investigative site (as source documents), 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.

8.1.3 Survival assessments

Survival assessments must be made according to the SoAs in Table 3 after study treatment discontinuation and during the observation period according to the SoAs in Table 4. 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 study 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.

8.1.4 Clinical outcome assessments

A Clinical Outcome Assessment (COA) is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. Patient-Reported Outcome (PRO) is one of the types of COAs. PRO, an umbrella term referring to all outcomes and symptoms, is directly reported by the patient. PRO has become a significant endpoint when evaluating effectiveness of treatments in clinical studies. The following PROs have been administered in this study: EORTC QLQ-C30; EORTC QLQ-LC13, CCI , CCI , CCI , CCI , and CCI . Each is described below.

8.1.4.1 EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group in 1993. It consists of 30 items and measures symptoms, functioning, and global health status/quality of life (QoL) (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, and nausea and vomiting); a 2-item global QoL 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 (see Appendix I).

The EORTC QLQ-LC13 is a well-validated complementary module measuring lung cancer associated symptoms (Bergman et al 1994). The QLQ-LC13 includes questions assessing cough, hemoptysis, dyspnea, site-specific pain, sore mouth, dysphagia, peripheral neuropathy, alopecia, and pain medication (see Appendix I).

8.1.4.2 CCI

The CCI will be used to explore the impact of treatment and disease state on health state utility.

The CCI, developed by the CCI, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal CCI. The CCI questionnaire comprises [redacted] questions that cover [redacted] dimensions of health CCI

8.1.4.3 CCI

CCI

8.1.4.4 CCI

CCI

8.1.4.5 Administration of patient-reported outcome questionnaires

The PRO instruments will be self-administered by the patients using a handheld electronic device. Patients will start to report PROs on Cycle 1 Day 1 before dosing (baseline assessments), to ensure that the device is correctly set up and working properly.

Thereafter, PRO assessments should be completed by the randomized patients at home according to the SoAs in Table 2 and Table 3. Multiple PRO assessments scheduled for the same time do not have to be completed on the same day, but should be completed within a window of ±3 days prior to treatment administration.

The instructions below should be followed when collecting PRO data via an electronic device:

- The research nurse or appointed site staff must explain to patients the value and relevance of electronic patient-reported outcomes (ePRO) participation so they are motivated to comply with questionnaire completion. Inform the patient that these questions are being asked to find out, directly from them, how they feel
- PRO questionnaires must be completed prior to treatment administration and before discussion of health status to avoid biasing the patient's responses to the questions.
- Each site must allocate the responsibility for the administration of the ePRO devices to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if patient has any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items. The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. The patients should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided in the ePRO device.

- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device if the patient is completing the ePRO at home.
- All questionnaires must be completed using the ePRO device; paper questionnaires are not allowed in this study.
- If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient should be exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and in the eCRF.

A key aspect of study success is to have high PRO compliance. To minimize missing data, compliance must be checked and discussed with the patient at each site visit, and the reason(s) why the patient could not complete assessments should be documented in source documents and in eCRF. If compliance drops below 85%, a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the SoAs (Table 2 and Table 3).

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 [Table 2 and Table 3]).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as 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 11 (clinical chemistry), Table 12 (hematology), and Table 13 (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 11 Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH[e]
Chloride[c]	T3 free[f] (reflex)
Creatinine[d]	T4 free[f] (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, either lipase or amylase is acceptable.
[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, 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] Creatinine clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).
[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.
[f] 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.

AE Adverse Event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone.

Table 12 Hematology

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

[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.

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

Table 13 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

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

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

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

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

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

8.2.2 Medical history

A complete medical history will be obtained at the second screening prior to randomization (Table 2) and on the day of or prior to entry into the observation period (Table 4); medical history information will be obtained only in in the event of a reported SAE during the first screening period or surveillance period (Table 1). A complete medical history may also be obtained from screen failed patients (see Section 5.5).

Findings from current medical history will be assigned a baseline grade according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 guidelines, whenever applicable. As a result, increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the baseline grade or below.

8.2.3 Physical examinations

No physical examination will be performed during the first screening (initiated by the signing of ICF1).

Physical examinations will be performed according to the assessment schedules (see the SoAs [Table 2 and Table 3]). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at the second screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and

symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

8.2.4 Vital signs

Vital signs (BP, pulse, temperature, and respiration rate) will be evaluated according to the SoAs (Table 2 and Table 3). Body weight is also recorded at each visit along with vital signs.

First infusion of durvalumab or placebo

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

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

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

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab. If there are no clinically significant concerns after the first cycle, reducing the observation period after durvalumab administration to 30 minutes is recommended, at the Investigator's discretion.

Subsequent infusions of durvalumab or placebo

BP, pulse, and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and 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 CRF page.

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

8.2.5 Electrocardiograms

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

In case of clinically significant ECG abnormalities, including a 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.

8.2.6 Early patient review for safety

It is recommended that patients are contacted 2 weeks after receiving the first 3 cycles of durvalumab or placebo (Cycle 1 Day 14, Cycle 2 Day 14, and Cycle 3 Day 14) of IP(s) to ensure early identification and management of toxicities.

8.2.7 WHO/ECOG performance status

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

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

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

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

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

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

5 Dead

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

8.2.8 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) 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 will be collected.

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

8.3 Collection of adverse events

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

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

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject'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 on 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 subject is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

SAEs will be collected from the time of the patient signing ICF1 and for patients who participate in the surveillance and observation periods. Both AEs and SAEs will be collected from the time the patient signs ICF2a, which initiates the second screening, until the follow-up period is completed (90 days after the last dose of IP). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset

toxicity to IP then it should be recorded in patient source notes as an AE or SAE as applicable and (in the case of an SAE) reported.

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

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject'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 adverse events and serious adverse events

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All events will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up

Any AEs that are unresolved at the patient's last AE assessment are followed up by the Investigator for as long as medically indicated (this may be beyond the 90 days after last dose of IP). AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Seriousness criteria

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

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

8.3.5 Causality collection

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

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

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

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

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

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

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

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

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN 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 recurrence

Events, which are unequivocally due to RECIST 1.1-defined disease recurrence, should not be reported as an AE during the study.

8.3.10 New cancers

The development of a new cancer (new non-NSCLC malignancy) 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 resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the 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 IP, then it should also be reported as an SAE.

8.3.12 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP and may require close monitoring. An AESI may be serious or 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 in regard to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs/imAEs observed with anti-PD-L1 agents such as durvalumab include pneumonitis, hepatitis, diarrhea/colitis, and intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism), adrenal insufficiency, hypophysitis/hypopituitarism, and Type I diabetes mellitus, nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis, and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

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

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

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

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

Note for CSP v2.0: Please refer to Section 10.3.2.

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). 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) after the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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 CRF.

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 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 adverse events 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 one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

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

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

8.4.1.1 Regulatory reporting requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

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

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB or and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.2 Pregnancy

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

If a patient become pregnant while in surveillance, the patient will be withdrawn from surveillance.

If a pregnancy is reported after the patient has received any IP, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

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

8.4.2.1 Maternal exposure

If a patient becomes pregnant while in surveillance, the patient will be withdrawn from surveillance. If a patient becomes pregnant after they are randomized in this study, IP should be discontinued immediately.

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

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

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

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of IP. Please follow the local prescribing information relating to contraception.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of 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/ IRBs prior to use.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment.

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

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

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

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

8.4.4 Medication error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2), and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4.5 Specific toxicity management and dose modification information – Durvalumab

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).

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

Comprehensive toxicity management guidelines (TMG) have been developed to assist Investigators with the recognition and management of toxicities associated with the use of the immune checkpoint inhibitor durvalumab (PD-L1 inhibitor). These guidelines are applicable when durvalumab is used alone or in combination (concurrently or sequentially) with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents), as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised, however, to use local practice guidelines and consult local references for the management of toxicities observed with the SoC chemotherapy regimen(s) administered. The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

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

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

Dose Delays: Patients may delay dosing under certain circumstances.

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

- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
- Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see current IB for durvalumab).

If unsure of how to manage a patient, please contact the Study Physician at AstraZeneca to discuss individual cases.

8.5 Pharmacodynamics

Plasma ctDNA will be evaluated during and after study treatment as a pharmacodynamic parameter. See Section 8.7.2.1 for information on method related to on-study evaluation of plasma samples for ctDNA. No other pharmacodynamic parameters were evaluated in this study.

8.6 Genetics

8.6.1 Collection of mandatory genetic samples

The patient's consent to participate in the genetic MRD testing components of the study is mandatory and will be obtained in ICF1. See Section 8.7.1.2 for details on sample collection, analyses performed, and data storage. This **mandatory** genetic testing is conducted for the detection of MRD and is distinct from the optional genetic research component of the study. As part of this mandatory genetic testing, germline DNA (exome only) is analyzed to enable the design of the personalized panel for MRD detection and subsequent testing for ctDNA.

See Section 8.7.1, Appendix E, and the Laboratory Manual for additional information on collection of mandatory genetic samples.

8.6.2 CCI

CCI

CCI

CCI

8.6.3 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of

15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.7 Biomarkers

By participating in this study, the patient consents to the mandatory collection and use of donated biological samples as described here. Samples will be obtained from all screened patients. Mandatory samples (described in Section 8.7.1) will be collected from all patients who participate in the first screening period (initiated by the signing of ICF1). Samples for exploratory endpoints (described in Section 8.7.2) will be collected according to the SoAs from patients who participate in the surveillance, second screening, treatment, and/or follow-up period(s) and patients in the observation arm.

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 evaluating biological and/or clinical response to immunotherapy as described in the exploratory analyses section.

The results may be pooled with biomarker data from other durvalumab studies to evaluate biological responses across indications.

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

8.7.1 Mandatory biomarkers

8.7.1.1 Assessment of *EGFR/ALK* mutation status

Results from local *EGFR/ALK* testing of either a pre-surgery biopsy or the resected tumor tissue performed as part of local clinical practice may be used for this study, provided testing was performed using a well-validated, local regulatory-approved kit.

If a patient's *EGFR/ALK* status was previously determined for MERMAID-1 (D910LC00001), testing does not need to be repeated, provided a well-validated, local regulatory-approved kit was used to test. Patients **must** sign ICF1 for MERMAID-2 (D910MC00001) to allow the Sponsor retrospective access to these results (see Section 5.4).

EGFR/ALK wild-type patients will be enrolled in the study. If local testing or the results of local testing are unavailable, *EGFR/ALK* will be tested by a central reference laboratory using resected tumor tissue.

8.7.1.2 Minimal residual disease

Tumor samples and whole blood for whole exome sequencing and development of personalized assay

This study requires comparison of genetic data from a patient's tumor and blood cells to identify tumor-specific mutations for MRD determination (see Section 8.6.1). Countries, centers, or patients that do not permit or consent to such analyses will not be able to participate in the study.

Detection of MRD in solid tumors requires a complex multi-step assay. Firstly, WES of the patient's tumor is performed on the resected tumor tissue and controlled for germline mutations by WES of the patient's whole blood (as indicated in Table 1). A Sponsor-approved personalized panel is then developed, comprised of the patient's tumor variants expressed at high frequency (see Appendix E for more detail). This panel is then used to identify the presence of these variants on ctDNA extracted from the patient's plasma and the patient is considered MRD+ if the panel detects patient-specific tumor variants. This personalized approach allows detection of the patient's tumor variants in DNA at high sensitivity. Tumor and whole blood samples, as well as WES data, will be used for diagnostic development and exploratory research.

The buffy coat layers obtained from a separate baseline whole blood sample will be retained and may be analyzed for germline mutations for future diagnostic development.

If a patient's MRD panel has already been created during screening for MERMAID-1 (D910LC00001), that panel can be used for this study (see Section 5.4).

Details on tumor and whole blood sample collection, processing, storage, and shipment are provided in the Laboratory Manual.

Plasma samples for determination of MRD status based on ctDNA

Once plasma has been drawn, cell-free DNA is extracted and a polymerase chain reaction is performed using primers from the patient-specific panel designed based on the WES data (the generation of which is described above). The resulting amplicons are then sequenced and analyzed by the proprietary Analysis MRD bioinformatics pipeline at the designated organization, which reports on the presence or absence of ctDNA and detection of MRD.

A plasma sample will be collected 8 weeks ± 1 week after the completion of adjuvant therapy (which can include PORT) or 12 weeks ± 1 week after surgery (for patients who do not undergo further curative therapy), as indicated in the SoAs (Table 1). **Collection** of this plasma sample marks the start of surveillance.

Note: The Sponsor will obtain the pre-surgery plasma samples (if collected) from patients who were screen fails during the first screening period for MERMAID-1 (D910LC00001) before enrolling in MERMAID-2 (D910MC00001) (see Section 5.4).

In addition, surveillance, on- and post-treatment, and observation plasma samples will be collected longitudinally for retrospective exploratory evaluations of ctDNA and to support exploratory endpoints (see Section 8.7.2.1). Plasma samples, including derived DNA, will be used for diagnostic development and exploratory research. No treatment decisions will be made based on the results from these samples.

All samples submitted for ctDNA analysis will be coded to prevent patient identification. Sequencing data and variant calls from ctDNA analysis will be stored in a secure system at designated organizations and/or at AstraZeneca to analyze the sample.

Details on plasma collection, processing, storage, and shipment are provided in the Laboratory Manual.

8.7.1.3 Tissue samples for PD-L1 TC expression assessment and biomarker research

PD-L1 TC expression will be evaluated prospectively on resected tumor tissue collected during surgical resection in all screened patients. Data will be compared between arms to determine if baseline PD-L1 status is prognostic and/or predictive of outcomes associated with durvalumab versus placebo. Baseline tumor requirements are described in Section 5.1.

MANDATORY: Provision of tumor tissue from the primary resection, formalin-fixed and embedded in paraffin, for the purpose of PD-L1 TC expression analysis (and for enabling exploratory analyses as described in Section 8.7.2.2).

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

PD-L1 TC analysis will be performed by at a central reference laboratory testing service using the Ventana SP263 PD-L1 IHC assay.

If a patient's PD-L1 status has already been determined during screening for MERMAID-1 (D910LC00001), those results can be used for this study provided the Ventana SP263 PD-L1 IHC assay was used (see Section 5.4).

A brief description of exploratory tumor markers to be explored is provided in Section 8.7.2.2.

8.7.2 Exploratory biomarkers

Additional exploratory analyses may be undertaken on participant's samples to identify other biomarkers of sensitivity and resistance to study interventions and our understanding of cancer.

WES data generated during the development of the personalized panel (described above in Section 8.7.1.2) may also be used for exploratory purposes to better understand NSCLC and/or to identify biomarkers (eg, tissue TMB) which may correlate with patient outcomes.

Blood and tumor samples for exploratory biomarker analyses will be obtained according to the schedules presented in the SoAs (Table 1, Table 2, Table 3, and Table 4). Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Measurements for randomized patients at baseline, on treatment, and/or at RECIST 1.1-defined disease recurrence will be correlated with outcomes. Note that samples will be obtained from patients randomized to each treatment group. Comparisons may be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with durvalumab versus placebo, subgrouped by histology.

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 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.

8.7.2.1 Plasma and serum

Plasma samples will be collected throughout the course of the study to assess the relationship between treatment effect on ctDNA clearance and DFS endpoint.

Plasma analyses may also include evaluating baseline mutations to treatment, changes in ctDNA levels on treatment, TMB, and correlations with clinical outcome. Overall mutational burden or somatic mutations/genomic alterations, RNA, and/or protein markers in plasma may be assessed using state-of-the-art methodologies.

Serum samples will be collected for analysis of circulating soluble prognostic and pharmacodynamic biomarkers, including, but not limited to, proinflammatory, regulatory, and chemotactic cytokines and chemokines.

8.7.2.2 Tumor markers

Tissue obtained as part of screening procedures and for establishing PD-L1 TC expression status may be analyzed for additional markers. TMB may also be assessed in tumor tissue. Based on availability of tissue, a panel of immune-relevant markers expressed on tumor-infiltrating lymphocytes or on tumor cells may be assessed.

Attributes of tumor microenvironment that could be assessed using various methods, which may include, but are not limited to, high content imaging, multiplex RNA/DNA/protein analysis with spatial resolution such as Mass Spec, in situ hybridization, or other technologies will be correlated with response and clinical outcome.

Exploratory analysis of RNA (mRNA/miRNA/lncRNA), DNA, or protein using state-of-the-art technologies including, but not limited to, RNAseq, WES, and QRT-PCR may be conducted to study association with response and clinical outcome.

OPTIONAL: Provision of tumor tissue upon recurrence, formalin-fixed and embedded in paraffin is strongly encouraged. The Investigator must consult with the Study Physician if such sampling is not feasible. In addition, if the patient refuses to provide this sample, the reason for this refusal must be captured. After evaluation per local clinical practice (if applicable), any remaining sample(s) of the recurrent tumor should be submitted for exploratory analyses of biomarker changes compared to baseline (ie, resected tumor tissue from surgery).

8.7.2.3 Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results other than MRD measurements necessary for eligibility 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 purpose 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.

8.7.2.4 Optional Genomic Initiative samples

Details on the optional genetic research study can be found in Section 8.6.2.

8.7.3 Storage, re-use, and destruction of biomarker samples

Samples will be stored for a maximum of 15 years 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.

8.7.4 Labeling and shipment of biological samples

The PI 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 "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.

8.7.5 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of shipments.

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 will keep documentation of receipt upon arrival.

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

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

8.7.6 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 PI will:

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

9 STATISTICAL CONSIDERATIONS

Note for CSP v2.0: <u>All analyses of the objectives and endpoints will be descriptive only and considered exploratory.</u> Interim analysis will not be performed. Medical resource use analysis will not be performed. Please see Section 10.4 for additional information.

The primary aim of the study is to compare the efficacy and safety of durvalumab to placebo in terms of DFS (using Investigator assessments according to RECIST 1.1) in randomized patients who are PD-L1 TC≥1% with an initial diagnosis of stage II-III NSCLC who have undergone curative intent therapy.

- All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.
- Analyses will be performed by AstraZeneca or its representatives.

- A statistical analysis plan (SAP) will be written to provide further details and will be finalized in advance of DBL.

9.1 Statistical hypotheses

The formal statistical analysis will be performed to test the main hypotheses:

- H0: No difference between durvalumab and placebo
- H1: Difference between durvalumab and placebo

The primary objective of this study is to compare the efficacy of durvalumab to placebo in terms of DFS in randomized patients who are PD-L1 TC≥1% following curative intent therapy. A secondary objective is to compare the efficacy of durvalumab to placebo in terms of DFS in the FAS. The details on the multiple testing procedure for controlling the type I error rate can be found in Section 9.5.7.

9.2 Sample size determination

Approximately 284 patients with stage II-III NSCLC who are MRD+ will be randomized 1:1 to durvalumab or placebo. Of the patients randomized into the study, at least 170 patients are required to be PD-L1 TC≥1% at study entry. The primary analysis is planned to be performed in the PD-L1 TC≥1% analysis set. An analysis on the FAS (all MRD+ stage II-III NSCLC patients randomized) will be performed as a secondary objective of the study. Randomization will be stratified by PD-L1 status (TC<1% vs TC≥1%), time from the start of surveillance to the emergence of MRD (≤6 months vs >6 months), and prior neoadjuvant immunotherapy (Yes vs No). In this study, the start of surveillance is defined as the day the plasma sample used to determine a patient's MRD status post-curative intent therapy is collected.

The study is sized for the primary endpoint of DFS in the PD-L1 TC≥1% analysis set and for the secondary endpoint of DFS in the FAS.

The analysis of the primary endpoint (DFS) will occur when approximately 118 DFS events have occurred (69% maturity) in the PD-L1 TC≥1% analysis set. If the true DFS HR is 0.55 in the PD-L1 TC≥1% analysis set, the study will provide at least 90% power to demonstrate a statistically significant difference for DFS with overall 2-sided significance level of 5%; this translates to 3.2-month benefit in median DFS over 4 months on placebo, or 8.4% difference in 2-year DFS rate over 1.5% on placebo, if DFS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of 0.7.

The study is also sized to provide at least 90% power for the DFS endpoint in the FAS. The analysis will be performed at the same time as the primary analysis, when it is expected that approximately 197 DFS events have occurred (69% maturity) in the FAS. If the true DFS HR is 0.63 in this population, this will provide at least 90% power to demonstrate a statistically significant difference for DFS, assuming overall 5% 2-sided

significance level; this translates to a 2.3-month benefit in median DFS over 4 months on placebo, or 5.6% difference in 2-year DFS rate over 1.5% on placebo, if DFS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of 0.76.

It is estimated that analysis of DFS will occur approximately CCI after the first patient has been randomized assuming a CCI recruitment period and allowing for patients to have a minimum follow-up of CCI

OS will also be analyzed in the PD-L1 TC≥1% analysis set and in the FAS analyzed at the time of the DFS analysis. In the PD-L1 TC≥1% analysis set if the true HR is 0.79 then it is anticipated that approximately 59 events (35% maturity) will have occurred. This translates to a 4.3 month benefit in median OS over 16 months on placebo. In the FAS, if the true HR is 0.89, then it is anticipated that approximately 102 events (36% maturity) will have occurred. This translates to a 2 month benefit in median OS over 16 months on placebo. OS will be analyzed similarly to DFS.

A further analysis of OS will be performed at approximately 127 events (75% maturity) in the PD-L1 TC≥1% analysis set. At this time there is also expected to be approximately 218 events (77% maturity) in the FAS. It is anticipated this analysis will occur approximately 60 months after first patient is randomized. If events are accruing slower than expected, then the DCO may occur 60 months after the first patient is randomized, regardless of number of events accrued.

9.3 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 14.

Table 14 Summary of outcome variables and analysis populations

Outcome	Population
Efficacy data	
DFS	PD-L1 TC≥1% analysis set
	Full analysis set
PFS, CCI, CCI	PD-L1 TC≥1% analysis set
	Full analysis set
OS	PD-L1 TC≥1% analysis set
	Full analysis set
PROs	PD-L1 TC≥1% analysis set
	Full analysis set
Demography	PD-L1 TC≥1% analysis set
	Full analysis set
Safety data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital signs	Safety Analysis Set

AEs Adverse events; DFS Disease-free progression; OS Overall survival; PD-L1 Programmed death ligand 1; PD-L1 TC Tumor-specific PD-L1 expression; PFS Progression-free survival; PROs Patient-reported outcomes; TC Tumor cells; CCI ; CCI .

9.3.1 Full analysis set

The FAS will include all randomized patients. The FAS will be used for all efficacy analyses including PROs. Treatment groups 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 are included in the analysis in the treatment group to which they were randomized.

9.3.2 PD-L1 TC≥1% analysis set

The PD-L1 TC≥1% analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 TC≥1% as defined by the Ventana SP263 PD-L1 IHC assay (ie, 1% PD-L1–membrane expression in tumoral tissue) at randomization. The PD-L1 TC≥1% analysis set will be the primary analysis set for all efficacy and PRO analyses.

9.3.3 Safety analysis set

The SAS will consist of all randomized patients who received any amount of study treatment. Safety data will not be formally analyzed but summarized using the SAS, according to the treatment received. If a patient receives any amount of durvalumab, they will be summarized in the durvalumab treatment group. If a patient only receives placebo, they will be summarized in the placebo treatment group.

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of efficacy variables

9.4.1.1 RECIST 1.1-based endpoints

The analysis of the primary endpoint, DFS, will be based on the Investigator assessments using RECIST 1.1.

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 study treatment or receives another anticancer therapy.

Please refer to Appendix G for further details.

Blinded Independent Central Review

A secondary analysis of the DFS endpoint will be performed based on data assessed by a BICR for all patients.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data and the relevant scan dates for each timepoint (ie, for visits where recurrence is/is not identified).

Further details of the BICR will be documented in the Imaging Charter.

9.4.1.2 Primary endpoint: disease-free survival

DFS is defined as the time from the date of randomization until the date of disease recurrence (local, regional, or distant disease recurrence or second primary NSCLC) using Investigator assessments according to RECIST 1.1, or date of death due to any cause, whichever occurs first.

Patients who are disease-free, ie, have not experienced disease recurrence, and alive at the time of analysis will be censored at the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient experiences disease recurrence or dies after 2 or more missed visits, the patient will be censored at the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the patient has no evaluable assessments or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline, then they will be treated as an event with the date of death as the event date. The primary endpoint analysis of DFS will be based on Investigator RECIST 1.1 assessments.

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

DFS rate at 6 and 12 months is defined as the proportion of patients alive and disease-free at 6 and 12 months respectively, estimated from Kaplan-Meier plots of the primary endpoint of DFS.

9.4.1.3 Secondary efficacy endpoint: 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 (if agreed to by the patient and in compliance with local data privacy laws/practices) will be made 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.

9.4.1.4 Secondary efficacy endpoint: progression-free survival

PFS is defined as the time from the date of randomization to the date of post-recurrence disease progression (using local standard practice) or death. Patients alive, and for whom a disease progression has not been observed, should be censored at the last time known to be alive and without a disease progression; ie, censored at the last progression assessment date if the patient has not had a progression or died or at the last disease recurrence assessment date if the patient has not had a disease recurrence or died.

9.4.1.5 Secondary efficacy endpoint: CCI [redacted] CCI [redacted]

[redacted]. Any patient not known to have had a subsequent therapy/procedure or not known to have died at the time of the analysis will be censored at the last known time to have not received subsequent therapy; ie, the last follow-up visit where this was confirmed.

9.4.1.6 Secondary efficacy endpoint: CCI [redacted] CCI [redacted]

[redacted] Any patient not known to have died at the time of the analysis and not known to have had a second subsequent therapy/procedure will be censored at the last known time to have not received second subsequent therapy, ie, the last follow-up visit where this was confirmed.

9.4.2 Calculation or derivation of safety variables

9.4.2.1 Adverse events

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. “On

treatment" will be defined as assessments between date of start dose and 90 days following discontinuation of IP (ie, the last dose of durvalumab/placebo). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

The SAS will be used for reporting of safety data.

Adverse events observed up until 90 days following discontinuation of the last dose of durvalumab/placebo or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only as a number of AEs up to 90 days following discontinuation of durvalumab/placebo are likely to be attributable to subsequent therapy. However, to assess the longer-term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of durvalumab/placebo (ie, without taking subsequent therapy into account). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) 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.

9.4.2.2 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs (to be administered at baseline and as clinically indicated), and physical examinations, the baseline value will be the latest result obtained prior to the start of study treatment.

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 only include evaluable patients, ie, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline to be evaluable, the patient need only have 1 post-dose value recorded.

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

9.4.3 Calculation or derivation of patient-reported outcome variables

Symptoms and overall QoL will be assessed using the EORTC QLQ-C30 and QLQ-LC13 module (secondary endpoints). Questionnaires will be scored according to published scoring guidelines or the developer's guidelines, if published guidelines are not available.

All PRO analyses will be conducted on both the PD-L1 TC≥1% analysis set and the FAS.

9.4.3.1 EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social) and 3 symptom scales (fatigue, pain, and nausea and vomiting), 5 individual items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), and a global measure of health status. The EORTC QLQ-LC13 is a lung cancer specific module from the EORTC for lung cancer comprising 13 items/questions (cough, hemoptysis, dyspnea, site-specific pain, sore mouth, dysphagia, peripheral neuropathy, 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/QoL scale according to the EORTC QLQ-C30 Scoring Manual (Fayers et al 2001) 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 with baseline will be evaluated. A minimum clinically relevant 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 relevant deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline (defined as Day 1, pre-dose) of ≥10. A clinically relevant 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 15.

Table 15 Visit responses for symptoms and health-related quality of life

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

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 deterioration in symptom and functional scales/items and global health status/QoL, based on the clinically meaningful cut-offs, will be evaluated.

See SAP for further details.

9.4.3.2 Calculation or derivation of CCI

CCI data will be presented using summaries and descriptive statistics. Additionally, CCI data may be further explored. Further details will be provided in the SAP.

9.4.3.3 CCI

CCI data will be presented using summaries and descriptive statistics. Additionally, data may be further explored. Further details will be provided in the SAP.

9.4.3.4 Calculation or derivation of health economic variables

CCI index

The CCI index comprises CCI (See Section 8.1.4.2). For each dimension, respondents will 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 CCI 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 CCI. These data will be converted into a weighted health state index by applying scores from CCI 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 CCI to CCI crosswalk will be applied CCI. In addition to the descriptive system, respondents also assess their health on the day of assessment on a VAS, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

Health care resource use (HOSPAD)

The Health Resource Use Module will be assessed in terms of symptoms for admission and type of admission (planned/unplanned hospitalization, outpatient visits, or emergency department visits).

To investigate the impact of treatment and disease on health care resource use, the following variables will be captured:

Planned and unplanned hospital attendances beyond study protocol-mandated visits (including physician visits, emergency room visits, day cases, and admissions)

- Primary sign or symptom the patient presents with
- Length of hospital stay
- Length of any time spent in an ICU

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalization or start of IP if the start of IP is after the start date of hospitalization (length of hospital stay=end date of hospitalization – start date of hospitalization + 1). Patients with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalization. The length of ICU stay will be calculated using the same method.

9.4.4 Calculation or derivation of pharmacokinetic variables

9.4.4.1 Pharmacokinetic analysis

Not applicable for this study.

9.4.4.2 Immunogenicity analysis

Not applicable for this study.

9.4.5 Calculation or derivation of biomarker variables

Biomarker status, as defined in the exploratory objectives, will be assessed for evaluable patients in each cohort according to pre-specified criteria that will be detailed in the SAP.

9.4.6 Calculation or derivation of pharmacogenetic variables

In the case of **optional** genetic data, only the date that the patient gave consent to participation in the optional genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The optional genetic data generated from the study will be stored in the AstraZeneca Laboratory Information Management System (LIMS) database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the **mandatory** main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis. Data will be reported outside the CSR (please see Appendix C).

9.5 Statistical analyses

The patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data will be described in the SAP. 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 group. 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.

For efficacy variables and analyses performed on the FAS, baseline is defined as the last visit prior to randomization, for all other reporting, baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the PD-L1 TC≥1% analysis set and FAS. Safety data will be summarized on the SAS.

Results of all statistical analysis will be presented using a 95% CI and 2 sided p-value, unless otherwise stated.

9.5.1 Efficacy analyses

The primary aim of the study is to assess the efficacy of durvalumab versus placebo in terms of DFS, using Investigator assessments according to RECIST 1.1, in the PD-L1 TC≥1% analysis set. DFS, using Investigator assessments according to RECIST 1.1, in the FAS is a secondary endpoint.

Table 16 details which endpoints are to be subjected to formal statistical analyses, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint. Note, all endpoints compare durvalumab versus placebo in the PD-L1 TC≥1% analysis set and all randomized patients (FAS) unless otherwise indicated. Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

Table 16 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
DFS	Primary analysis using stratified log-rank test using Investigator assessments according to RECIST 1.1 for PD-L1 TC≥1% analysis set. Secondary analysis using stratified log-rank test using Investigator assessments according to RECIST 1.1 for FAS Secondary analysis using stratified log-rank test using BICR assessments (RECIST 1.1) for PD-L1 TC≥1% analysis set Secondary analysis using stratified log-rank test using BICR assessments (RECIST 1.1) for FAS Estimate of DFS rates at 6 and 12 months based on the Kaplan-Meier curve
OS	Stratified log-rank test
PFS, CCI, CCI	Stratified log-rank test
Change from baseline (EORTC QLQ-C30 and QLQ-LC13)	Summary statistics, change from baseline including mixed model repeated measures (MMRM)
Time to deterioration (EORTC QLQ-C30 and QLQ-LC13)	Stratified log-rank test

For the PD-L1 TC≥1% analysis set 2 stratification factors will be included in the model; time from start of surveillance to emergence of MRD (≤6 months vs >6 months) and prior neoadjuvant immunotherapy (Yes vs No). For the FAS 3 stratification factors will be included in the model; PD-L1 status (TC<1% vs TC≥1%), time from start of surveillance to emergence of MRD (≤6 months vs >6 months) and prior neoadjuvant immunotherapy (Yes vs No).
BICR Blinded independent central review; DFS Disease-free survival; EORTC European Organisation for Research and Treatment of Cancer ; FAS Full analysis set; OS Overall survival; PD-L1 Programmed cell death ligand-1; PFS Progression-free survival; 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; TC Tumor cells; CCI ; CCI .

Analyses of data from the observation cohort will be described in the SAP.

9.5.1.1 Primary endpoint: disease-free survival

DFS (using Investigator assessments according to RECIST 1.1) will be analyzed using the log-rank test stratified by time from start of surveillance to emergence of MRD (≤6 months vs >6 months), and prior neoadjuvant immunotherapy (Yes vs No) on the PD-L1 TC≥1% analysis set.

The treatment effect will be estimated in terms of the HR and its associated 95% CI from a Cox proportional hazards model (Cox 1972) stratified by time from start of surveillance to emergence of MRD (≤6 months vs >6 months), and prior neoadjuvant immunotherapy (Yes vs No) on the PD-L1 TC≥1% analysis set.

The stratification factor covariates in the statistical modeling will be based on the values entered into IWRS at randomization, even if it is subsequently discovered that these values were incorrect. For the purpose of statistical analysis of the primary and relevant secondary endpoints, a plan for reducing the number of strata cells will be included in the SAP in case there are insufficient events in one level of any strata.

Kaplan-Meier plots of DFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a DFS event will be provided along with median DFS with 95% CI for each treatment estimated based on the Kaplan-Meier curves.

The DFS rates at month 6 (DFS-6) and month 12 (DFS-12) will be estimated based on the Kaplan-Meier curves along with their 95% CIs and presented by treatment arms.

Subgroup analyses will be conducted comparing DFS between durvalumab versus placebo in the following subgroups of the PD-L1 TC≥1% analysis set and FAS (but not limited to):

- PD-L1 status (TC <1% versus ≥1%)
- PD-L1 status (TC <25% and ≥25%)
- TMB (high, low)
- Histology (squamous versus non-squamous)
- Sex (male versus female)
- Age (<65 versus ≥65 years of age)
- Smoking status (smoker versus non-smoker [never smoked])
- Race (Asian versus non-Asian)

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

No adjustment to the significance level for subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of DFS.

Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. A model will be constructed, containing treatment and the stratification factors, to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test. Interactions between treatment and stratification factors will also be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985 (Gail and Simon 1985).

Additionally, for each subgroup, the HR (durvalumab plus SoC chemotherapy: placebo plus SoC chemotherapy) and 95% CI will be calculated from a Cox proportional hazards model with treatment as the only covariate. These will be presented on a forest plot including the HR and 95% CI.

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 20 events in a subgroup), the relationship between that subgroup and DFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

9.5.1.2 Secondary endpoints

Disease-free survival

A secondary analysis of DFS in the FAS will be performed using the same methodology as for the primary analysis described above, but with the additional strata of PD-L1 status (TC<1% vs TC≥1%).

In addition, a secondary analysis of DFS, using BICR assessment according to RECIST 1.1, in the PD-L1 TC≥1% analysis set and the FAS will be performed using the same analysis described for the Investigator assessments.

Overall survival

OS will be analyzed similarly to the DFS for the PD-L1 TC≥1% analysis set and the FAS. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have died, those who are still alive at the DCO (those who are 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 arm.

Progression-free survival

PFS (using local standard practice) will be analyzed similarly to the DFS for the PD-L1 TC≥1% analysis set and FAS. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event will be provided, along with the median for each treatment.

CCI and CCI

CCI and CCI will be analyzed similarly to the DFS for the PD-L1 TC≥1% analysis set and FAS. Kaplan-Meier plots will be presented by treatment group, along with the number and percentage of patients who have a CCI event or are censored for various reasons, along with the median for each treatment.

9.5.1.3 Patient-reported outcomes

EORTC QLQ-C30 and QLQ-LC13

The primary PRO measures will be subject-reported lung cancer symptoms assessed using the EORTC QLQ-LC13 and EORTC QLQ-C30, namely:

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

In addition, physical and role functioning and overall global health status/QoL domains of the EORTC-CT30 are furthermore pre-specified endpoints of interest.

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 group. 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 improved, stable, and worsened as defined in Table 15) will also be produced for each treatment group.

A Mixed-effect Model with Repeated Measures will be utilized to model the change from baseline in EORTC QLQ-C30 and QLQ-LC13 symptoms (primary PRO measures only), EORTC QLQ-C30 global health status/QoL, and each functional domain over time.

Time to deterioration will be analyzed for each of the symptom scales/items, function scales, and global health status/QoL using a stratified log-rank test as described for the primary analysis of DFS. 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 relevant deterioration as well as who are censored will also be provided along with the medians for each treatment group.

Additional analyses and data visualizations may be considered. Further details will be provided in the SAP.

CCI [redacted]
CCI [redacted] data will be presented using summaries and descriptive statistics. Further details will be provided in the SAP.

CCI [redacted]
CCI [redacted] data will be presented using summaries and descriptive statistics. Further details will be provided in the SAP.

Health state utility

Descriptive statistics will be calculated for each scheduled visit/timepoint in the study, for each study group, and as a total. These will report the number of patients, the number of CCI [redacted] questionnaires completed at each visit, and the number and proportion of patients responding to each dimension of the CCI [redacted] Additionally, summary statistics (eg, n, mean, median, standard deviation, minimum, and maximum) will be reported for the CCI [redacted] index score and the EQ-VAS score, and the change from baseline for the CCI [redacted] index score and the EQ-VAS score.

Graphical plots of the mean CCI index score and EQ-VAS score, including change from baseline, and associated 95% CI by scheduled visits/timepoints in the study may be produced. To support submissions to payers, additional analyses may be undertaken, and these will be outlined in a separate Payer Analysis Plan.

Medical resource use

The potential impact the disease and treatment has on health care resource use will be analyzed for the purposes of submissions to payers. Descriptive statistics (as appropriate, including means, median, ranges or frequencies, and percentages) will be provided for each arm on the different types of hospital admissions, the length of stay of people admitted to the hospital for at least 1 overnight stay, and the length of stay of people admitted to intensive care/high dependency units, as well as the primary sign or symptom the patient presents with. To support submissions to payers, additional analyses may be undertaken, and these will be outlined in a separate Payer Analysis Plan.

An exploratory health economic analysis of hospital episodes including type of contact (hospitalization, outpatient, or day case), reason, length of stay by ward type (including ICU), procedures, and tests may be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of durvalumab in comparison to SoC, and will be outlined in the payer analysis plan. This would include providing descriptive statistics as appropriate, including means, median, and ranges.

9.5.2 Safety analyses

All safety and tolerability data will be presented by treatment arm using the SAS.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [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, vital signs, and ECGs (conducted at baseline and as clinically indicated). Exposure to durvalumab and placebo will be summarized. Time on study and durvalumab, including any dose delays, will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.5.3 Pharmacokinetic data

Not applicable for this study.

9.5.4 Immunogenicity data

Not applicable for this study.

9.5.5 Pharmacokinetic/pharmacodynamic relationships

Not applicable for this study.

9.5.6 Biomarker data

The relationship of PD-L1 TC expression and, if applicable, of exploratory biomarkers to clinical outcomes (including but not restricted to) of DFS and OS will be presented.

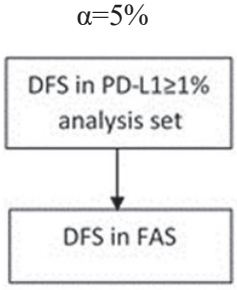
PD-L1 TC expression determined by IHC will be reported in the CSR. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.5.7 Methods for multiplicity control

In order to provide strong control of the type I error rate, α=5% (2-sided), a multiple testing procedure with gatekeeping strategy will be used across the primary endpoint of DFS in the PD-L1 TC≥1% analysis set and the secondary endpoint of DFS in the FAS. The first two layers of the MTP are shown in Figure 4. If DFS is significant in the FAS the alpha may be recycled to other secondary endpoints. Full details of the MTP, including testing of any additional secondary endpoints, will be specified in the SAP prior to DBL.

The overall 5% type I error rate will be allocated to the DFS analysis on the PD-L1 TC≥1% analysis set. If that analysis is statistically significant, 5% alpha (2-sided) will be allocated to the DFS analysis in the FAS.

Figure 4 Multiple testing procedure for controlling the type 1 error rate



DFS Disease-free survival; FAS Full analysis set; PD-L1 TC≥1% Expression of PD-L1 on tumor membrane, at any intensity, in ≥1% of tumor cells.

9.6 Interim analyses

An interim analysis of OS will be performed at the time of the DFS analysis. At this time it is expected that approximately 59 events (35% maturity) will have occurred in the PD-L1 TC≥1% analysis set and approximately 102 events (36% maturity) will have occurred in the FAS.

A further analysis of OS will be performed at approximately 127 events (75% maturity) in the PD-L1 TC≥1% analysis set. At this time there is also expected to be approximately

218 events (77% maturity) in the FAS. It is anticipated this analysis will occur approximately 60 months after first patient is randomized. If events are accruing slower than expected then the DCO may occur 60 months after the first patient is randomized, regardless of number of events accrued. An alpha spending function will be used to control the overall type I error for the interim and the final analysis of OS at the 5% level. Details of the OS testing plan will be provided in the SAP.

9.6.1 Data monitoring committee (DMC)

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.

An IDMC comprised of independent experts will meet approximately 12 months after the first subject has been dosed with IP or after approximately 50 patients have received at least 1 dose of IP (whichever occurs first) to assess the safety and tolerability of durvalumab. The IDMC will review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety findings. The frequency of subsequent reviews will be determined by the IDMC but will be no more frequent than every 6 months. The IDMC safety reviews will be conducted in an unblinded manner.

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

10 RATIONALE FOR AND PROCEDURES FOLLOWING CSP V2.0 IMPLEMENTATION

At the time of CSP v2.0 implementation at site, Section 10 (this section) should be fully utilized as the reference point for the study. Original protocol language is maintained in version 2.0 of the CSP where relevant in order to ensure that the history of the study is accessible to study site staff for reference. Please see Sections 1-9 for notes regarding their applicability and updated text following implementation of CSP v2.0 at site.

10.1 Overall rationale

Two Phase III clinical studies have reported positive results for PD-(L)1 inhibitors (used as monotherapy) in the adjuvant setting. IMpower010 is a Phase III trial which randomized 1280 patients with completely resected Stage IB (≥4cm) to Stage IIIA NSCLC (UICC/AJCC version 7) after cisplatin-based chemotherapy to atezolizumab, given every 3 weeks for up to 16 cycles, or to best supportive care (Felip et al 2021). The primary endpoints tested hierarchically were DFS in: (i) the PD-L1 ≥1%, Stage II-IIIA population; (ii) the all-randomized Stage II-IIIA population; and (iii) the intent-to-treat population. At interim analysis the first and second of these were found to be statistically significant with HRs of 0.66 (95% CI 0.50, 0.88) and 0.79 (95% CI 0.64, 0.96), respectively. These data led, in October 2021, to FDA approval of atezolizumab for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II-IIIA NSCLC whose tumors have PD-L1 expression ≥1% (using a Ventana SP263 PD-L1 IHC assay). PEARLS/KEYNOTE-091 is a Phase III study which randomized 1177 patients with completely resected Stage IB (≥4cm) to Stage IIIA NSCLC (UICC/AJCC version 7) ± adjuvant chemotherapy to pembrolizumab or placebo (given every 3 weeks for up to 18 cycles) (Paz-Ares et al 2022). The dual primary endpoints were DFS in the overall population and DFS in the PD-L1≥50% stage IB-IIIA population. At a second interim analysis, the HR for the first of these endpoints was statistically significant (0.76; 95% CI 0.63, 0.91).

One Phase III clinical study has reported positive results for nivolumab (anti-PD-1 immunotherapy) in the neoadjuvant setting. In the Checkmate816 study, 358 patients with Stage IB (≥4cm) to Stage IIIA NSCLC (UICC/AJCC version 7) were randomized to neoadjuvant platinum-based chemotherapy with or without open label nivolumab (given every 3 weeks for up to 3 cycles) (Forde et al 2022). The co-primary endpoints were pathological complete response rate and event-free survival (EFS). The trial was positive for both primary endpoints. The hazard ratio for EFS was 0.63 (97.38% CIs 0.43-0.91) at interim analysis. This regimen was approved by the FDA in March 2022, for the treatment of patients with resectable (tumors ≥4cm or node-positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.

Considering the approval of neoadjuvant and adjuvant immunotherapy options for patients with resectable Stage II-III NSCLC, AstraZeneca has decided to close enrollment early to

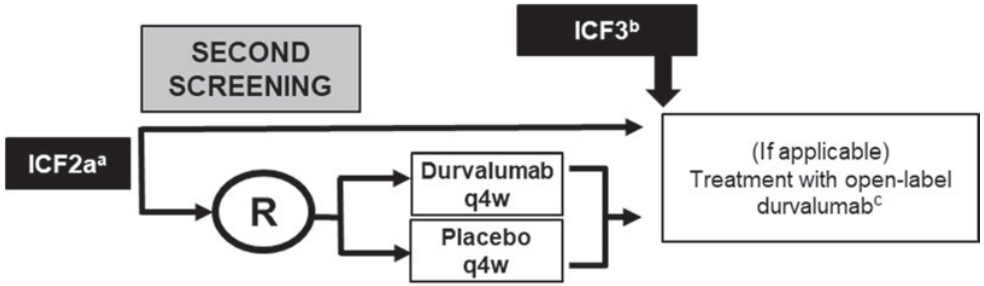
MERMAID-2 (D910MC00001). A total of 416 patients have signed informed consent for the study. This section describes the procedures required for all patients enrolled in the study and ensures that eligible patients have access to open-label durvalumab where appropriate (see Section 10.2 for details). At the time of implementation of CSP v2.0 at site, durvalumab will be supplied to sites for patients eligible to start open-label treatment. Study assessments will cease (except for serious adverse event identification and reporting and pregnancy reporting) and patients will continue with standard of care safety and efficacy assessments (based on local clinical practice).

10.2 Next steps for patients

At the time of CSP v2.0 implementation at site, given the current disposition of patients within the study, it is expected that the majority of patients will be discontinued from the study.

The following subsections describe the procedures to be followed for patients at various stages of the study following implementation of this amendment at site as summarized in Figure 5.

Figure 5 Patients with opportunity to receive open-label durvalumab following CSP v2.0 implementation at site



[a] Any eligible patient has signed ICF2a and who is either in second screening or currently receiving study treatment (either durvalumab or placebo) at the time CSP v2.0 is implemented at site will have the opportunity to receive open-label durvalumab. If patients do not choose to receive open-label durvalumab, or where Investigators deem this to be inappropriate, patients will discontinue the study after all required data have been entered in the study database.
[b] Patients who choose to receive open-label durvalumab, and where Investigators deem this to be appropriate, must sign a new informed consent (ICF3).
[c] See Section 10.3.1 for details regarding treatment with open-label durvalumab. In general, patients who choose to receive open-label durvalumab may do so until treatment completion or discontinuation criteria are met (whichever occurs first). The Investigator should refer to the discontinuation criteria summarized in Section 7.1 for further guidance on treatment discontinuation.

Note: Prospective MRD testing will stop at time of CSP v2.0 implementation at site. All patients in first screening, surveillance, or study-specific follow-up at the time of CSP v2.0 implementation at site will discontinue the study as specified in Section 10.2.1.3. Site staff must enter all required data in the study database prior to discontinuing a patient from the study.

ICF Informed consent form; MRD Minimal residual disease; NSCLC Non-small cell lung cancer; q4w Every 4 weeks; R Randomization.

10.2.1 Patients in first screening, surveillance, or follow-up

10.2.1.1 Patients in first screening or surveillance

At the time of CSP v2.0 implementation at site, patients in first screening or surveillance will be discontinued from the study.

Table 17 outlines the minimum data requirements that must be entered in the study database for all patients who are not randomized. Only the indicated data are required to be entered prior to discontinuation of any patient who is not randomized from the study.

Table 17 Required data entry for patients in first screening or surveillance

All enrolled (but not randomized) patients	Additional data required for patients with MRD result[a]

• Demographics (age, sex, ethnicity, race, region)[b]
• Smoking history and pack-years
• Stage (post-surgery)
• Local *EGFR/ALK* status[c]
• Date of surgery[c]
• Date(s) of sample collection[c]
• Reason(s) for screen failure (if applicable)
• Reason(s) for discontinuation
• Patient status at completion or discontinuation of study
• Any SAE related to study procedures
	• Prior therapy for NSCLC under study (if applicable)
	• Pre-surgical details (including imaging[c])
	• Histology, pre- and post-surgery
	• Specific surgical details:
	  ○ Extent of resection
	  ○ Pleural invasion status
	  ○ Nodal disease/confirmation of node-negative disease
	  ○ Extracapsular disease
	  ○ Mediastinal lymph node examination/dissection
	  ○ Confirmation of complete resection
	  ○ Extended pulmonary resection performed
	• Post-surgical scan data[c]

[a] Includes patients in surveillance and/or who received an MRD status under MERMAID-1 (D910LC00001) prior to transferring to MERMAID-2 (D910MC00001).
[b] Where allowed by local laws and regulations.
[c] Where available.
ALK Anaplastic lymphoma kinase; EGFR Epidermal growth factor receptor; MRD Minimal residual disease; NSCLC Non-small cell lung cancer; SAE Serious adverse event.

10.2.1.2 Randomized patients in study-specific follow-up

At the time of CSP implementation at site, randomized patients in study-specific follow-up (randomized patients who are not actively receiving study treatment) will be discontinued from the study. Investigators and all randomized patients at that site will be unblinded to study treatment allocation.

All data must be entered into the study database prior to discontinuation of each patient.

10.2.1.3 Discontinuation of patients from the study

A visit for patients who will be discontinued from study must occur **within 31 days of CSP v2.0 implementation at site.** The purpose of this visit is to collect safety data, to ensure

all patients are fully informed of the changes to the study and the implications of these changes, and to ensure that indicated data are collected and entered accurately into the study database. This visit may be performed on site or via telemedicine. The nature of the visit, and what has been discussed, must be recorded in the source documents. At a minimum, the following assessments will be performed: assessments of AEs/SAEs and changes in concomitant medications.

Any safety events identified after the patient has been discontinued from the study should be managed per local standard of care. No study assessments (e.g., blood samples or imaging) will be performed for after patient discontinuation from study.

10.2.2 Patients in second screening or randomized and receiving study treatment

At the time of CSP v2.0 implementation at site, Investigators and all randomized patients at that site will be unblinded to study treatment allocation. Patients in second screening (signed ICF2a but not yet randomized) who are deemed eligible and all patients currently receiving study treatment (regardless of treatment arm allocation) will have the option to receive open-label durvalumab (see Section 10.3.1).

For patients in second screening or currently receiving study treatment, there must be a visit **within 31 days of CSP v2.0 implementation at site** to discuss the option to start or continue open-label durvalumab. This visit can be performed on site or via telemedicine; the discussion between the patient and Investigator and its outcome must be recorded in the source documents. If this visit does not occur within 31 days of CSP v2.0 implementation at site, the patient will be considered lost to follow-up.

- For patients who do not choose to receive open-label treatment, or where Investigators deem this to be inappropriate, there must be a visit **within 31 days of CSP v2.0 implementation at site** to ensure all applicable data are collected and entered accurately into the study database. This visit may be performed on site or via telemedicine (and can coincide with the discussion indicated above) and must be recorded in the source documents. Once this final visit has been completed, the patient will then be discontinued from the study (see Section 10.2.1.3).
- For patients who choose to receive open-label durvalumab (and where Investigators deem this to be appropriate) they must sign the new ICF (ICF3) **within 31 days of CSP v2.0 implementation at site, and prior to receipt of open-label durvalumab**.

10.3 End of study/study closure

10.3.1 Treatment with open-label durvalumab

Eligible patients who sign the new ICF (ICF3) may receive open-label durvalumab. This will be for a maximum of 13 cycles (including any durvalumab already received in a blinded manner). There will only be the following exceptions:

- Patients who have already received ≥ 13 cycles of durvalumab within the MERMAID-2 study prior to CSP v2.0 implementation at site, at the discretion of the Investigator and patient, may continue to receive treatment with open-label durvalumab but **must not exceed** 26 cycles of durvalumab in total. In such a scenario, treatment will end following the patient's 26th cycle of durvalumab.
- In **exceptional** circumstances, patients who have received <13 cycles of durvalumab at the time of CSP v2.0 implementation at site may receive up to a maximum of 26 cycles. This must be agreed with the global study medical team prior to obtaining patient consent and take into account prevailing clinical evidence for treatment duration.

Patients should be treated according to the investigational site's standard of care procedures and the medical judgment of the Investigator. The nature and content of each discussion with each patient regarding the treatment plan must be recorded in the source documentation.

The Investigator should refer to the discontinuation criteria (summarized in Section 7.1) for guidance on treatment discontinuation.

10.3.2 Safety data to be collected

Any AEs and SAEs will be collected for a minimum of 90 days after the last dose of study treatment, but only SAEs will be reported. In addition, it is recommended that Investigators monitor the patient's safety laboratory results periodically for at least 90 days after the last dose of study treatment in order to manage AEs consistent with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5).

10.3.3 End of study definition

The end of the study is defined as when the last patient has received their last dose of durvalumab. Following implementation of CSP v2.0, the DCO will occur after the last patient has either discontinued the study or has signed consent (ICF3) to receive open-label durvalumab, whichever occurs later.

10.4 Statistical considerations

Under CSP v2.0, as a result of the decision by AstraZeneca to close enrollment to the study and end study assessments early, all analyses of the objectives and endpoints listed in Section 3 will be descriptive only and considered exploratory.

Further details will be included in the SAP.

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12 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 authorized representative and answer all questions regarding the study.

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

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

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

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

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study. This does not apply to the mandatory genetic testing required to generate the personalized panel required for MRD assay.

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

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

A 4 Data protection

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 authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

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

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

All patient data relating to the study will be recorded on electronic CRF (eCRF) 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 electronically signing the eCRF.

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

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 eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects 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 entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

A 9 Publication policy

The results of this study may be published or presented at scientific meetings once the primary analysis is completed and the study is unblinded. No other publications prior to that timepoint is allowed.

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

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

Subsequent to the primary publication, if an investigator plans to publish any subset of data, or case report, 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.

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

The term AE is used to include both serious and 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 (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject 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 subject or may require medical treatment to prevent one of the outcomes listed above.
- Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.
- Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor

B 3 Life threatening

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

B 4 Hospitalization

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 subject 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 judgment must be used.

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

B 6 CTCAE grade

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

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

B 7 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another 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 IP 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 recognized that could have led to an error

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the 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 eg, kept in the fridge when it should be at room temperature
- 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 Investigator at each center keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps 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

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

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 are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

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

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

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. 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
- **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 Genetics (for Optional Genetic Research Study)

This appendix relates to the **optional** genetic research study only. This is separate from the mandatory genetic components of this study. Details pertaining to the mandatory genetic samples and analyses that are required in this study are addressed in the Laboratory Manual.

D 1 Use/analysis of DNA

Genetic variation 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 etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic 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 DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient´s DNA (ie, the entire genome).

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

The Sponsor will store the DNA 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 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic 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 genetic research, patients must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

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

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:

Subjects may withdraw from this genetic 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 Appendix C 2.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients pre-dose at the first dosing visit. Although DNA is stable, 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 first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics 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 genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA 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 DNA extraction 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 genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

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 organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical 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 B.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic 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 center. 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 genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype 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 genetic data 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 also have access to his or her genetic 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 genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations 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 genetic 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 genetic 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 Mandatory Genetic analysis for Minimal Residual Disease

This appendix relates to the mandatory genetic component of this study.

Use/analysis of DNA in mandatory genetic study

Minimal residual disease (MRD) will be detected using a Sponsor-approved, complex personalized multi-step assay. Firstly, whole exome sequencing (WES) of the patient's tumor is performed on primary resection sample and controlled for by germline mutations by WES of whole blood (as indicated in the Schedule of Activities Table 1), using CCI [redacted] Germline exome sequencing will be performed at a depth of >25x, whereas tumor exome sequencing will have a mean sample coverage of CCI [redacted] This personalized approach allows detection of the patient's tumor variants in circulating tumor DNA (ctDNA) at high sensitivity. Tumor and whole blood samples, including DNA derived from those samples, as well as WES data, will be used for diagnostic development and exploratory research.

Sample coding and storage

All samples submitted for MRD will be coded to prevent patient identification. Sequencing data and variant calls from MRD analysis will be stored in a secure system at designated organizations to analyze the sample and/or at AstraZeneca. Germline data analysis will be conducted for the purpose of identifying tumor-specific variants not present in the patient's non-cancerous cells.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this mandatory genetic research component, are outlined in Appendix B.

Informed consent

Patients must sign Informed Consent Form 1 (ICF1) of the overall study to participate in this mandatory genetic component of the study.

Patient data protection

AstraZeneca will not provide individual genotype 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 genetic data 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 also have access to his or her genetic 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 genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.

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

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

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

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether 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 (IMP).

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

F 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN 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 ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

F 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 subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

Central laboratories being used:

When a subject meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- 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 subject meets PHL criteria (see Section F 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Local laboratories being used:

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 subject meets PHL criteria (see Section F 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

F 4 Follow-up

F 4.1 Potential Hy's Law Criteria not met

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

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

F 4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:

  Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.

  Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used

Complete the three Liver CRF Modules as information becomes available

A 'significant' change in the subject'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.

F 5 Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality 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 IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. 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.

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

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

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

- Send updated 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 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

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

F 6 Laboratory tests

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA

Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly

REFERENCES

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

NOTE: for evaluation of disease recurrence, please refer to the RECIST 1.1 definition of new lesions.

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this Appendix. Additional special guidance is provided for evaluation of scans collected after a RECIST 1.1-defined radiological progression.

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of Target Lesions (TLs), Non-Target Lesions (NTLs), and New Lesions (NLs) is provided in Table 18.

Table 18 Summary of imaging modalities for tumor assessment

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

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

CT and MRI

Computed tomography (CT) with intravenous (IV) contrast is the preferred imaging modality (although magnetic resonance imaging [MRI] with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each patient throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the

Schedule of Activities [SoA; Table 2]), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artifacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; 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. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

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

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen. 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.

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these timepoints are specified in the SoA (Table 2). Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including liver and adrenal glands)
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including liver and adrenal glands)
- IV contrast-enhanced CT or MRI of the head and neck
- IV contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when patients have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen CT with IV CT contrast (most preferred)
2 Chest CT without IV contrast + abdomen MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study
3 Chest-abdomen CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the patient has compromised renal function
4 Chest-abdomen MRI with IV MRI contrast, if CT cannot be performed at any time during the study

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤5-mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT 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.

Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Plain X-ray

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

Isotopic bone scan

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

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

FDG-PET/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography/CT (FDG-PET/CT) scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[1] not present on baseline or prior FDG-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the FDG-PET scan. The PET portion of the PET/CT introduces additional data that may bias an Investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for 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 introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may

1 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.

not provide an accurate assessment of the true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other tumor assessments

Clinical examination

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

Histology and cytology

Histology or tumor markers 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, and pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Furthermore, an overall assessment of complete response (all other disease disappears/reverts to normal) would be changed to partial response if an effusion remains present radiologically.

Measurability of tumor lesions at baseline

RECIST 1.1 measurable lesions at baseline:

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable lesions at baseline:

- Truly non-measurable lesions include the following:
  Bone lesions (see exception below for soft tissue component)
  Leptomeningeal disease
  Ascites, pleural effusion, or pericardial effusion

[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

Inflammatory breast disease

Lymphangitic involvement of skin or lung

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10-mm to <15-mm short axis diameter at baseline[3])
- Previously irradiated lesions[4] <<*Study Specific: Previously irradiated lesions are typically allowed only as (non-measurable) Non-Target Lesions; however, some studies may allow a previously irradiated measurable lesion as a Target Lesion if this is the only lesion available.*>>
- Brain metastasis

Special considerations regarding lesion measurability at baseline:

- Bone lesions

  Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.

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

RECIST 1.1 TL selection at baseline:

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 TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible

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

[4] Localized post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

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

Special cases for TL assessment at baseline:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.

RECIST 1.1 NTL selection at baseline:

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of tumor response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter

for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.
- 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. The choice of "Too large to measure" in the case report form will trigger an overall visit response of PD.
- When a TL has had an intervention, the following apply:

  Target Lesion Intervention may include radiotherapy, embolization, excisional biopsy, surgery, etc. that is not a part of study treatment and might adversely affect the size of that Target lesion

  If an Intervention on a Target Lesion is ticked in the case report form, the diameter of the lesion is still recorded (0 mm if no longer present) and is included in the sum of diameters.

  If a Target Lesion Intervention is ticked, the Intervention must be reported for all subsequent assessments of that Target lesion.

  If a Target Lesion has an Intervention, the only Overall Visit Responses allowed to be recorded by the Investigator are NE or PD, with PD if the sum of diameters exceeds a 20% increase and at least a 5 mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.

  No visit with a recorded Target Lesion Intervention can be used as the minimum (nadir) sum of diameters.

Table 19 RECIST 1.1 evaluation of target lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable disease (SD)	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir)—This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	Only relevant if no TLs present at baseline.

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

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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.

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 unequivocal progression by NTLs. A modest 'increase' in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of stable disease (SD) or progressive disease (PR) of target disease will therefore be extremely rare.

Table 20 RECIST 1.1 evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of 1 or more NTLs.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.

Not evaluable (NE)	Only relevant when 1 or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if no NTLs present at baseline

CR Complete response; NE Not evaluable; NTL Non-target lesion; PD Progression of disease; TL Target lesion.

RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the case report form. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If a NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) new lesion has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

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

RECIST 1.1 evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 21.

Table 21 RECIST 1.1 overall visit response

Target Lesions	Non-Target Lesions	New Lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (non-CR/non-PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE

Target Lesions	Non-Target Lesions	New Lesions	Overall visit response
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/Non-PD for Overall Response if only non-target lesions (no TLs) are present at baseline.
Note: An overall assessment of Complete Response (all other disease disappears/reverts to normal) would be changed to Partial Response if ascites remains present radiologically.
CR Complete response; NA Not applicable (only relevant if there were no target lesions at baseline or non-target lesions at baseline), NE Not evaluable; NED No Evidence of Diseases (only relevant if there were neither target lesions nor non-target lesions at baseline); PD Progressive disease; PR Partial response; SD Stable disease; TL Target Lesion.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For patients with TLs (at baseline): complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), or not evaluable (NE)
- For patients with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For patients with no disease at baseline: NED (no evidence of disease; available as an option in the electronic case report form), PD, or NE

Evaluation of scans subsequent to RECIST 1.1-defined progression

A follow-up scan is requested at least 4 weeks after a RECIST 1.1-defined radiological progression and no longer than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the Investigator for patient management and further treatment decisions, and since the published RECIST 1.1 criteria (Eisenhauer 2009) do not provide guidance on how to assess scans acquired after RECIST 1.1-defined PD, supplemental instructions for Investigators on how to evaluate these follow-up scans are provided below. An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if *any* of the following criteria are met in the subsequent follow-up scan:

- ≥20% increase and at least a 5-mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥5 mm in the sum of diameters at the follow-up scan timepoint compared with the immediate prior timepoint
- significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint
- significant progression (worsening) of previously new lesions (pre-existing new lesions) at the follow-up scan timepoint compared with the immediate prior timepoint
- additional brand-new unequivocal lesions at the follow-up scan timepoint

Central imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (iCRO) for QC, storage, and for Blinded Independent Central Review (BICR). Guidelines for image acquisition, de-identification, storage of digital copies at the investigative site (as source documents), and transfer to the iCRO will be provided in a separate document. Electronic image transfer from the sites to the iCRO is strongly encouraged. 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.

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 H Contraception Requirements

The following contraception requirements should be verified/adjusted for each study and should be further adjusted to take into account Clinical Trial Facilitation Group guidelines for embryotoxicity if observed with the study intervention.

Contraception requirements for this study are as follows.

H 1 Female Participants

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

Women will be considered post-menopausal if they have been amenorrhoeic 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 amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy 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 amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago.

Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table 22). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to use it throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of study intervention).

Non-sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant. Female participants should refrain from breastfeeding throughout this period.

H 2 Male Participants with a Female Partner of Childbearing Potential

Non-sterilized male participants (including males sterilized by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception such as male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and the drug washout period (90 days after the last dose of study intervention) to prevent pregnancy in a partner.

If more than 1 treatment group is included in the study, add additional time periods as necessary here (eg, <<XX>> days after the last dose of <<study intervention 1>> or <<XX>> days after the last dose of <<study intervention 2>>).

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation or banking throughout this period.

Vasectomised (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing fetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 22).

H 3 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table 22. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 22 Highly Effective Methods of Contraception (<1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Tubal occlusion • Intrauterine device (provided coils are copper-banded)	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®)[a] • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a] • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Mini pill: Progesterone-based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[d] Hormonal methods not prone to drug-drug interactions.

Appendix I CCI

This appendix includes example copies of the following CCI questionnaires:

- European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire
- EORTC 13-item Lung Cancer Quality of Life Questionnaire
- CCI
- CCI
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ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|
Your birthdate (Day, Month, Year): |_|_| |_|_| |_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_| |_|_| |_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

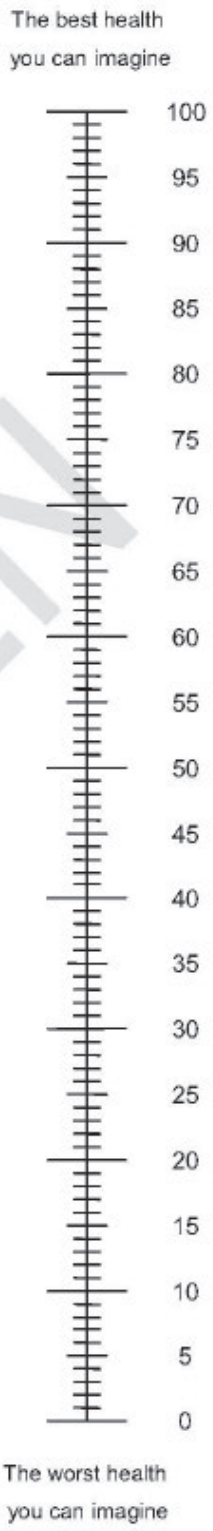
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Study Number: D0000C00000		Site Number:
Subject Number:	Visit Number:	Assessment Date:

CCI [redacted]

[redacted]

Study Number: D0000C00000		Site Number:
Subject Number:	Visit Number:	Assessment Date:

CCI [redacted]

[redacted]


CCI

Appendix J Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BP	blood pressure
CD	cluster of differentiation
CI	confidence interval
CL	clearance
CRO	Contract Research Organization
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DBL	database lock
DCO	data cut-off
DFS	disease-free survival
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items
ePRO	electronic Patient-reported Outcomes
CCI	CCI
FAS	full analysis set
FDA	United States Food and Drug Administration
FDG-PET	^{18}F-Fluoro-deoxyglucose positron emission tomography
GCP	Good Clinical Practice
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus

Abbreviation or special term	Explanation
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iCRO	imaging Contract Research Organization
ICU	intensive care unit
IDMC	independent data monitoring committee
IEC	independent ethics committee, synonymous to ethics committee (EC) and IRB
IHC	immunohistochemistry
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IO	immune-oncologic
IP	investigational product
IRB	institutional review board
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally.
IV	intravenous
IWRS	interactive web response system
LIMS	Laboratory Information Management System
mAb	monoclonal antibody
mRNA	messenger ribonucleic acid
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NTL	non-target lesion
OS	overall survival
PD	progression of disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival

Abbreviation or special term	Explanation
CCI	CCI
CCI	CCI
PI	Principal Investigator
PK	pharmacokinetic(s)
PORT	post-operative radiotherapy
PR	partial response
CCI	CCI
PS	performance status
q3w	every 3 weeks
q4w	every 4 weeks
CCI	CCI
CCI	CCI
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	stable disease
SoA	Schedule of Activities
SoC	standard of care
sPD-L1	soluble programmed cell death ligand 1
SpO_2	saturation of peripheral oxygen
CCI	CCI
TL	target lesion
TMB	tumor mutational burden
CCI	CCI
UICC/AJCC	Union for International Cancer Control–American Joint Committee on Cancer
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VATS	video-assisted thoracoscopic surgery
WES	whole exome sequencing
w/v	weight per volume
WHO	World Health Organization

SIGNATURE PAGE

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