Clinical Study Protocol	
Drug Substance	Durvalumab
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A Phase III, Randomized, Multicenter, Double-blind, Placebo-controlled Study to Determine the Efficacy of Adjuvant Durvalumab in Combination with Platinum-based Chemotherapy in Completely Resected Stage II-III NSCLC (MERMAID-1)

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VERSION HISTORY

Version 1.0, 09 March 2020
Initial creation
Version 2.0, 02 April 2021
The primary purpose of this amendment is to simplify and clarify aspects of the screening procedures; to provide flexibility during screening; to reflect real world practice; removal of never-smokers from the patient population and to provide additional information and guidance to sites and Investigators. 1. Removal of never-smokers from the eligible patient population. 2. Updated the timing of the DFS analysis. **Sections updated: 1.2; 9.2.** 3. Clarification of number of tumor-specific variants required to develop the patient's personalized MRD assay. Changed from "up to 50" to read "50" exactly. **Sections updated: 1.1; 1.2; 4.1; 5.1.1 (Inclusion criterion #8), 5.4; 8.7.1.2; Appendix E.** 4. Removal of pharmacokinetic (PK) and anti-drug antibodies (ADA) secondary endpoints, sample collection, and analysis. **Sections updated: 1.1; 1.2; 3; 9.3; 9.5; Table 2; Table 3; Figure 1. Sections removed: 8.5; 9.3.4; 9.3.5; 9.4.4; 9.5.3-9.5.5.** 5. Removed requirement for MRD- patients to be consented prior to surgery and give a pre-surgical plasma sample, and removed window around pre-surgical plasma collection. **Sections updated: 1.1; 4.1; 5.1.1 (Inclusion criteria #1 and #7); 8.7.1.2; Table 1; Table 4.** 6. Clarification of what is the latest a patient can be enrolled in the study/sign ICF1. **Sections updated: 1.1; 4.1; 5.1.1 (inclusion criterion #1); Table 1; Table 4.** 7. Removed requirement that all screened patients will be tested for PD-L1. **Sections updated: 1.2; 4.1; 8.7.1.3; Table 1.** 8. Expanded post-surgical blood collection window from Week 3-4 (Day 21-28) to Week 3-5 (Day 21-35). **Sections updated: 1.1; 4.1; 5.1.1 (Inclusion criteria #1 and #9); 8.7.1.2; Table 1; Table 4; Figure 1.**

9. Addition of wording to allow telemedicine and/or home nursing for select visits, subject to local laws and regulations, and following a discussion with the Investigator and Sponsor. **Sections updated: 4.1; Table 1; Table 2; Table 3.**

10. Added flexibility to timing of brain scan required for complete staging. **Sections updated: 5.1.1 (Inclusion criterion #5); Table 1; Table 4.**

11. Clarification of post-surgical scan timing. **Sections updated: 1.2; 4.1; 5.1.1 (Inclusion criterion #11); 8.1; Table 1; Table 2; Table 4; Table 5.**

12. Clarification that only SAEs related to study procedures must be reported during first screening (i.e. after ICF1 is signed but prior to signature of ICF2). **Sections updated: 6.4; 8.3.2; 8.3.11; 8.4.1; Table 1.**

13. Removal of microbiome (stool) sample collection and exploratory endpoint. **Sections updated: 1.2; 3; 4.2.3.1; Table 2; Table 3. Section removed: 8.8.2.4.**

14. Clarification of disease assessment frequency. **Sections updated: 7.1.1; 8.1; Table 2; Table 3.**

15. Removal of mandatory confirmatory scan post-recurrence. **Sections updated: 1.2; 6.1.4; 7.1.1; 8.1.1.1; Table 2; Table 3.**

16. Update of duration of ePRO collection during follow-up. **Section updated: Table 3.**

17. Addition of optional tumor biopsy at recurrence to include follow-up period. **Section updated: Table 3.**

18. Clarification of acceptable *EGFR/ALK* results. **Sections updated: 1.2; 4.1; 5.2 (Exclusion criterion #2); 8.7.1.1; Table 1; Table 5; Figure 1.**

19. Provision of guidance in selecting patients with higher mutational load. **Sections updated: 1.2; 4.1.**

20. Addition of immune cell (IC) PD-L1 expression to exploratory endpoints. **Sections updated: 1.2; 3; 8.7.2.2.**

21. Clarification regarding collection of data following data cut-off and timing of overall survival analysis/final overall survival analysis. **Sections updated: 1.2; 4.4; 6.1.4; 6.6.**

22. Extended time to DFS analysis from 3 months to 4 months post-last subject in. **Sections updated: 1.2; 9.2.**

23. Clarification that DFS will be determined using the RECIST 1.1 definition of new lesions. **Sections updated: 4.2.3; 8.1; Appendix G.**

24. Rationale for fixed dosing. **Section updated: 4.3.3.**

25. Update to and clarification of acceptable pre-surgical imaging modalities and timing. **Sections updated: 5.1.1 (Inclusion criterion #5).**

26. Clarification and definition of complete resection. **Section updated: 5.1.1 (Inclusion criterion #6).**

27. Clarification regarding window for randomization. **Section updated: 5.1.2 (Inclusion criterion #12).**

28. Clarification of non-leukocyte depleted blood transfusions. **Section updated: 5.2 (Exclusion criterion #7).**

29. Clarification regarding prohibited prior radiotherapy. **Sections updated: 5.2 (Exclusion criterion #17); Table 5.**

30. Update to "Lifestyle Restrictions" section (regarding birth control and pregnancy). **Section updated: 5.3. Sections added: Table 18; Appendix H.**

31. Addition of re-screening criteria. **Section updated: 5.4.**

32. Addition of Table 7 – Minimum data entry requirements. **Section updated: Table 1. Section added: Table 7.**

33. Clarification of why and when a patient may be screen-failed. **Sections updated: 5.4; 6.2.1.**

34. Combined handling instructions for durvalumab and placebo as both are "IP" in this double-blinded study. **Section updated: 6.1.2.1; Table 8. Section removed: 6.1.2.3.**

35. Update to guidance regarding post-operative radiotherapy (PORT). **Sections updated: 6.4; 6.4.1; Table 10; Figure 2.**

36. Removal of text related stopping treatment due to rapid tumor progression. **Section updated: 6.1.4.**

37. Clarified that PD-L1 results will be blinded; unblinding will occur should the Investigator request to be unblinded to treatment. **Sections updated: 6.2.4 and 6.2.5.**

38. Additional guidance on steroids prior to chemotherapy. **Section updated: Table 9.**

39. Update to guidance regarding antibiotic use prior to randomization. **Section updated: Table 9.**

40. Removal of Toxicity Management Guidelines webportal as webportal has been decommissioned. **Sections updated: 6.5; 8.3.12; 8.3.13; 8.4.5.1.**

41. Additional guidance regarding treatment post-primary DFS analysis and post-recurrence. **Section updated: 6.6; 7.1.**

42. Additional guidance regarding dating disease recurrence. **Section updated: 8.1.1.2.**

43. Removal of ePRO completion threshold. **Section updated: 8.1.4.5.**

44. Allowance for HIV and hepatitis to be tested during first screening; if negative, not necessary to test low-risk patients again during second screening. **Sections updated: 8.2.1; Table 1; Table 2.**

45. Updated section "Optional Genomics Initiative genetic sample". **Section updated: 8.6.2.**

46. Update to publication policy. **Section updated: Appendix A9.**

47. Update to exome coverage description. **Section updated: Appendix E.**

48. Update to Appendix G to reflect the primary endpoint of disease-free survival and to provide additional guidance regarding RECIST 1.1 definition of new lesions. **Sections updated: Appendix G; Table 17. Sections removed: Table 18, Table 19.**

49. Appendix H is now Appendix I; Appendix I is now Appendix J.

50. Added references Abbosh et al 2020; Moding et al 2020; Nagashi et al 2018; Offin et al 2019; Papadimitrakopoulou et al 2018; Nishio et al 2020; Rolia et al 2016; Pinato et al 2019. **Section updated: 10.**

51. Minor administrative/editorial changes were made throughout the protocol for clarity and consistency.

Version 3.0, 06 May 2021

1. Updated numbering in sections 5.2 Exclusion Criteria and 5.3 Lifestyle Restrictions
2. Update of Safety analysis set (SAS) definition. **Section updated: 9.3.3.**
3. Clarification regarding prohibited prior radiotherapy. **Sections updated: Section 5.2 (Exclusion criterion #17), Table 5**

Version 4.0, 02 August 2022

The primary purpose of this amendment was to revise planned analyses of objectives and endpoints based on the reduced sample size, following AstraZeneca's decision to close enrollment on 25 May 2022.

1. Caveat added throughout the protocol regarding activities planned prior to CSP V4.0 that will not be performed due to decision by AstraZeneca to close enrollment early.
2. Removal of footnote related to open-label treatment for patients still on durvalumab and the collection of safety data and efficacy scans due to early study enrollment closure**. Section updated: 1.1, Table 2 and Table 3**
3. Added recently published data from Phase III studies that led to the decision to close study enrollment. **Sections updated: 1.2, 2.1, 2.2.3.1, 2.2.3.3, and 2.3.3**
4. Addition of text regarding change in primary objective and endpoint. **Sections updated: 1.2, 2.3.3, 3, and 9.1**
5. Primary objective and endpoint analysis population changed from MRD+ patients to all randomized patients (FAS). **Sections updated: 1.2, 3, 8.1, and 9**
6. Secondary objective and endpoint analysis population comparing durvalumab and placebo using Investigator assessments according to RECIST 1.1 changed from all (FAS) to MRD+. **Sections updated: 1.2, 3, 8.1, and 9**
7. Secondary endpoint of DFS using BICR assessment according to RECIST 1.1 was removed. **Sections updated: 1.2, 3, 8.1, 9.4.1.1, 9.5.1, and 9.5.1.2**

8. Removed collection of PROs. **Sections updated: 1.1 (Table 2 and Table 3) and 8.1.4**

9. Collection and analysis of health care resource use removed. **Sections updated: 1.1 (Table 2 and Table 3), 1.2, 3, 8.8, 9.4.3.4, and 9.5.1.5**

10. Analysis of EORTC QLQ-30 and EORTC-QLQ-LC13 moved from secondary to exploratory analysis. **Section updated: 1.2 and 3**

11. Removed statement that health care resource use will be used to support assessment of durvalumab by health technology agencies. **Section updated: 4.2.3.1**

12. Addition of text indicating decision to close study enrollment, updated number of enrolled patients following study enrollment closure, and indicating final number of study centers. **Sections updated: 1.2, 4.1, and 5**

13. Reference to "primary DFS analysis" removed from table heading in SoA and updated assessment duration. **Section updated: 1.1 (Table 3)**

14. Addition of text that enrollment to the study has now closed. **Sections updated: 1.2, 1.3, 2.1, 4.1, and 5**

15. Update of first patient enrolled and estimated last patient completion. **Section updated: 1.2**

16. Removal of text for long-term survival follow up. **Sections updated: 1.2, 6.1.4, 6.6**

17. Removal of text for long-term OS collection and study roll over**. Sections updated: 1.2, 4.4, 6.1.4 and 6.6**

18. End of study definition updated to account for early closure of study enrollment. **Sections updated: 1.2 and 4.4**

19. Text added to clarify that the DCO for primary DFS analysis will follow last patient last visit. **Sections updated: 4.4 and 6.1.4**

20. Clarification that the primary DFS analysis will be performed due to closure of study enrollment. **Sections updated: 1.2, 6.6, and 9.1**

21. Statistical methods, analyses, and efficacy outcomes were updated to account for AstraZeneca's decision to close study enrollment early leading to revision

of objectives and endpoints based on the revised sample size. **Sections updated: 1.2, 2.1, 3, 4.2.3, and 9**

22. Study schema Figure 2 was added with revised ample size to account for AstraZeneca's decision to close study enrollment early. **Sections updated: 1.3 and 4.1**

23. New section added to clarify rationale for AstraZeneca's decision to close study enrollment early. **Section added: 4.1.1**

24. A new section was added for a rationale to continue using placebo in this version of the CSP. **Section added: 4.3.5**

25. Guidance for post data cut-off evaluation was removed. **Section updated: 6.1.4**

26. Clarification added that the patient's MRD status will not be unblinded at the time of treatment unblinding. **Section updated: 6.2.5**

27. Further guidance added for Investigators regarding patients who withdraw from the study. **Section updated: 7.3**

28. Update of procedures for the collection of safety data following the final DCO. **Section updated: 8.3.13**

29. Removed sensitivity analysis of DFS, using Investigator assessments according to RECIST 1.1, as they may no longer be required due to the exploratory nature of analyses. **Section updated: 9.5.1.1**

30. Minor administrative/editorial changes were made throughout the protocol for clarity and consistency

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

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1 PROTOCOL SUMMARY

1.1 Schedule of activities

This study will employ a 2-tiered consent and screening process that begins prior to surgery in 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 (initiated by the signing of Informed Consent Form 1 [ICF1]) for the period before, during, and after surgery but prior to final determination of eligibility for randomization in the study. The purpose of this first screening period is to collect and analyse tumor and blood samples necessary to determine the minimal residual disease (MRD) status of the patient. This is done by performing whole exome sequencing (WES) of the patient's resected tumor tissue and whole blood to identify tumor-specific DNA variants. A personalized panel comprised of 50 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 in the patient's plasma. The development of the MRD assay requires mandatory genetic testing.

Table 2 includes the procedures conducted during the second screening (initiated by the signing of Informed Consent Form 2 [ICF2] once a patient's MRD status is known) through the treatment period. The procedures for the follow-up period are presented in Table 3.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw to occur at the timepoints indicated in the schedule of activities (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 both treatment arms (durvalumab/placebo ± standard of care chemotherapy)

- One cycle is equal to 21 days (every 3 weeks [q3w]) during the durvalumab plus standard of care (SoC) chemotherapy or placebo plus SoC chemotherapy combination portion of the study, and 28 days (every 4 weeks [q4w]) during the durvalumab/placebo monotherapy portion of the study.

- Patients may delay dosing under certain circumstances.
  - For durvalumab/placebo:
    - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (See Section 8.4.5.1), due to either an immune or a non-immune related adverse event (AE).
    - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of disease (Response Evaluation Criteria in Solid Tumors [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's Brochure [IB] for durvalumab). If there is a dosing delay while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment remain at least 21 days.

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

	Prior to surgery[a]	Surgery[a]	Post-surgery			For details, see Section
Week	**Up to day of surgery**		**1[b]**	**3-5**	**Prior to randomization**	
Day	**Up to 0**	**0**	**1-8**	**21-35**		
Histologically confirmed NSCLC (WHO 2015 classification), stage IIA to select (ie, T3N2 or T4N2) stage IIIB (according to IASLC v8.0)[a]	X		X			5.1.1
Pre-surgical contrast-enhanced CT/MRI of chest and abdomen (including liver and adrenals)[a,c]	X					5.1.1
Brain MRI (preferred) or brain CT with IV contrast	X[d]					5.1.1
ICF1[e]	X					5.1, 5.1.1
Study procedures						
Eligibility[f]	<----------X---------->					Table 4, Table 5, Table 7, 5.1.1, 5.2, 5.4
Demography, including initial disease characteristics and tobacco use[g]	X		X			5.1, Table 7
Surgery/confirmation of complete resection[a] Complete surgical information[a]		X	X			5.1.1
EGFR/ALK testing of tumor tissue[h]	X		X[i,j]			8.7.1.1
Whole blood sample for WES[k]	X					8.7.1.2
Plasma sample collection for MRD evaluation and exploratory analyses	X[l]			X[m,n]		8.7.1.2, 8.7.2.1

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

	Prior to surgery[a]	Surgery[a]	Post-surgery			For details, see Section
Week	**Up to day of surgery**		**1[b]**	**3-5**	**Prior to randomization**	
Day	**Up to 0**	**0**	**1-8**	**21-35**		
Resected tumor tissue sample for pathology confirmation, WES, and development of personalized panel[i,j]			X			8.7.1.2
Resected tumor tissue collected for exploratory analyses[i,j]			X			8.7.1.2
Resected tumor tissue sample sent for prospective PD-L1 testing[i,j]			X[o]			8.7.1.3
SAEs related to study procedures	<----------X[p]---------->					8.3
Concomitant medications/medical history/concomitant procedures	<----------X[p,q] ---------->					5.1, 5.2, 6.4, 8.2.2, Table 9
Disease assessments (as assessed by Investigator using RECIST 1.1)					X[r]	

[a] Stage II or III diagnosis should be confirmed using biopsy or resected tumor tissue results prior to randomization. Confirmation of diagnosis and surgery will not be considered study procedures. However, the date of surgery and post-surgical stage must be recorded for every enrolled patient. For every patient whose MRD status is determined during first screening, additional study-specific information obtained prior to, during, and after surgery (as outlined in the study inclusion criteria, see Section 5.1.1), including pre-surgical imaging details and complete surgical information, must be captured in the appropriate eCRFs of the study database (see Table 7 and Section 5.4).

[b] The assessments listed in the Week 1 (Day 1-8) post-surgery column should be performed as soon as possible after surgery, but no later than Week 3 (d21) post-surgery to allow timely shipment of the samples (i.e. tumor and whole blood) required to develop the personalized MRD panel. ***Exception:*** Patients identified after Week 3 (d21) post-surgery but prior to Week 5 (d35) post-surgery may be allowed to enrol in the study, depending on the outcome of the discussion with the study physician.

[c] Combination FDG-PET/CT is acceptable for pre-operative staging in absence of contrast-enhanced CT of chest and abdomen.

[d] The brain MRI (preferred) or brain CT should be performed pre-operatively per standard of care. However, if this scan is not performed prior to surgery, this scan must be conducted during first screening (ie, prior to signing ICF2 and entering second screening).

[e] 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. ICF1 can be signed either prior to surgery (***preferred***) or as soon as possible after surgery (see footnote *b* above) and will obtain consent for the mandatory genetic component of this study. ***Exception:*** Patients may be allowed to enrol/sign ICF1 after Week 3 (d21) post-surgery but prior to Week 5 (d35) post-surgery depending on the outcome of the discussion with the study physician.

[f] Eligibility criteria assessed during the first screening period include requirements that must have been met pre-surgery, at surgery, and/or post-surgery as summarized in Table 4 and Table 5 and detailed in Section 5.1.1. The reason(s) for screen failure must be captured in the appropriate eCRF for each enrolled patient subsequently determined to be ineligible

[g] Demographics must be captured in the appropriate eCRFs for every enrolled patient (see Table 7 and Section 5.4).

[h] *EGFR/ALK* testing should be performed on a pre-surgical biopsy wherever possible; however, if a pre-surgical biopsy is not available or evaluable, testing will be conducted on the resected tumor tissue while the personalized panel is in development. Testing only needs to be done at **one** of these timepoints. Results from local testing are acceptable, provided testing was performed using a well-validated, local regulatory-approved test; results from testing performed during screening for another AstraZeneca study may be used. If local testing and/or previous results are not available, *EGFR/ALK* testing will be performed centrally. Patients will still be allowed to continue study screening procedures and development of the personalized panel would continue while testing is ongoing; however, *EGFR* and *ALK* status must be known prior to randomization as patients with *EGFR* mutations or *ALK* translocations are not eligible. ***Note:*** Where *EGFR/ALK* results are obtained from a pre-surgical tissue biopsy as part of standard local practice, the patient must be confirmed as *EGFR/ALK* wild-type prior to signing ICF1 and enrolling in the study.

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

[j] FFPE samples of resected tumor tissue will be collected.

[k] The whole blood sample for germline WES will only be collected at **one** time, either before or after surgery. For patients who enrol in the study prior to surgery, it is **preferred** that the whole blood sample for germline WES is collected and sent to the diagnostic lab prior to surgery. For patients who do not enrol in the study before their surgery, a whole blood sample for germline WES must be sent as soon as possible post-surgery (after they sign ICF1) for development of the personalized panel.

[l] All patients who sign ICF1 prior to surgery must have a plasma sample collected before or on the day of surgery (prior to the surgery itself). Patients will not be excluded from randomization based on the analysis of this pre-surgical sample. This sample may be collected at the same time as the whole blood sample for germline WES.

[m] A plasma sample will be collected at Week 3-5 (Day 21-35) post-surgery to determine MRD status. Investigators will not be notified of MRD status and eligibility will be managed through the IWRS.

[n] An additional plasma sample will be collected at the same time as the post-surgery sample described in footnote *m*. This sample will be held as a baseline sample for exploratory analyses.

[o] Programmed cell death-ligand 1 (PD-L1) tumor cell (TC) expression will be evaluated by a central reference laboratory on the resected tumor tissue collected during the first screening period. PD-L1 status is required for randomization.

[p] Only SAEs specifically related to study procedures (ie, study-specific blood draws and [if performed during first screening] the post-surgical scan) should be reported during the first screening period (ie, after ICF1 has been signed but prior to signature of ICF2) and recorded in the eCRF. Concomitant medications, medical history and concomitant procedures related to this event should only be recorded in the eCRF if such an SAE is reported.

[q] Concomitant post-surgery procedures should be captured in the appropriate sections of the eCRF.

[r] A CT scan of the chest (including liver and adrenal glands) must be performed within 28 + 7 days (i.e. within 35 days) **prior to randomization** to confirm no evidence of disease and to serve as the patient's baseline scan. A brain MRI (preferred) or brain CT may be performed if clinically indicated (at the discretion of the Investigator). This scan may occur during first or second screening (Table 2).

Note: For some visits, telemedicine and/or home visits (at the patient's home or other appropriate location) may be permitted. Telemedicine and/or home visits are permitted only where feasible, allowed by local laws and regulations, and following consultation with the Investigator and the Sponsor.
ALK Anaplastic lymphoma kinase; d Day; eCRF Electronic case report form; *EGFR* Epidermal growth factor receptor; FFPE Formalin-fixed paraffin-embedded; IASLC International Association for the Study of Lung Cancer; ICF1 Informed consent form 1; IWRS Interactive web response system; MRD Minimal residual disease; MRD- MRD-negative; MRD+ MRD-positive; NSCLC Non-small cell lung cancer; PD-L1 Programmed cell death-ligand 1; SAE Serious adverse event; w Week; WES Whole exome sequencing; WHO World Health Organization.

Table 2 Schedule of assessments for second screening and 12-month treatment period (initiated by the signing of ICF2)

	Screening	C1	C2	C3	C4	C5 to C14 or until RECIST 1.1-defined disease recurrence	For details, see Section
Week	**-4 to -1**	**0**	**q3w ±3d[b] unless dosing needs to be held for toxicity reasons**			**q4w ±3d[b] unless dosing needs to be held for toxicity reasons**	
Day	**-28 to -1**	**1[a]**	**q21d ±3d[b] unless dosing needs to be held for toxicity reasons**			**q28d±3d[b] unless dosing needs to be held for toxicity reasons**	
ICF2[c]	X						5.1.2
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	8.2.3
Vital signs[d]	X	X	X	X	X	X	8.2.4
ECG[e]	X	As clinically indicated					8.2.5
Concomitant medications	<----------					---------->	6.4
Concomitant procedures[f]	<----------					---------->	6.4.1
Eligibility criteria[g]	X						Table 4, Table 5, Table 7, 5.1, 5.2, 5.4
Laboratory Assessments							
Clinical chemistry[h]	X	X[i]	X	X	X	X	Table 11
Hematology[h]	X	X[i,j]	X	X	X	X	Table 12
TSH, (reflex free T3 or free T4[k])	X	X[l]	X	X	X	X	Table 11

Table 2 Schedule of assessments for second screening and 12-month treatment period (initiated by the signing of ICF2)

	Screening	C1	C2	C3	C4	C5 to C14 or until RECIST 1.1-defined disease recurrence	For details, see Section
Week	**-4 to -1**	**0**	**q3w ±3d[b] unless dosing needs to be held for toxicity reasons**			**q4w ±3d[b] unless dosing needs to be held for toxicity reasons**	
Day	**-28 to -1**	**1[a]**	**q21d ±3d[b] unless dosing needs to be held for toxicity reasons**			**q28d±3d[b] unless dosing needs to be held for toxicity reasons**	
Urinalysis	X	As clinically indicated					Table 13
Hepatitis B and C and HIV[m]	X						8.2.1
Pregnancy test[n]	X	X	X	X	X	X	8.2.1
Monitoring							
WHO/ECOG performance status	X	X	X	X	X	X	8.2.7
AE/SAE assessment	<----------					---------->	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[n,o,p]		X	X	X	X	X	6.1
SoC chemotherapy[p,q]		X	X	X	X		6.1.2.2
Other assessments and assays							
Plasma sample for exploratory analyses[r]		Sample collected on Day 1 of each treatment cycle					8.7.2.1
Whole blood for gene expression (PaxGene mRNA)[r]		X			X	C14 or recurrence	8.7.2.3
Serum for soluble biomarkers[r]		X			X	C14 or recurrence	8.7.2.1

Table 2 Schedule of assessments for second screening and 12-month treatment period (initiated by the signing of ICF2)

	Screening	C1	C2	C3	C4	C5 to C14 or until RECIST 1.1-defined disease recurrence	For details, see Section
Week	**-4 to -1**	**0**	**q3w ±3d[b] unless dosing needs to be held for toxicity reasons**			**q4w ±3d[b] unless dosing needs to be held for toxicity reasons**	
Day	**-28 to -1**	**1[a]**	**q21d ±3d[b] unless dosing needs to be held for toxicity reasons**			**q28d±3d[b] unless dosing needs to be held for toxicity reasons**	
Study Participant Feedback Questionnaire (SPFQ)		X				C8	8.9
Optional Gx sample (DNA element for long-term storage/future use)		X					8.6.2
Efficacy evaluations							
Disease assessments (as assessed by Investigator using RECIST 1.1)	X[s]	Disease assessments occur q12w ± 1w (relative to the date of randomization) until appearance of RECIST 1.1-defined disease recurrence or until primary DFS analysis, whichever occurs first.[t]					8.1, 8.1.1.1, Appendix G
Tumor biopsy (optional)		At recurrence[u]					8.7

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

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

[b] The 3-day window applies to these visits, although the time between 2 consecutive doses of durvalumab/placebo cannot be less than 21 days.

[c] A patient will be able to sign ICF2 and enter second screening once their MRD result is available in IWRS. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including second screening/baseline evaluations. The procedures outlined in this table will be initiated by the signing of ICF2.

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

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

[f] Concomitant procedures initiated post-treatment, including PORT, will be recorded in the appropriate sections of the eCRF.

[g] The reason(s) for screen-failure must be captured in the appropriate eCRF for any patient found to be ineligible for randomization during the second screening period (see Table 7 and Section 5.4).

[h] Collected prior to dosing of each cycle and as clinically indicated. Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[i] 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.

[j] For coagulation parameters, activated partial thromboplastin time (APTT; either as a ratio or as an absolute value, in seconds) and international normalized ratio (INR) 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.

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

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

[m] If negative hepatitis B and C and HIV serology was determined during the first screening period, these tests do not need to be repeated *unless* the patient is at high risk for infection.

[n] 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 3-4 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

[o] Durvalumab or placebo will be administered on Day 1 of each cycle. During the combination portion of treatment (Cycles 1 through 4), durvalumab will be infused first, followed by SoC chemotherapy.

[p] The first day of SoC administration will be Day 1 of each cycle. At these visits, in addition to SoC administration, the following assessments will be performed: targeted physical examinations, vital signs, concomitant medications, clinical chemistry, hematology, WHO/ECOG performance status, and AE/SAE assessment. Please refer to Table 8.

[q] 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.

[r] Samples should be collected pre-dose on Day 1 of each treatment cycle.

[s] A CT scan of the chest (including liver and adrenal glands) must be performed within 28 + 7 days (i.e. within 35 days) **prior to randomization** to confirm no evidence of disease and to serve as the patient's baseline scan. A brain MRI (preferred) or brain CT may be performed if clinically indicated (at the discretion of the Investigator).

[t] The on-study scan schedule of q12w ±1w relative to the date of randomization **must** be followed regardless of any delays in dosing. Additional scans will be completed per standard practice post-recurrence.

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

Note: For some visits, telemedicine and/or home visits (at the patient's home or other appropriate location) may be permitted. Telemedicine and/or home visits are permitted only where feasible, allowed by local laws and regulations, and following consultation with the Investigator and the Sponsor.

AE Adverse event; C Cycle; C1D1 Cycle 1, Day 1; CT Computed tomography; D Day; DFS Disease-free survival; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; FFPE Formalin-fixed paraffin-embedded; Gx Genomics research; HIV Human immunodeficiency virus; ICF2 Informed consent form 2; IP Investigational product; LFT Liver function test; mRNA Messenger ribonucleic acid; PORT Post-operative radiation therapy; q3w Every 3 weeks; q4w Every 4 weeks; q12w Every 12 weeks; RECIST Response Evaluation Criteria in Solid Tumors; SAE Serious adverse event; SoC Standard of care; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; w Week; WHO World Health Organization.

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

	Time since last dose of IP (weeks)			For details, see Section
Week	**4 (±3d)**	**12 (±1w)**	**q12w until disease recurrence (±1w)**	
Physical examination (full)	X			8.2.3
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X			8.2.4
Pregnancy test[a]	X	As clinically indicated		8.2.1
AE/SAE assessment[b]	X			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[c]			8.2.7
Subsequent anticancer therapy[d] and progression assessment[e]	<----------		---------->	8.1
Survival status		X	X[f]	8.1
Hematology	X	X		Table 12
Clinical chemistry	X	X		Table 11
TSH (reflex free T3 or free T4[g])	X	X		Table 11
Plasma sample for exploratory analyses	q12w ±2w (preferably to coincide with time of scan) Sample at time of disease recurrence (if applicable)			8.7.2.1
Study Participant Feedback Questionnaire (SPFQ)	X			8.9
Disease assessments (as assessed by the Investigator using RECIST 1.1)	Disease assessments occur q12w ±1w until appearance of RECIST 1.1-defined disease recurrence or until completion of the study or until primary DFS analysis, whichever occurs first.[h]			8.1
Tumor biopsy (optional)	At recurrence[i]			8.7

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

[b] 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 (also see Section 8.3.13).
[c] 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.
[d] Details of any treatment for NSCLC (including surgery and/or radiotherapy) post the last dose of IP must be recorded in the eCRF through the completion of the study. At minimum, collect the start date and description of the subsequent anticancer therapy.
[e] Post-recurrence progression assessed by Investigator based on scans performed per SoC.
[f] Patients may be contacted in the week following data cut-offs to confirm survival status.
[g] Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[h] The on-study scan schedule of q12w ±1w relative to the date of randomization **must** be followed regardless of any delays in dosing.
[i] FFPE samples of recurrent tumor biopsy will be collected from consenting patients.

Note: For some visits, telemedicine and/or home visits (at the patient's home or other appropriate location) may be permitted. Telemedicine and/or home visits are permitted only where feasible, allowed by local laws and regulations, and following consultation with the Investigator and the Sponsor.
AE Adverse event; D day; DFS Disease-free survival; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; IP Investigational product; NSCLC Non-small cell lung cancer; OS Overall survival; PFS Progression-free survival; q4w Every 4 weeks; q12w Every 12 weeks; q21d Every 21 days; q28d Every 28 days; RECIST Response Evaluation Criteria in Solid Tumors; SAE Serious adverse event; SoC Standard of care; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization; w Week.

1.2 Synopsis

International Coordinating Investigators:

Protocol Title: A Phase III, Randomized, Multicenter, Double-blind, Placebo-controlled Study to Determine the Efficacy of Adjuvant Durvalumab in Combination with Platinum-based Chemotherapy in Completely Resected Stage II-III NSCLC

Short Title: MERMAID-1

Rationale:

Up to 30% of patients with NSCLC present with surgically resectable disease (Molina et al 2008). For patients with stage II-IIIA and select IIIB disease, surgery and adjuvant SoC chemotherapy results in 5-year disease-free survival (DFS) rates of only ~40% (Wakelee et al 2017). Adjuvant chemotherapy following resection of NSCLC is standard practice to reduce risk of disease recurrence. The majority of patients who remain event-free at 5 years are cured by surgery alone yet receive adjuvant treatment because there is currently no clear way to determine who will benefit from adjuvant chemotherapy.

There is evidence that identification of minimal residual disease (MRD) through detection of circulating tumor DNA (ctDNA) post-surgery can accurately predict disease recurrence (Abbosh et al 2017, Abbosh et al 2020, Chaudhuri et al 2017). Recent data from the TRACERx lung study reported on 78 patients with stage I-III NSCLC had 608 plasma samples analysed for ctDNA in pre- and post-operative settings. ctDNA was detectable at or before clinical relapse in 37 of the 45 patients who suffered clinical relapse of their disease. Conversely, ctDNA was only detected in 1 of 199 timepoints analysed for 23 patients who did not suffer relapse of their lung cancer during a median of 1184 days of study follow-up. In 10 of 10 patients who developed second primary cancers during follow-up no ctDNA was detected, reflecting specificity of the MRD assay toward the primary tumor that was excised at

surgery. Data from TRACERx also provided evidence that ctDNA detection could occur prior to normal surveillance imaging (CT or PET-CT scans), suggesting that detection of ctDNA can (in some cases) identify occult metastatic disease in advance of normal radiological surveillance (Abbosh et al 2020

Abbosh C, Frankell A, Garnett A, Harrison T, Weichert M, Licon A, et al. Phylogenetic tracking and minimal residual disease detection using ctDNA in early-stage NSCLC: A lung TRACERx study. Philadelphia, PA: American Association for Cancer Research; 2020; CT023.

). An additional study reported that NSCLC patients who were MRD- had excellent outcomes, regardless of whether they received immunotherapy as consolidation treatment (Moding et al 2020). Interestingly, NSCLC patients who were found to be MRD+ after completing chemoradiation therapy had better outcomes if they went on to receive consolidation immunotherapy treatment compared to those MRD+ patients who did not. These data suggest that immunotherapy improves outcomes for NSCLC patients who are MRD+ after completion of SoC (Moding et al 2020).

Taken together, these data demonstrate that 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). Therefore, MRD+ patients could 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.

Long-term survival can be improved through administration of adjuvant chemotherapy immediately following surgery (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). This contrast demonstrates a vulnerability of residual cancer following surgery to systemic therapy and provides a rationale to conduct studies to accelerate adoption of novel therapies earlier in the disease course.

Durvalumab can be effective in situations of residual cancer as evidenced by improved PFS and overall survival (OS) observed with durvalumab versus placebo following definitive concurrent chemoradiation in the PACIFIC study (Antonia et al 2018, Gray et al 2019). 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 the combination of immunotherapy and chemotherapy in the adjuvant setting, where patients have undergone a complete resection but may have residual disease, would provide additional benefits to single agent immunotherapy and improve DFS. However, current immunooncologic (IO) therapy development in the adjuvant

setting is based on sequential chemotherapy followed by immunotherapy (eg, BR.31, ANVIL, IMpower010, and KEYNOTE-091). This study was originally designed to test the hypothesis of an MRD-driven treatment paradigm, wherein MRD status would inform targeted escalation of adjuvant therapy only in patients who are MRD+ post-surgery and are thus at high risk for disease recurrence while preventing post-surgery overtreatment of MRD- patients, the majority of whom have been cured by surgery alone.

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 (Union for International Cancer Control [UICC]/American Joint Committee on Cancer [AJCC] version 7) after cisplatin-based chemotherapy to atezolizumab, given every 3 weeks for up to 16 cycles, or 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; (iii) the intent-to-treat population. At interim analysis the first and second of these were found to be statistically significant with hazard ratios (HR) of 0.66 (95% confidence interval [CIs] 0.50-0.88) and 0.79 (95% CIs 0.64-0.96), respectively. In October 2021, these data led to Food and Drug Administration (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 immunohistochemistry [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% CIs 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 (pCR) rate and event-free survival (EFS). The trial was positive for both primary endpoints. The HR 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.

It is expected that access to (neo)adjuvant PD-(L)1 inhibitors will increase over the coming years. Despite this anticipated shift in treatment landscape, it remains unclear if concomitant

administration of chemotherapy with PD-(L)1 inhibitors, and if early intervention with this combination in post-surgical MRD+ patients, will drive further improvements in treatment outcomes. An exploratory analysis of ctDNA in IMpower010 demonstrated worse DFS outcomes for the patients whose baseline MRD status was MRD+, highlighting further a significant unmet need for MRD+ patients (Zhou et al 2021).

The original research hypothesis for this study was that concurrent durvalumab plus SoC chemotherapy would be more effective than placebo plus SoC chemotherapy for the treatment of MRD+ patients who have undergone complete resection of stage II-III NSCLC when administered in the adjuvant setting. Given the above anticipated changes in treatment landscape for patients with resectable NSCLC, enrollment to this study was closed on 25 May 2022. In order to optimize the ongoing scientific and clinical utility of this study, the statistical analyses have been amended to reflect the reduced sample size of the study (see Section 9).

As presented in the objectives and endpoints table below, under CSP V4.0, as a result of the decision to close study enrollment early, meaning the intended patient numbers will not be reached, the primary objective of this study will now compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the FAS rather than in the MRD+ analysis set.

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by DFS in all patients	DFS in FAS (using Investigator assessments according to RECIST 1.1)
Secondary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by DFS in MRD+ patients	DFS in MRD+ analysis set (using Investigator assessments according to RECIST 1.1)
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by OS in MRD+ patients and in all patients	OS in MRD+ analysis set and in FAS
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability profile of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy in MRD+ and in all patients	AEs, physical examinations, vital signs, and laboratory findings

Objectives and Endpoints

Exploratory objectives:	Endpoint/variable:
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy on post-recurrence outcomes	PFS (using local standard practice) CCI CCI
To assess the efficacy of durvalumab + SoC chemotherapy to clear ctDNA compared to placebo + SoC chemotherapy in MRD+ patients	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 relationship between treatment effect on DFS and treatment effect on ctDNA endpoints	ctDNA endpoints (as defined above) and DFS
To assess prognostic significance of MRD detection as determined by ctDNA in NSCLC	Time from randomization to DFS (MRD+ vs MRD-)
To assess the association of TMB with efficacy of durvalumab + SoC chemotherapy compared with placebo + SoC chemotherapy	DFS, OS in patients with TMB
To investigate the relationship between a patient's baseline PD-L1 TC and IC expression and efficacy outcomes with durvalumab + SoC chemotherapy compared with placebo + SoC chemotherapy	IHC analysis of PD-L1 TC and IC expression and spatial distribution within the tumor microenvironment relative to efficacy outcomes (ie, DFS, OS)
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 will be compared at baseline, on treatment, post-treatment, and/or at recurrence. 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 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	Prespecified items on the PRO-CTCAE Patient global assessments

Objectives and Endpoints

To assess patient-reported symptoms, functioning, and HRQoL in MRD+ patients treated with durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy	Change from baseline and time to deterioration in EORTC QLQ-C30 and EORTC QLQ-LC13
To explore the impact of treatment and disease on health state utility	CCI , descriptor, and VAS

AE Adverse events; ctDNA Circulating tumor DNA; DFS Disease-free survival; EORTC European Organisation for Research and Treatment of Cancer; FAS Full analysis set; CCI ; HRQoL Health-related Quality of Life; IC Immune cell; IHC Immunohistochemistry; MRD Minimal residual disease; MRD+ Minimal residual disease-positive; MRD- Minimal residual disease-negative; NSCLC Non-small cell lung cancer; OS Overall survival; PD-L1 Programmed cell death-ligand 1; PFS Progression-free survival; PRO-CTCAE Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; QLQ-C30 30-item Core Quality of Life Questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RNA Ribonucleic acid; RECIST Response Evaluation Criteria in Solid Tumors; SoC Standard of care; TC Tumor cell; TMB Tumor mutational burden; VAS Visual analog scale.

Overall design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-arm study to evaluate the efficacy and safety of durvalumab plus SoC chemotherapy compared to placebo plus SoC chemotherapy in patients with completely resected stage II-III NSCLC who are MRD+ post-surgery.

Prior to CSP V4.0, this study was designed to screen approximately CCI patients and randomize approximately CCI patients with stage II-III NSCLC (according to IASLC Staging Manual in Thoracic Oncology v8.0) (select stage IIIB patients with T3N2 or T4N2 disease may be eligible; see Section 5.1.1), whose tumors are epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) wild type, and who have undergone complete resection. Eligible patients must be current or former smokers. Randomized patients were expected to include approximately CCI MRD+ and CCI MRD- patients. The study has opened in 188 centers globally.

Following a decision to close recruitment on 25 May 2022, a total of 691 patients have been enrolled, and a total of approximately 100 patients are now expected to be randomized within the study.

The study requires a 2-tiered screening/consent process as described below. **Note that enrollment has closed for this study.**

First screening (initiated by the signing of ICF1)

First screening begins when the patient signs ICF1. It is ***preferred*** that patients are identified and enrolled prior to surgery (Table 1); however, patients are permitted to sign ICF1 following surgery. Surgery is not a study procedure.

During first screening, *EGFR* and *ALK* will be assessed. A pre-surgical biopsy sample is the preferred sample type; however, if a pre-surgery biopsy sample is not available or evaluable, testing will be conducted after surgery on the resected tumor tissue. Patients will still be allowed to continue with first screening procedures while testing is ongoing but will be excluded from second screening and randomization if their tumor sample tests positive for *EGFR* mutations and/or *ALK* translocations. Local testing must be performed using a well-validated, local regulatory approved test; results from testing performed during screening for another AstraZeneca study may be used. *EGFR/ALK* will be tested centrally if results from testing either locally or in the context of screening for another AstraZeneca study are not available.

Note: Where *EGFR/ALK* results are obtained from a pre-surgical tissue biopsy as part of standard local practice, the patient must be confirmed as *EGFR/ALK* wild-type prior to signing ICF1 and enrolling in the study.

This study requires mandatory genetic testing. 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 50 of the patient's tumor variants expressed at high frequency. This panel is then used to identify the presence of ctDNA extracted from the patient's plasma. The patient is considered MRD+ if the panel detects ctDNA.

Note: Patients who have higher levels of tumor-specific mutations are more likely to have sufficient mutations to satisfy the requirement for a successful panel build. Patients with driver mutations and/or non-smokers tend to have a lower mutational burden (Nagahashi et al 2018, Offin et al 2019).

Exclusion of never-smokers may decrease the screen -failures due to EGFR mutation or ALK translocation positive status that can occur late in the screening process. It may increase the probability that patients will be eligible by removing the population of patients who are likely to have lower mutational burden and therefore unlikely to satisfy the requirement for a successful panel build.

A pre-surgery plasma sample will be collected from every patient who signs ICF1 prior to surgery. These samples will be tested retrospectively using the personalized panel to determine if the patient's tumor is capable of shedding ctDNA prior to surgery for exploratory purposes. In addition, a plasma sample will be collected at Week 3-5 (Day 21-35) post-surgery and used to determine a patient's MRD status. Investigators will not be notified of MRD status, and eligibility to continue to second screening will be managed through the interactive web response system (IWRS).

While it is ***preferred*** that patients enrol in the study prior to surgery, ICF1 can be signed after surgery. As a plasma sample must still be collected at Week 3-5 (Day 21-35) post-surgery to

determine a patient's MRD status, ICF1 should be signed no later than Week 3 (Day 21) post-surgery to ensure the personalized panel is built and MRD result is obtained within the screening timeframe. Patients identified after Week 3 (d21) post-surgery but prior to Week 5 (d35) post-surgery may be allowed to enrol in the study depending on the outcome of the discussion with the study physician. A whole blood sample and resected tumor tissue must be collected and sent to the diagnostic lab **as soon as possible** after ICF1 is signed for development of the personalized panel.

Programmed cell death-ligand 1 (PD-L1) tumor cell (TC) expression will be evaluated by a central reference laboratory on the resected tumor tissue collected during the first screening period. PD-L1 status is required for randomization.

Second screening (initiated by the signing of ICF2)

Following determination of MRD status during the first screening period, patients will enter the second screening period (Table 2) to confirm that they are eligible for randomization to treatment.

Note: If the scan performed after surgery (Table 1 and Table 2) falls outside of the 28 day +7 days window **prior to randomization**, then an additional scan must be performed to confirm no evidence of disease**.**

Prior to CSP V4.0, approximately CCI patients (approximately CCI MRD+ and CCI MRD-) were to be randomized 1:1 to treatment with durvalumab q3w for 4 cycles plus SoC chemotherapy q3w for up to 4 cycles or placebo q3w for 4 cycles plus SoC chemotherapy q3w for up to 4 cycles followed by durvalumab or placebo monotherapy q4w for up to an additional 10 cycles (for a total of 12 months of treatment), until disease recurrence, or until other specific treatment discontinuation criteria are met (whichever occurs first).

In addition to blinding to treatment, Investigators will not be notified of the patient's MRD status to limit potential bias upon interpreting the scans.

Study Period:

Date of first patient enrolled: 17 July 2020

Estimated date of last patient completed: Q3 2023

Number of patients:

Prior to CSP V4.0, approximately CCI patients were to be screened in order to randomize approximately CCI eligible patients in a 1:1 ratio to concurrent durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy. The approximate number of screened patients was based on the anticipated prevalence of MRD+ patients at the Week 3-5 (Day 21-35) post-surgery timepoint based on previously published data (Abbosh et al 2017)

and data internal to the Sponsor. Patients will be stratified by disease stage (stage II vs stage III), MRD status (MRD+ vs MRD-), and PD-L1 TC expression (<1% vs ≥1%). Of the patients randomized into the study, approximately CCI patients were expected to be MRD+ as determined by the assay results from the personalized panel. At the time of study initiation, the number of MRD- patients was originally capped at CCI. As the total number of randomized patients will not reach CCI, the number of MRD- patients will be less than CCI. MRD- patients will be included in this study to evaluate whether MRD+ is distinct from MRD- status as a prognostic marker for disease recurrence and to provide clinical and translational data to facilitate the development of an MRD-driven treatment paradigm.

Under CSP V4.0, the planned number of randomized patients will not be met. This is a result of the decision by AstraZeneca to close study enrollment early.

Treatments and treatment duration:

Adjuvant study treatments (durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy) should be initiated by Week 9 post-surgery (once MRD status has been determined) but can be delayed up to 12 weeks (+ 7 days) after surgery. Data have shown that patients can still benefit from delayed adjuvant chemotherapy started up to 16 weeks after surgery (Salazar et al 2017).

Durvalumab or placebo

- Durvalumab 1500 mg or placebo by intravenous (IV) infusion over 60 minutes in combination with chemotherapy (regimens specified below), starting at Week 0, q3w, for 4 cycles, followed by durvalumab 1500 mg or placebo by IV infusion over 60 minutes q4w for up to 10 additional cycles (for a total of 12 months of treatment) unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

  (Please note, if a patient's weight falls to 30 kg or below [≤30 kg], then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo q3w or 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 1500 mg or placebo q3w or q4w).

SoC chemotherapy

Patients will receive one of the following SoC regimens, based on tumor histology and Investigator's discretion, as adjuvant therapy following complete resection.

- Squamous tumor histology:
  - Paclitaxel plus carboplatin: paclitaxel 200 mg/m^2 and carboplatin area under the serum drug concentration-time curve (AUC) 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles.
- Non-squamous tumor histology:

- Pemetrexed plus cisplatin (preferred*): pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles.
- Pemetrexed plus carboplatin: pemetrexed 500 mg/m^2 and carboplatin AUC 5 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles.

**In the event of unfavorable tolerability, patients can switch from cisplatin to carboplatin therapy at any point during the study. However, it is recommended that patients receive at least 1 cycle of cisplatin.*

Duration of treatment

Unless specific treatment discontinuation criteria are met, treatment with 4 cycles of durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy (q3w) will be administered, followed by treatment with durvalumab or placebo monotherapy for up to 10 additional cycles (q4w) (for a total of 12 months of treatment) or until evidence of RECIST 1.1-defined disease recurrence using Investigator assessments (whichever occurs first).

Post-treatment follow-up period

After completion of 12 months (14 cycles) of treatment, patients will be followed for safety, ctDNA, disease recurrence, and survival status at specified intervals until the primary DFS analysis.

Patients may not receive retreatment in this study.

Follow up of patients post discontinuation of study drug

Patients who have discontinued treatment due to toxicity or symptomatic deterioration will be followed up with disease assessments until disease recurrence, primary DFS analysis, or death (whichever comes first). These patients are not eligible for retreatment at any time.

Survival

All patients randomized in the study should be followed for survival until study completion.

End of study

The end of study is defined as the date of the last visit of the last patient in the study, which is approximately 12 months following last patient randomized.

Disease assessments

Efficacy assessments of the primary endpoint of DFS will be derived using Investigator assessments according to RECIST 1.1 and prespecified 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 and survival until the primary DFS analysis. OS is a secondary endpoint of the study.

Tumor evaluations utilize images from computed tomography (CT; preferred) or magnetic resonance imaging (MRI), each preferably with IV contrast, of the chest and abdomen (including liver and adrenal glands) collected during second 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.

Data Monitoring Committee

An independent data monitoring committee (IDMC) comprised of independent experts will meet 12 months after the first patient has been dosed with investigational product (IP) or after the first 50 patients have received at least 1 dose of IP (whichever occurs first) in order to assess the safety and tolerability of durvalumab and 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. 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

Prior to CSP V4.0, the primary objective of the study was to compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS, defined as time from the date of randomization until the date of disease recurrence (defined above) or date of death due to any cause (whichever occurs first) in the MRD+ analysis set. DFS in the full analysis set (FAS) was a secondary analysis. Under CSP V4.0, the primary analysis is planned to be performed on the FAS and an analysis on the MRD+ analysis set will be performed as a secondary objective of the study.

The FAS will include all randomized patients. The MRD+ analysis set will include all patients in the FAS who are determined to be MRD+ based on the result from the post-surgical plasma sample.

Patients will be stratified at randomisation by disease stage (stage II vs stage III), by MRD status (MRD+ vs MRD-), and by PD-L1 status (TC <1% vs TC ≥1%).

DFS will be analyzed using a stratified log-rank test. The treatment effect will be estimated in terms of hazard ratio (HR) together with the corresponding 95% confidence interval (CI) from a Cox proportional hazard model stratified by disease stage, PD-L1 status, and MRD status. For the secondary analysis in the MRD+ analysis set, the MRD status stratification factor will not be included. The stratification factor covariates in the statistical modeling will be based on the values entered into the 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. 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.

Prior to CSP V4.0, the study planned to screen approximately CCI patients to randomize approximately CCI patients with stage II-III NSCLC 1:1 to durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy. Of the patients randomized into the study, approximately CCI patients were required to be MRD+, as determined by the result from the post-surgical plasma sample. The number of MRD- patients was to be capped at CCI (*Exception:* MRD- patients who have signed ICF2 at the time the MRD- cohort cap is met could still be randomized).

Under CSP V4.0, the planned number of randomized patients will not be met. This is a result of the decision by AstraZeneca to close study enrollment early.

Prior to CSP V4.0, the study was sized for the primary endpoint of DFS in the MRD+ analysis set and the secondary endpoint of DFS in the FAS. The analysis of the primary endpoint (DFS) was planned to occur when approximately 151 DFS events had occurred (65% maturity) in the MRD+ analysis set. If the true DFS HR is 0.59 in the MRD+ analysis set, the study would have provided at least 90% power to demonstrate a statistically significant difference for DFS with overall 2-sided significance level of 5%; this translates to a 5.0-month benefit in median DFS over 7.2 months on placebo plus SoC chemotherapy, or 16% difference in 2-year DFS rate over 10% on placebo plus SoC chemotherapy, if DFS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of 0.73.

The study was also sized to provide at least 87% power for the DFS endpoint in the FAS. The analysis will be performed at the same time as the primary analysis, when it was expected that approximately 194 events had occurred (58% maturity) in the FAS. If the true DFS HR is 0.64 in this population, this would have provided at least 87% power to demonstrate a statistically significant difference for DFS, assuming overall 5% 2-sided significance level; this translates to a 6.2-month benefit in median DFS over 11.0 months on placebo plus SoC chemotherapy, or 16% difference in 2-year DFS rate over 22% on placebo plus SoC chemotherapy, if DFS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of 0.76.

The primary analysis for DFS was planned to occur approximately 51 months after the first patient has been randomized, assuming a 3-month lag before the first MRD+ patient was randomized, 44-month recruitment period, and a minimum follow-up of 4 months. Under CSP V4.0 the primary DFS analysis will now occur after the data cut-off (DCO).

Prior to CSP V4.0, to provide strong control of the type I error rate, α=5% (2-sided), a multiple testing procedure with a gatekeeping strategy was planned across the primary endpoint of DFS in the MRD+ analysis set and the secondary endpoint of DFS in the FAS, starting with testing the primary endpoint on the MRD+ analysis set. The overall 5% alpha was to be allocated to the analysis of DFS in the MRD+ analysis set. If that analysis was significant, the 5% alpha was to be recycled to the DFS endpoint in the FAS.

Under CSP V4.0, no methods for multiplicity control will be performed and all analyses will be exploratory.

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. Prior to CSP V4.0, in the MRD+ analysis set, if the true HR is 0.62, then it was anticipated that approximately 87 events (38% maturity) would have occurred. This translates to an 11.5 month benefit in median OS over 18.5 months on placebo plus SoC chemotherapy. In the FAS, if the true HR is 0.67, then it was anticipated that approximately 112 events (34% maturity) would have occurred. This translates to a 13.4 month benefit in median OS over 27.3 months on placebo plus SoC chemotherapy. OS will be analyzed similarly to DFS. Under CSP V4.0, these number of events will not be observed. This is a result of the decision by AstraZeneca to close study enrollment early.

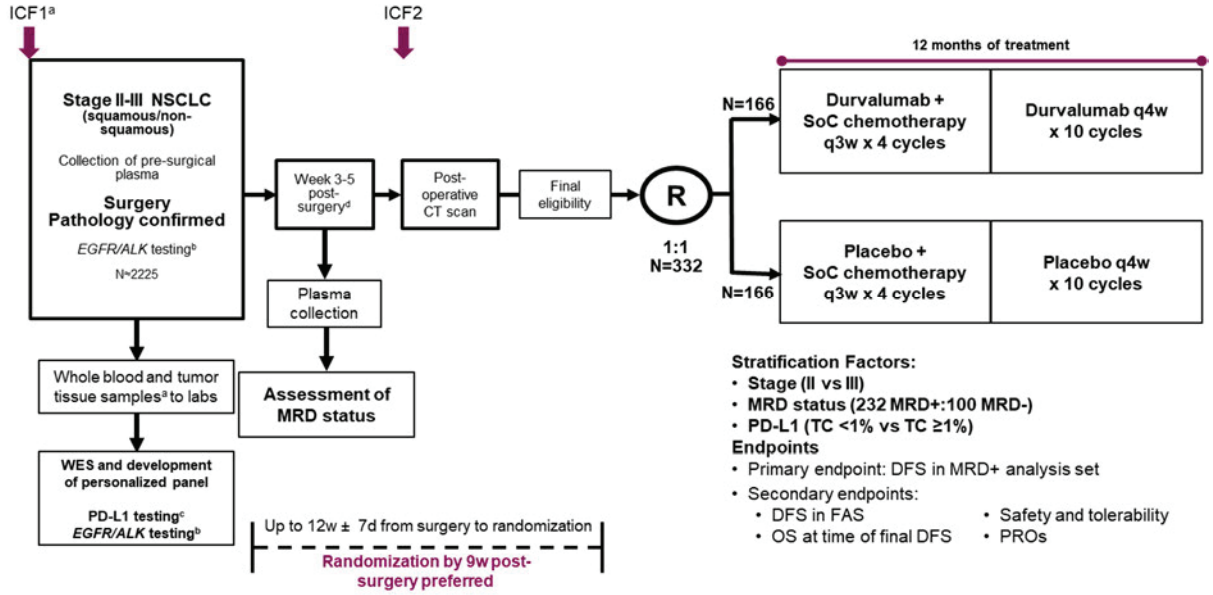
Prior to CSP V4.0, a further analysis of OS was planned to be performed at approximately 155 events (67% maturity) in the MRD+ analysis set. At this time there was expected to be approximately 190 events (57% maturity) in the FAS. It was anticipated that this analysis would occur approximately 72 months after the first patient was randomized. If events were accruing slower than expected, then the DCO would have occurred 72 months after the first patient was randomized, regardless of number of events accrued. Under CSP V4.0, the further analysis of OS at approximately 155 events will not be performed. Safety data will be summarized descriptively and will not be formally analyzed.

1.3 Schema

The original general study design is summarized in Figure 1. The inclusion criteria that must be met during the periods covered by the first and second screening are briefly summarized in Table 4. The timings of assessment of exclusion criteria relative to surgery (pre- and post-) are summarized in Table 5.

The revised study design, upon implementation of CSP V4.0, is summarized in Figure 2. All enrolled patients were screened and randomized according to the eligibility criteria based on CSP V1.0 or V3.0.

Figure 1 Study schema (original)



[a] While it is ***preferred*** that patients are identified and sign ICF1 prior to surgery, patients will be permitted to sign ICF1 after surgery. In this case, whole blood and resected tumor tissue must be collected as soon as possible for creation of the personalized panel. A plasma sample must still be collected at Week 3-5 (Day 21-35) post-surgery, even if creation of the personalized panel is delayed.

[b] *EGFR/ALK* status should be assessed on pre-surgical biopsy. If pre-surgical biopsy is not available or evaluable, testing will be conducted on resected tumor tissue while the personalized MRD panel is in development. Patients will still be allowed to continue with first screening procedures while testing is ongoing but will not be eligible for randomization if their tumor tissue tests positive for *EGFR* mutations or *ALK* translocations.

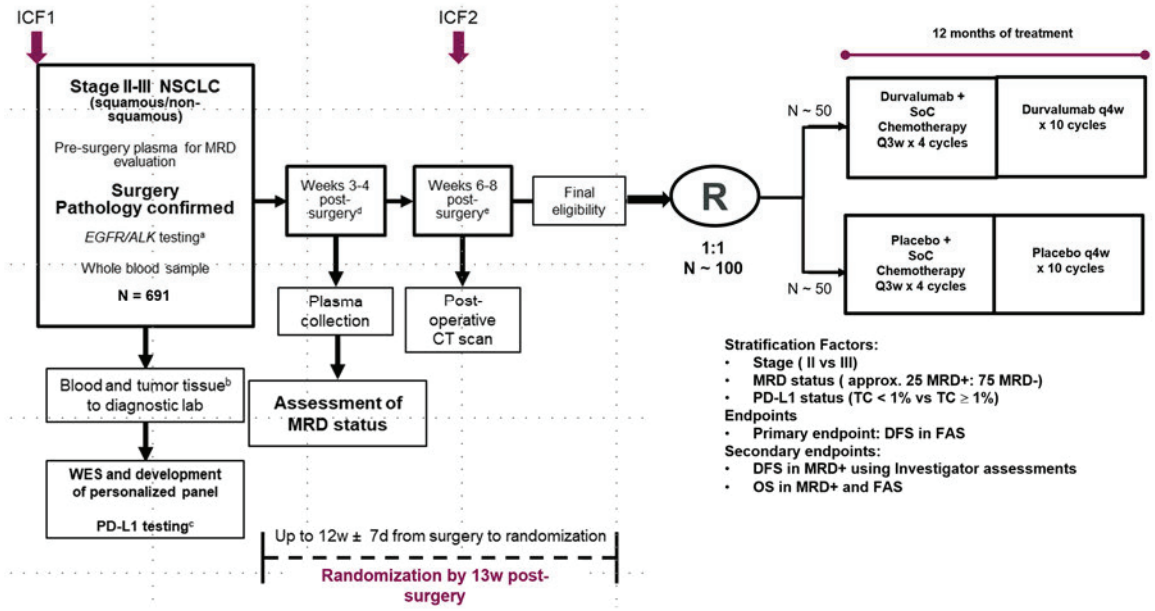
[c] PD-L1 status is required for randomization.

[d] The plasma sample used to determine MRD status must be collected at Week 3-5 (Day 21-35) post surgery. Investigators will not be notified of the patient's MRD status and eligibility to continue into second screening will be managed through the IWRS.

[e] A CT scan performed once a patient signs ICF2 (Table 2) can be used as the baseline scan provided this scan was performed 28 days + 7 days **prior to randomization**.

ALK Anaplastic lymphoma kinase; CT Computed tomography; d Day; DFS Disease-free survival; *EGFR* Epidermal growth factor receptor; FAS Full analysis set; ICF1 Informed consent form 1; ICF2 Informed consent form 2; MRD Minimal residual disease; MRD+ MRD-positive; MRD- MRD-negative; NSCLC Non-small cell lung cancer; OS Overall survival; PD-L1 Programmed cell death-ligand 1; PD-L1 TC<1%/≥1% Expression of PD-L1 on tumor membrane, at any intensity, in<1% or ≥1% of tumor cells; PRO Patient-reported outcomes; q3w Every 3 weeks; q4w Every 4 weeks; R Randomization; SoC Standard of care; w Week; WES Whole exome sequencing.

Figure 2 Study schema (revised)



[a] While it is ***preferred*** that patients are identified and sign ICF1 prior to surgery, patients will be permitted to sign ICF1 after surgery. In this case, whole blood and resected tumor tissue must be collected as soon as possible for creation of the personalized panel. A plasma sample must still be collected at Week 3-5 (Day 21-35) post-surgery, even if creation of the personalized panel is delayed. **Note that enrollment has closed for this study.**

[b] *EGFR/ALK* status should be assessed on pre-surgical biopsy. If pre-surgical biopsy is not available or evaluable, testing will be conducted on resected tumor tissue while the personalized MRD panel is in development. Patients will still be allowed to continue with first screening procedures while testing is ongoing but will not be eligible for randomization if their tumor tissue tests positive for *EGFR* mutations or *ALK* translocations.

[c] PD-L1 status is required for randomization.

[d] The plasma sample used to determine MRD status must be collected at Week 3-5 (Day 21-35) post surgery. Investigators will not be notified of the patient's MRD status and eligibility to continue into second screening will be managed through the IWRS.

[e] A CT scan performed once a patient signs ICF2 (Table 2) can be used as the baseline scan provided this scan was performed 28 days + 7 days **prior to randomization**.

ALK Anaplastic lymphoma kinase; CT Computed tomography; d Day; DFS Disease-free survival; EGFR Epidermal growth factor receptor; FAS Full analysis set; ICF1 Informed consent form 1; ICF2 Informed consent form 2; MRD Minimal residual disease; MRD+ MRD-positive; MRD- MRD-negative; NSCLC Non-small cell lung cancer; OS Overall survival; PD-L1 Programmed cell death-ligand 1; PD-L1 TC<1%/≥1% Expression of PD-L1 on tumor membrane, at any intensity, in<1% or ≥1% of tumor cells; PRO Patient-reported outcomes; q3w Every 3 weeks; q4w Every 4 weeks; R Randomization; SoC Standard of care; w Week; WES Whole exome sequencing

Table 4 Timing of inclusion criteria assessment relative to screening periods

First screening (initiated by the signing of ICF1) (Section 5.1.1)		Second screening (initiated by the signing of ICF2) (Section 5.1.2)	
1	Signature of ICF1 (***preferred*** prior to surgery, but allowed up to Week 3 [d21] post-surgery)[a]	1	Signature of ICF2 after determination of MRD status and prior to second screening and randomization
2	Age ≥18 years	2	No evidence of disease recurrence confirmed by CT and/or MRI[d]
3	Male and/or female	3	WHO/ECOG PS 0 or 1
4	Diagnosis of histologically confirmed NSCLC with resectable (stage IIA to select [ie, T3N2 or T4N2] stage IIIB) disease[b]	4	Completed postoperative wound healing
5	Imaging of chest/abdomen and brain[c] prior to surgery	5	Able to tolerate 4 cycles of platinum-based chemotherapy
6	Complete resection as per protocol definition (Section 5.1.1)	6	Adequate organ and marrow function based on specified criteria
7	Collection of pre-surgical plasma sample *if* enrolled before surgery	7	Life expectancy ≥12 weeks
8	Confirmation of resected tumor tissue and whole blood sample appropriate for WES for creation of personalized MRD panel	8	Body weight ≥30 kg
9	Collection of resected tumor tissue for prospective PD-L1 testing		
10	Collection of post-surgical plasma sample to determine MRD status		
11	No evidence of disease recurrence confirmed by CT and/or MRI[d]		

[a] ***Exception:*** Patients may be allowed to enrol/sign ICF1 after Week 3 (d21) post-surgery but prior to Week 5 (d35) post-surgery depending on the outcome of the discussion with the study physician. **Note that enrollment has closed for this study.**

[b] Individuals who have diagnosis of histologically confirmed NSCLC (WHO 2015 classification) with resectable (stage II-III) disease (according to IASLC Staging Manual in Thoracic Oncology v8.0). Select (ie, T3N2 or T4N2) stage IIIB patients will be eligible, provided that they are upstaged to T3N2 or T4N2 based on confirmed pathology. Patients who are staged as T3N2 or T4N2 prior to surgery are not eligible.

[c] The brain MRI (preferred) or brain CT should be performed pre-operatively per standard of care. However, if this scan is not performed prior to surgery, this scan should be conducted during first screening (ie, prior to signing ICF2 and entering second screening).

[d] The CT scan performed post-surgery during first or second screening (indicated in Table 1 and Table 2) may be used as the baseline scan provided this scan was performed 28 days + 7 days **prior to randomization** (Table 1 and Table 2). If this post-operative scan falls outside of the 28 day + 7 days window **prior to randomization**, an additional contrast-enhanced CT scan of the chest and abdomen (including liver and adrenal glands) must be performed **before the patient is randomized** to confirm no evidence of disease recurrence.

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). All criteria must be assessed prior to randomization.

CT Computed tomography; ECOG Eastern Cooperative Oncology Group; IASLC International Association for the Study of Lung Cancer; ICF1 Informed consent form 1; ICF2 Informed consent form 2; MRD Minimal residual disease; MRI Magnetic resonance imaging; NSCLC Non-small cell lung cancer; PD-L1 Programmed cell death-ligand 1; PS Performance status; WES Whole exome sequencing; WHO World Health Organization.

Table 5 Timing of exclusion criteria assessment relative to informed consent

First screening	Second screening
Prior to or immediately following surgery	**Pre-randomization**
• *EGFR/ALK* mutant (results of testing either a pre-surgical biopsy [**preferred**] or resected tumor tissue [if biopsy not available/evaluable])[a] • Mixed small cell and NSCLC pathology • Candidates who undergo only wedge resections or deemed unresectable • Requirement for re-resection • History of allogeneic organ or bone marrow transplantation • Active or prior documented autoimmune or inflammatory disorders • History of another primary malignancy (with specified exceptions) • History of active, primary immunodeficiency • Known allergy or hypersensitivity to any of the IPs • Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection • Prior exposure to durvalumab • Female patients who are pregnant or breastfeeding • Judgment by the Investigator that the patient should not participate in the study • Radiotherapy treatment for NSCLC in the neoadjuvant setting • Evidence of disease recurrence within 28 days (+ 7 days) prior to randomization[b]	• Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment • Received any adjuvant therapy for NSCLC • Medical contraindication to platinum-based therapy • Evidence of disease recurrence within 28 days (+ 7 days) prior to randomization[b] • Uncontrolled intercurrent illness • History of active, primary immunodeficiency • Active infection, including tuberculosis, HBV, HCV, or HIV • Receipt of live attenuated vaccine within 30 days of IP dosing • Current or prior use of immunosuppressive medication within 14 days of IP dosing • Current enrollment in another clinical study, unless observational or during follow-up of interventional study • Judgment by the Investigator that the patient should not participate in the study

[a] Where *EGFR/ALK* testing on a pre-surgical tissue biopsy is performed as standard of care, patients should be confirmed *EGFR/ALK* wild-type prior to enrolling in the study.

[b] A CT scan performed after a patient signs ICF2 (Table 2) can be used as the baseline scan provided this scan was performed 28 days + 7 days **prior to randomization** to confirm no evidence of disease recurrence.

For details, see the full list of exclusion criteria in Section 5.2. Some criteria must be checked at both screenings and therefore appear multiple times. All eligibility criteria must be assessed prior to randomization.

If a patient meets any exclusion criteria during first screening, he/she will not be eligible to continue into second screening. If a patient meets any exclusion criteria during second screening, he/she will not be eligible for randomization in the study.

ALK Anaplastic lymphoma kinase; CT Computed tomography; *EGFR* Epidermal growth factor receptor; HBV Hepatitis B; HCV Hepatitis C; HIV Human immunodeficiency virus; IP Investigational product; NSCLC Non-small cell lung cancer.

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. However, it is challenging to determine who will benefit from adjuvant chemotherapy. There is evidence that identification of MRD through detection of ctDNA post-surgery can accurately predict disease recurrence (Abbosh et al 2017, Abbosh et al 2020

Abbosh C, Frankell A, Garnett A, Harrison T, Weichert M, Licon A, et al. Phylogenetic tracking and minimal residual disease detection using ctDNA in early-stage NSCLC: A lung TRACERx study. Philadelphia, PA: American Association for Cancer Research; 2020; CT023.

, Chaudhuri et al 2017). Recent data from the TRACERx lung study, 78 patients with stage I-III NSCLC had 608 plasma samples analysed for ctDNA in pre- and post-operative settings (Abbosh et al 2020

Abbosh C, Frankell A, Garnett A, Harrison T, Weichert M, Licon A, et al. Phylogenetic tracking and minimal residual disease detection using ctDNA in early-stage NSCLC: A lung TRACERx study. Philadelphia, PA: American Association for Cancer Research; 2020; CT023.

). ctDNA was detectable at or before clinical relapse in 37 of the 45 patients who suffered clinical relapse of their disease. Conversely, ctDNA was only detected in 1 of 199 timepoints analysed for 23 patients who did not suffer relapse of their lung cancer during a median of 1184 days of study follow-up.

Durvalumab can be effective in situations of residual cancer as evidenced by improved PFS and OS observed with durvalumab versus placebo in the PACIFIC study (Antonia et al 2018, Gray et al 2019). 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 the combination of immunotherapy and chemotherapy in the adjuvant setting, where patients have undergone a complete resection but may have residual disease, may provide additional benefits to single agent immunotherapy and improve DFS. However, current IO therapy development in the adjuvant setting is based on sequential chemotherapy followed by immunotherapy (eg, BR.31, ANVIL, IMpower010, and KEYNOTE-091). On this basis, the Sponsor has opted to exploit the emerging clinical value of MRD as an adjuvant biomarker for risk of disease recurrence to inform targeted escalation of adjuvant therapy only in patients with evidence of residual disease post-surgery

and are thus at high risk for disease recurrence while preventing overtreatment of MRD- patients, the majority of whom have been cured by surgery alone.

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 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; (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% CIs 0.50-0.88) and 0.79 (95% CIs 0.64-0.96), respectively. In October 2021, these data led 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% CIs 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 (pCR) 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.

It is expected that access to (neo)adjuvant PD-(L)1 inhibitors will increase over the coming years. Despite this anticipated shift in treatment landscape, it remains unclear if concomitant administration of chemotherapy with PD-(L)1 inhibitors, and if early intervention with this combination in post-surgical MRD+ patients, will drive further improvements in treatment outcomes. An exploratory analysis of ctDNA in IMpower010 demonstrated worse DFS outcomes for the patients whose baseline MRD status was MRD+, highlighting further a significant unmet need for MRD+ patients (Felip et al 2021).

The original research hypothesis for this study was that concurrent durvalumab plus SoC chemotherapy would be more effective than placebo plus SoC chemotherapy in treating MRD+ patients who have undergone complete resection of stage II-III NSCLC when administered in the adjuvant setting. Given the above anticipated changes in treatment landscape for patients with resectable NSCLC, enrollment to this study was closed on 25 May 2022. In order to optimize the ongoing scientific and clinical utility of this study, the statistical analyses have been amended to reflect the reduced sample size of the study (see Section 9).

2.2 Background

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

2.2.1 Immunotherapies

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

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The 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) CCI [redacted]. 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 TCs or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the TCs 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 TCs 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 (IC). This activity overcomes PD-L1-mediated inhibition of antitumor

immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of nonclinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 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.

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

Nonclinical data have now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as CTLA-4 and PD-L1 has promising clinical activity. Ipilimumab was first granted United States Food and Drug Administration approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies, including metastatic melanoma, squamous and 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 G1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on IC. It is being developed by AstraZeneca for use in the treatment of cancer. 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. Refer to the current durvalumab IB for a complete summary of nonclinical and clinical information, including safety, efficacy, and PK. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1 and Section 8.3.12.

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; GLOBOCAN 2018) in 2018. NSCLC represents 80% to 85% of all lung cancers (Pinato et al 2019

Pinato DJ, Howlett S, Ottaviani D, Urus H, Patel A, Mineo T, et al. Association of Prior Antibiotic Treatment With Survival and Response to Immune Checkpoint Inhibitor Therapy in Patients With Cancer. JAMA Oncol. 2019 Dec 1;5(12):1774-1778. Erratum in: JAMA Oncol. 2020 Feb 1;6(2):302.

Pisters and LeChevalier 2005). Up to 30% of patients with NSCLC present with surgically resectable disease (Molina et al 2008).

Despite presentation with resectable disease, surgery and adjuvant SoC chemotherapy results in 5-year DFS rates of only ~40% in stage II-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 (Douillard et al 2010). Additional adjuvant chemotherapy regimens have shown similar benefits, as reflected in national guidelines (NCCN 2019).

2.2.3.1 Value of mono- and combination immunotherapy in NSCLC

An efficacy plateau has been reached with platinum-based doublet chemotherapy in NSCLC, with duration of response and tolerability as additional areas of concern. Therefore, other

mechanisms and modalities have been explored to improve upon chemotherapy-based SoC. The opportunity to capitalize the anticancer activities of the immune system greatly expanded with the identification of checkpoint inhibitor agents. 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 (Mok et al 2019, Reck et al 2016). Consolidation therapy with durvalumab following radical treatment of locally advanced NSCLC resulted in OS benefit versus placebo (Antonia et al 2018). In addition, combination chemotherapy and pembrolizumab conferred OS benefit compared to chemotherapy alone in both non-squamous and squamous NSCLC, independent of tumoral PD-L1 expression (Gandhi et al 2018, Paz-Ares et al 2018).

In summary, these agents have demonstrated clinically meaningful responses in metastatic NSCLC, with some patients exhibiting durable responses even after discontinuing therapy (Martinez et al 2019). As indicated in Section 2.1, (neo)adjuvant treatment options with anti-PD-(L)1 therapy are now approved. Ongoing studies are assessing the efficacy of adjuvant immunotherapy in NSCLC (eg, BR.31, ANVIL, Impower010, and KEYNOTE-091).

2.2.3.2 Detection of minimal residual disease in NSCLC

MRD, as indicated by detection of ctDNA, may reveal the existence of clinically indiscernible residual tumor following curative intent therapy (surgery ± chemotherapy/radiotherapy). 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.

MRD detection in patients with lung cancer has been investigated in 3 independent studies. Recent data from the TRACERx lung cancer study, 78 patients with stage I-III NSCLC had 608 plasma samples analysed for ctDNA in pre- and post-operative settings (Abbosh et al 2020

Abbosh C, Frankell A, Garnett A, Harrison T, Weichert M, Licon A, et al. Phylogenetic tracking and minimal residual disease detection using ctDNA in early-stage NSCLC: A lung TRACERx study. Philadelphia, PA: American Association for Cancer Research; 2020; CT023.

). ctDNA was detectable at or before clinical relapse in 37 of the 45 patients who suffered clinical relapse of their disease. Conversely, ctDNA was only detected in 1 of 199 timepoints analysed for 23 patients who did not suffer relapse of their lung cancer during a median of 1184 days of study follow-up. In a study by Chaudhuri et al, 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). An additional study reported that NSCLC patients who were MRD- had excellent outcomes, regardless of whether they received immunotherapy as consolidation treatment (Moding et al 2020). NSCLC patients who were found to be MRD+ after completing chemoradiation therapy had better outcomes if they went on to receive consolidation immunotherapy treatment compared to those MRD+ patients who did not. These data suggest that immunotherapy improves outcomes for NSCLC patients who are MRD+ after completion of SoC (Moding et al 2020).

Taken together, these studies demonstrate the potential utility of MRD detection for identifying patients who are at high risk of experiencing disease recurrence.

Detection of MRD is technically challenging due to the ultra-low frequency of ctDNA molecules in patient plasma (Abbosh et al 2018). In this study, the Sponsor will leverage an advanced, sensitive, personalized assay predicated on sequencing the 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 prior to adjuvant SoC 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 postoperative setting (Douillard et al 2010), 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). This contrast demonstrates a vulnerability of post-surgery residual cancer to systemic therapy and provides a rationale to conduct studies to accelerate adoption of novel therapies earlier in the disease course.

Use of MRD as a biomarker has the potential to accelerate adoption of novel therapeutic strategies in this setting. For example, the lack of clarity over residual disease status results in large recruitment numbers for adjuvant studies to achieve adequate power to investigate a novel therapeutic strategy. Consequently, adjuvant trials can take in excess of a decade to read out (Wakelee et al 2017). Additionally, escalation of adjuvant therapy in MRD- patients cured after surgery would result in unnecessary increased risk of treatment-associated toxicity.

Establishing ctDNA clearance as a novel surrogate of OS or DFS could accelerate the adoption of novel therapeutic strategies in the adjuvant NSCLC setting to clear therapeutically vulnerable residual disease following SoC curative intent therapy. Two studies conducted in patients with either metastatic NSCLC or metastatic 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 studies of agents that target EGFR (Friends of Cancer Research White Paper 2018). Recently, exploratory analyses of the IMpower010 study demonstrated poorer DFS outcomes for patients with detectable ctDNA post surgery, and a numerically improved HR for atezolizumab versus best supportive care for patients who were ctDNA+ versus ctDNA- (0.61 [95% CIs 0.39-0.64] versus 0.72 [95% CIs 0.52-1.00], respectively (Zhou et al 2021).

2.2.3.4 Monotherapy in advanced NSCLC

Randomized controlled studies of mAbs targeting PD-1 first demonstrated benefit in second-line or later metastatic NSCLC setting in 2015, with nivolumab (anti-PD-1 mAb) improving survival versus docetaxel in patients with squamous or non-squamous NSCLC (Brahmer et al 2015, Borghaei et al 2015, Horn et al 2017). These trials have been followed by multiple studies in the first-line setting, demonstrating that pembrolizumab can offer survival benefit in patients with PD-L1 tumor proportion scores (TPS) of at least 1% (Reck et al 2016, Reck et al 2019). CheckMate 026 did not demonstrate a benefit of nivolumab versus platinum-based chemotherapy in patients with advanced untreated NSCLC and at least 1% PD-L1 expression; analyses in PD-L1 >5% and >50% populations also failed to show a benefit of intervention with nivolumab over platinum-based chemotherapy (Carbone et al 2017).

In the monotherapy arms MYSTIC study (Study D419AC00001) of first-line durvalumab in patients with advanced metastatic NSCLC, patients with PD-L1 high (≥25% TC) NSCLC, the median PFS was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; HR 0.87 (99.5% CI: 0.593, 1.285; p=0.324). The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; the 24-month OS rate was 38.3% vs 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms, respectively.

2.2.3.5 Combination IO therapy and chemotherapy in NSCLC

Despite improvements in outcome with single agent immune checkpoint inhibition, only a minority of NSCLC patients respond to treatment. For example, in KEYNOTE-024 (pembrolizumab versus chemotherapy for untreated metastatic NSCLC) the objective response rate (ORR) to treatment was 44.8%, despite an inclusion criterion mandating PD-L1 TPS levels of at least 50% (Reck et al 2016). Combining chemotherapy with immunotherapy has been demonstrated to improve on these response rates and facilitates more aggressive treatment of patients with metastatic disease prior to decline in performance status that inexorably occurs with progression of disease (PD).

In the combination therapy arms of MYSTIC in which durvalumab was given as first-line therapy in combination with IO agent tremelimumab in patients with advanced metastatic NSCLC, patients with PD-L1 high (≥25% TC) NSCLC, median PFS was 3.9 months for

durvalumab + tremelimumab and 5.4 months for chemotherapy; HR 1.05 (99.5% CI: 0.722, 1.534; p=0.705). The median OS was 11.9 months for the durvalumab + tremelimumab arm and 12.9 months for the chemotherapy arm. The 24-month OS rate was 35.4% vs 22.7% and the 12-month PFS rate was 25.8% vs 14.3% for the durvalumab + tremelimumab and chemotherapy arms, respectively.

In metastatic non-squamous NSCLC, first-line combination checkpoint inhibition and chemotherapy has demonstrated efficacy versus chemotherapy alone. KEYNOTE-189 demonstrated that a combination of pembrolizumab plus a platinum agent and pemetrexed improved OS versus platinum agent and pemetrexed alone, regardless of PD-L1 TPS and despite significant crossover of the chemotherapy arm to checkpoint inhibitors at progression (Gandhi et al 2018, Gadgeel et al 2019). ORR in the PD-L1 >50% TPS group was 61.4% (Gandhi et al 2018). IMpower150 evaluated both anti-angiogenic and checkpoint inhibitor treatment in combination with chemotherapy in patients with treatment-naïve non-squamous NSCLC (Socinski et al 2018). The study demonstrated improved OS in patients treated with atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) versus bevacizumab, carboplatin, and paclitaxel (BCP) alone (Socinski et al 2018). IMpower130 demonstrated improved OS in the intent-to-treat (ITT) *EGFR/ALK* wild-type population with atezolizumab, carboplatin, and nab-paclitaxel versus chemotherapy alone (West et al 2019). IMpower132 reported an improvement in PFS when atezolizumab was added to pemetrexed plus cisplatin or carboplatin for the treatment of chemotherapy-naïve *EGFR/ALK* wild-type patients with stage IV non-squamous NSCLC (Papadimitrakopoulou et al 2018, Nishio et al 2020)

Combination of chemotherapy and checkpoint inhibition has also shown benefit as a first-line treatment for treatment-naïve metastatic squamous NSCLC. KEYNOTE-407 was a double-blind, Phase III study that evaluated pembrolizumab plus carboplatin and paclitaxel (or nab-paclitaxel) versus carboplatin and paclitaxel (or nab-paclitaxel) alone (Paz-Ares et al 2018). Combination checkpoint inhibition and chemotherapy resulted in survival benefit versus chemotherapy alone, regardless of PD-L1 expression, and occurred despite the crossover of 31.7% of the chemotherapy only arm to immunotherapy at progression in the ITT population (Paz-Ares et al 2018). ORR in the PD-L1 >50% TPS group was 60.3% (Paz-Ares et al 2018).

IMpower131 evaluated atezolizumab in combination with nab-paclitaxel and carboplatin versus nab-paclitaxel and carboplatin alone in treatment-naïve stage IV squamous NSCLC (Johnson et al 2021

Johnson M, Cho BC, Luft A, Alatorre-Alexander A, Geater SL, Laktionov K, et al. Durvalumab ± tremelimumab + chemotherapy as first-line treatment for mNSCLC: results from the phase 3 POSEIDON study [abstract PL02.01]. J Thorac Oncol. 2021;16(10 Suppl):S844.

Jotte et al 2018). OS benefit was observed in the PD-L1-enriched population (≥50% of TCs or ≥10% of tumor-infiltrating IC expressing PD-L1). However, this subgroup was not formally tested, and in the overall study population, there was no OS benefit with the addition of atezolizumab to carboplatin and nab-paclitaxel (Jotte et al 2019).

In summary, published studies suggest benefit of combination chemotherapy and checkpoint inhibitor therapy versus chemotherapy alone in NSCLC, and treatment benefit was enriched in patients with high PD-L1 TPS scores. These data from the advanced or locally advanced NSCLC setting suggest that early interception of MRD with IO therapy following resection of early-stage NSCLC could improve survival outcomes versus SoC adjuvant chemotherapy alone.

2.2.4 Durvalumab in combination with chemotherapy

The use of combination chemotherapy is a mainstay of oncology therapy. The goal of combination chemotherapy is to utilize agents that affect cancer cells by different mechanisms, thus reducing the risk of developing resistance. Current studies are now adding immunotherapies to chemotherapeutics to broaden antitumor responses. AstraZeneca is the Sponsor of several ongoing studies in NSCLC where durvalumab ± tremelimumab is administered with standard platinum-based chemotherapy. Regularly scheduled safety IDMC reviews have been conducted, and no safety concerns were raised in a Phase Ib study of durvalumab ± tremelimumab in patients with advanced solid tumors (Study D419SC00001; n=32).

In addition, there is a Phase Ib durvalumab ± tremelimumab in combination with standard platinum-based chemotherapy study (NCT02537418) run by the Canadian Cancer Trials Group (CCTG; n=118; Daaboul et al 2017). The combinations tested are tolerable and toxicities are manageable. Preliminary results from the CCTG study were presented for the NSCLC cohorts at the IASLC 2016 meeting; the overall ORR in the NSCLC cohort (n=24) was 52.9% (Juergens et al 2017).

In the ongoing Phase III Study D9106C00001 (AEGEAN; n=300 [planned]), durvalumab in combination with chemotherapy is administered in the neoadjuvant setting and as monotherapy in the adjuvant setting for patients with resectable stage II-III NSCLC.

Another Phase III, randomized, double-blind, placebo-controlled study, in which durvalumab is being given concurrently with platinum-based chemoradiotherapy in patients with locally advanced, unresectable NSCLC has recently completed recruitment (D933KC00001; PACIFIC-2).

Durvalumab has also demonstrated efficacy when administered in the first-line setting with platinum-based chemotherapy in metastatic NSCLC. Study D419MC00004 (POSEIDON; n=1013) is a Phase III randomized, open-label study of durvalumab ± tremelimumab in

combination with SoC platinum-based chemotherapy vs chemotherapy alone for the first-line treatment of patients with metastatic NSCLC (Johnson et al 2021). The study met the primary endpoint of PFS by showing a statistically significant and clinically meaningful improvement in patients treated with the combination of durvalumab and SoC platinum-based chemotherapy vs chemotherapy alone; analysis of the additional primary endpoint of OS in the durvalumab + chemotherapy treatment arm is pending. The safety and tolerability of the durvalumab ± tremelimumab and chemotherapy combinations were consistent with the known safety profile for these agents.

2.3 Benefit/risk assessment

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

See Section 9.7 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 , 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 CCI show a benefit of durvalumab plus SoC chemotherapy in patients with metastatic NSCLC (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 TCs. 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-Barré syndrome, myasthenia gravis).

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

In monotherapy clinical studies, AEs at an incidence of ≥20% include events such as fatigue, cough, decreased appetite, dyspnea, and nausea. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data, including AEs, serious AEs (SAEs), and Common Terminology Criteria for Adverse Event (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.

2.3.2.2 Durvalumab in combination with chemotherapy

As noted in Section 2.2.4, the safety and tolerability of durvalumab in combination with chemotherapy is being evaluated in several ongoing studies of NSCLC.

As of 12 July 2018, a total of 22 patients with advanced solid tumors have been treated with durvalumab and tremelimumab in combination with chemotherapy in CCI [redacted]. All patients had at least 1 AE (regardless of causality). AEs (all grades) reported in >20% of patients were nausea (68.2%); neutrophil count decreased (63.6%); decreased appetite (50.0%); cough, diarrhea, and rash (36.4% each); anemia and pyrexia (31.8% each); constipation, dizziness, insomnia, myalgia, platelet count decreased, and pruritus (27.3% each); alanine aminotransferase (ALT) increased, alopecia, dyspepsia, peripheral sensory neuropathy, vomiting, and white blood cell count decreased (22.7% each). All patients had AEs considered by the Investigator to be related to study treatment. Treatment-related AEs reported in >20% of patients were neutrophil count decreased (63.6%); nausea (59.1%);

decreased appetite, diarrhea, and rash (31.8% each); platelet count decreased and pruritus (27.3% each); and alopecia and peripheral sensory neuropathy (22.7% each). The majority of patients (19 [86.4%]) reported ≥Grade 3 AEs; 16 (72.7%) patients reported ≥Grade 3 treatment-related AEs. SAEs were reported in a total of 10 patients (45.5%). With the exception of pneumonia and pyrexia (3 patients each) and diarrhea and neutrophil count decreased (2 patients each), all other SAEs were reported in 1 patient each. One patient had a fatal AE of lung infection, which was considered treatment-related. A total of 13.6% of patients had AEs that led to permanent discontinuation of treatment.

In the CCTG study (NCT02537418), 118 patients were exposed to over 700 cycles of treatment, which began with chemotherapy combined with durvalumab ± tremelimumab until 4 to 6 cycles of chemotherapy ended; afterward, patients received further durvalumab ± tremelimumab treatment (Daaboul et al 2017). Recent data from the CCTG study show that chemotherapy combined with durvalumab ± tremelimumab did not increase immune-mediated AEs (imAEs), giving support to the combination being tolerable and manageable. Overall, 50% of patients had imAEs of any grade and 10% had ≥Grade 3 imAEs. Differences between the chemotherapy combination period and the durvalumab ± tremelimumab alone period were not significant, with the exception of biochemistry imAEs (chemotherapy combination 74% versus durvalumab ± tremelimumab 48%; p=0.003) and ALT/aspartate aminotransferase (AST) changes (41% versus 16% and 38% versus 9%, respectively; p=0.005). The imAEs that led to discontinuation of treatment in 15 patients were pneumonitis, hepatitis, nephritis, adrenal, myocarditis, gastrointestinal, thrombocytopenia, hyperthyroidism, and encephalitis. Pneumonitis and gastrointestinal imAEs were the most common, followed by nephritis. The few significant findings are likely due to the nature of combining numerous agents.

Additionally, a Phase III study of durvalumab with or without tremelimumab in combination with platinum-based chemotherapy for first-line treatment of patients with metastatic NSCLC is currently ongoing CCI [redacted]. Regular scheduled safety IDMC reviews have been conducted, and no safety concerns were raised. The study is continuing as planned (Johnson et al 2021).

External clinical data also support these findings. In KEYNOTE-189, in patients with NSCLC treated with pembrolizumab and chemotherapy or chemotherapy alone, the incidence of Grade 3 or worse AEs was 67.2% and 65%, respectively. In the pembrolizumab plus chemotherapy arm, the most common Grade 3 or worse AEs (AE frequency ≥5%) were anemia (16.3%), neutropenia (15.8%), thrombocytopenia (7.9%), asthenia (6.2%), fatigue (5.7%), and diarrhea (5.2%). In the chemotherapy alone arm, the most common Grade 3 or worse AEs (AE frequency ≥5%) were anemia (15.3%); neutropenia (11.9%); thrombocytopenia (6.9%); dyspnea (5.4%); and decreased neutrophil count, pancytopenia, and thrombocytopenia (3% each). AEs that led to death occurred in 6.7% of patients in the pembrolizumab plus

chemotherapy arm and 5.9% of patients in the placebo plus chemotherapy arm (Gandhi et al 2018).

For the IMpower150 study, AEs related to any treatment (as determined by the Investigator) occurred in 94.4% of patients in the ABCP arm and in 95.4% of patients in the BCP arm. The most common Grade 3 or 4 treatment-related AEs were neutropenia, decreased neutrophil count, febrile neutropenia, and hypertension (Socinski et al 2018).

For the KEYNOTE-407 and IMpower131 stage IV squamous NSCLC studies, the observed AEs were consistent with the known safety profiles of pembrolizumab and chemotherapy and atezolizumab and chemotherapy, respectively, with no new safety signals identified (Johnson et al 2021

Johnson M, Cho BC, Luft A, Alatorre-Alexander A, Geater SL, Laktionov K, et al. Durvalumab ± tremelimumab + chemotherapy as first-line treatment for mNSCLC: results from the phase 3 POSEIDON study [abstract PL02.01]. J Thorac Oncol. 2021;16(10 Suppl):S844.

Jotte et al 2018, Paz-Ares et al 2018).

Overall, the above data demonstrate that durvalumab in combination with chemotherapy is reasonably well tolerated and has an acceptable safety profile.

2.3.3 Overall benefit/risk

Recent progress in immunotherapy for NSCLC has been a substantive advance, although further improvement is needed, including predictive biomarkers and application to the curative setting. Additional 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 plus chemotherapy in the adjuvant setting could lead to improved outcomes. Therefore, in this Phase III study, the administration of durvalumab plus chemotherapy following complete resection in MRD+ patients will be investigated in patients with stage II-III NSCLC.

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 postoperative outcomes; the IDMC will report back to the Sponsor.

While neoadjuvant and adjuvant anti-PD-(L)1 treatment options have been approved by the FDA, leading to the decision to close this study to further enrollment, their availability remains limited globally. 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 administered in combination with platinum-doublet

chemotherapy following surgery is acceptable in patients with completely resected NSCLC, and the overall benefit/risk assessment supports the proposed study design and the objectives and endpoints have been updated. Despite the changes to the study, it is expected that this study will retain scientific and clinical utility that will be important to inform future clinical studies.

3 OBJECTIVES AND ENDPOINTS

As presented in Table 6, under CSP V4.0, as a result of the decision to close study enrollment early, meaning the intended patient numbers will not be reached, the primary objective of this study will now compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the FAS rather than in the MRD+ analysis set.

Table 6 Study objectives and associated endpoints/variables

Primary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by DFS in all patients	DFS in FAS (using Investigator assessments according to RECIST 1.1)
Secondary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by DFS in MRD+ patients	DFS in MRD+ analysis set (using Investigator assessments according to RECIST 1.1)
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy as measured by OS in MRD+ patients and in all patients	OS in MRD+ analysis set and in FAS
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability profile of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy in MRD+ patients and in all patients	AEs, physical examinations, vital signs, and laboratory findings
Exploratory objectives:	**Endpoint/variable:**
To assess the efficacy of durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy on post-recurrence outcomes	PFS (using local standard practice) CCI [redacted] CCI [redacted]

Table 6 Study objectives and associated endpoints/variables

To assess the efficacy of durvalumab + SoC chemotherapy to clear ctDNA compared to placebo + chemotherapy in MRD+ patients	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 relationship between treatment effect on DFS and treatment effect on ctDNA endpoints	ctDNA endpoints (as defined above) and DFS
To assess prognostic significance of MRD detection as determined by ctDNA in NSCLC	Time from randomization to DFS (MRD+ vs MRD-)
To assess the association of TMB with efficacy of durvalumab + SoC chemotherapy compared with placebo + SoC chemotherapy	DFS, OS in patients with TMB
To investigate the relationship between a patient's baseline PD-L1 TC and IC expression and efficacy outcomes with durvalumab + SoC chemotherapy compared with placebo + SoC chemotherapy	IHC analysis of PD-L1 TC and IC expression and spatial distribution within the tumor microenvironment relative to efficacy outcomes (ie, DFS, OS)
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 will be compared at baseline, on treatment, post-treatment and/or at recurrence. 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 Spectroscopy 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	Prespecified items on the PRO-CTCAE Patient global assessments
To assess patient-reported symptoms, functioning, and HRQoL in MRD+ patients treated with durvalumab + SoC chemotherapy compared to placebo + SoC chemotherapy	Change from baseline and time to deterioration in EORTC-QLQ-C30 and EORTC-QLQ-LC13

Table 6 Study objectives and associated endpoints/variables

To explore the impact of treatment and disease on health state utility	CCI , descriptor, and VAS

AE Adverse events; ctDNA Circulating tumor DNA; DFS Disease-free survival; EORTC European Organisation for Research and Treatment of Cancer; FAS Full analysis set; CCI ; HRQoL Health-related Quality of Life; IC Immune cell; IHC Immunohistochemistry; MRD Minimal residual disease; MRD+ Minimal residual disease-positive; MRD- Minimal residual disease-negative; NSCLC Non-small cell lung cancer; OS Overall survival; PD-L1 Programmed cell death-ligand 1; PFS Progression-free survival; PRO-CTCAE Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; 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; RNA Ribonucleic acid; SoC Standard of care; TC Tumor cell; TMB Tumor mutational burden; VAS Visual analog scale.

4 STUDY DESIGN

4.1 Overall design

For an overview of the study design, see Figure 1 (original study design) and Figure 2 (revised study design), 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.

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-arm study to evaluate the efficacy and safety of durvalumab plus SoC chemotherapy compared to placebo plus SoC chemotherapy in patients with completely resected stage II-III NSCLC who are MRD+ post-surgery.

Prior to CSP V4.0, the study was designed to screen approximately CCI patients and randomize approximately CCI patients with stage II-III NSCLC (according to IASLC Staging Manual in Thoracic Oncology v8.0) (select stage IIIB patients with T3N2 or T4N2 disease may be eligible; see Section 5.1.1), whose tumors are *EGFR* and *ALK* wild type, and who have undergone complete resection. Randomized patients were to include approximately CCI MRD+ and CCI MRD- patients. The number of MRD- patients was to be capped at CCI. As the total number of randomized patients will not reach CCI, the number of MRD- patients will be less than CCI. There was expected to be a split of approximately 30%/70% of Asian/non-Asian patients within the MRD- randomized population.

Following a decision to close recruitment on 25 May 2022, a total of 691 patients were enrolled, and up to approximately 100 patients are expected to be randomized within the study. The randomized population is expected to include up to approximately 25 MRD+ and 75 MRD- patients.

The study has opened in 188 centers globally. **Note that enrollment has closed for this study.**

First screening (initiated by the signing of ICF1)

First screening begins when the patient signs ICF1. It is preferred that patients are identified and enrolled prior to surgery (Table 1); however, patients are permitted to sign ICF1 following surgery. Pre-surgical workup and surgery are not considered study procedures.

During first screening, *EGFR* and *ALK* will be assessed. A pre-surgical biopsy sample is the **preferred** sample type; however, if a pre-surgery biopsy sample is not available or evaluable, testing will be conducted after surgery on the resected tumor tissue. Patients will still be allowed to continue with first screening procedures while testing is ongoing but will be excluded from second screening and randomization if their tumor sample tests positive for *EGFR* mutations and/or *ALK* translocations. Local testing must be performed using a well-validated, local regulatory approved test; results from testing performed during screening for another AstraZeneca study may be used. *EGFR/ALK* will be tested centrally if results from testing either locally or in the context of screening for another study are not available.

Note: Where *EGFR/ALK* testing of a pre-surgical tissue biopsy is performed locally as standard of care, the patient must be confirmed as *EGFR/ALK* wild-type prior to signing ICF1 and enrolling in the study.

This study requires mandatory genetic testing. 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 50 of the patient's tumor variants expressed at high frequency. This panel is then used to identify the presence of ctDNA extracted from the patient's plasma. The patient is considered MRD+ if the panel detects ctDNA.

Note: Patients who have higher levels of tumor-specific mutations are more likely to have sufficient mutations for a successful panel build. Patients with driver mutations and/or non-smokers tend to have a lower mutational burden (Nagahashi et al 2018, Offin et al 2019).

A pre-surgery plasma sample will be collected from all patients who sign ICF1 prior to surgery. These samples will be tested retrospectively using the personalized panel to determine if tumor-specific variants are detectable in the plasma-derived DNA prior to surgery for exploratory purposes. In addition, a plasma sample will be collected between Week 3-5 (Day 21-35) post-surgery and used to determine a patient's MRD status.

While it is **preferred** that patients sign ICF1 prior to surgery, patients will be permitted to enrol in the study after surgery. As a plasma sample must be collected at Week 3-5 (Day 21-35) post-surgery to determine a patient's MRD status, ICF1 should be signed no later

than Week 3 (Day 21) post-surgery to ensure the personalized panel is built and MRD result is obtained within the screening timeframe. Patients identified after Week 3 (d21) post-surgery but prior to Week 5 (d35) post-surgery may be allowed to enrol in the study depending on the outcome of the discussion with the study physician. A whole blood sample and resected tumor tissue must be collected and sent to the diagnostic lab **as soon as possible** after ICF1 is signed for development of the personalized panel.

Investigators will not be notified of MRD status, and eligibility will be managed through the IWRS.

Second screening (initiated by the signing of ICF2)
Following determination of their MRD status during the first screening period, patients will enter the second screening period (Table 2) to confirm that they are eligible for randomization to treatment.

Note: If the scan performed after surgery (Table 1 and Table 2) falls outside of the 28 day +7 days window **prior to randomization**, then an additional scan must be performed to confirm no evidence of disease**.**

Prior to CSP V4.0, approximately CCI patients were to be randomized 1:1 to treatment with durvalumab q3w for 4 cycles plus SoC chemotherapy q3w for up to 4 cycles or placebo q3w for 4 cycles plus SoC chemotherapy q3w for up to 4 cycles followed by durvalumab or placebo q4w for up to an additional 10 cycles (for a total of 12 months of treatment), until disease recurrence, or until other specific treatment discontinuation criteria are met (whichever occurs first). Approximately 100 patients are now expected to be randomized in the study.

Efficacy assessments of the primary endpoint of DFS will be derived using Investigator assessments according to RECIST 1.1 and prespecified 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 and survival until the primary DFS analysis. 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 second 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.

Selected visits may be performed via telemedicine or at the patient's home or other appropriate location by a qualified nurse, where feasible, allowed by local laws and regulations, and following consultation with the Investigator and Sponsor. These alternatives are optional, and all visits could be conducted as on-site visits if this is preferred. The patient must consent to have these visits performed at home.

All patients must be staged according to IASLC Staging Manual in Thoracic Oncology v8.0.

An IDMC comprised of independent experts will meet 12 months after the first patient has been dosed with IP or after the first 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.

4.1.1 Early Study Enrollment Closure

On 25 May 2022, AstraZeneca closed study recruitment. This was based on changes in the treatment landscape as outlined in Section 2.1. All randomized patients will be followed until the primary DCO when no further visits will occur. After the last patient last visit, the following are planned: DCO, DBL and primary DFS analysis. This will be followed by DBL and then the primary DFS analysis. The study will then be concluded.

4.2 Scientific rationale for study design

4.2.1 Overall rationale and study population

For patients with stage II-III disease, surgery and adjuvant SoC chemotherapy per National Comprehensive Cancer Network (NCCN) 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 with detection of MRD after surgery using ctDNA.

MRD- patients will be included in this study to evaluate whether MRD+ is distinct from MRD- status as a prognostic marker for disease recurrence and to provide clinical and translational data to facilitate the development of an MRD-driven treatment paradigm. The number of MRD- patients was to be capped at 100.

The stratification factors of stage (II versus III) and MRD status (MRD+ versus MRD-) were chosen to mitigate the risk of imbalance across treatment arms based on prognostic differences between stages and MRD status. As PD-L1 expression correlates with outcome in clinical trials evaluating IO therapy plus chemotherapy (Gadgeel et al 2019, Socinski et al 2018, Jotte et al 2019), patients will also be stratified according to PD-L1 status (TC <1% vs TC ≥1%) to mitigate the risk of imbalance across treatment arms for this prognostic factor.

In this study, adjuvant treatments should be initiated by Week 9 post-surgery (once MRD status has been determined) but can be delayed up to 12 weeks (+ 7 days) after surgery. Data

have shown that patients can still benefit from delayed adjuvant chemotherapy started up to 16 weeks after surgery (Salazar et al 2017).

4.2.2 Study design

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

The choice of SoC chemotherapy options provided in this study are paclitaxel + carboplatin (squamous patients only), pemetrexed + carboplatin (non-squamous patients only), or pemetrexed + cisplatin (non-squamous patients only). It is preferred that all non-squamous patients receive at least 1 cycle of cisplatin. In the event of unfavorable tolerability of cisplatin, non-squamous patients can switch from cisplatin to carboplatin therapy at any point during the study. During the first 4 treatment cycles, all patients will receive chemotherapy (the exact regimen selected by the Investigator from the SoC chemotherapy options listed above). The chemotherapy options provided in this study include agents that are commonly used in adjuvant therapy and allow sufficient flexibility for Investigators and patients to select the agents that reflect their normal clinical practice and national guidelines (NCCN 2019).

4.2.3 Primary and secondary outcome measures

The primary efficacy endpoint of this study is DFS in the FAS; DFS will be determined using the definition of a new lesion per RECIST 1.1. DFS (see Section 8.1.1) represents a direct measure of the study drug's efficacy. Historical data have shown that the DFS benefit seen in MRD+ patients treated with adjuvant chemotherapy 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.

Prior to CSP V4.0, the study was sized on the MRD+ population, since the study was aimed at testing the hypothesis that detection of MRD after surgery is a marker of high risk for recurrence and can be used to select patients in adjuvant studies. DFS in all patients was to be evaluated as a secondary outcome. The study was not sized for the MRD- population. After CSP V4.0, the study is not powered to detect statistical significance, and all analyses will be performed in an exploratory manner.

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

4.2.3.1 Rationale for exploratory endpoints

The potential clinical benefit of durvalumab post disease recurrence will be evaluated by the exploratory endpoints of PFS (using local standard practice), CCI (CCI), and CCI (CCI).

Biomarkers to be assessed are justified on the basis that they may identify subpopulations most likely to derive clinical benefit from therapy (predictive biomarkers) and to rapidly identify patients most likely to experience clinical benefit after treatment has started (early efficacy biomarkers), begin to collect data on potential surrogate 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, immune and stromal cell gene and protein expression profiles, and tumor mutational burden (TMB) analyses.

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, ctDNA will be assessed as an exploratory outcome.

The exploratory 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), will show the overall benefits and toxicity of the treatment from the patient's perspective and will aid in understanding the benefit/risk evaluation. These PRO questionnaires are well established instruments that have been previously included in cancer clinical studies.

CCI

4.3 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, nonclinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 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 tumors (D4190C00002).

4.3.1 PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg every 2 weeks (q2w) or 15 mg/kg 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 programmed cell death-ligand 1 [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 AUC at steady state (4 weeks). Median maximum drug concentration at steady state is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median trough drug concentration at steady state is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w, with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in the majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of antidrug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar AUC and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 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 for durvalumab monotherapy. This dose has been used in multiple studies previously with no safety concerns.

4.3.2 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.

4.3.3 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from 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 a 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.

A fixed dose of 1500 mg durvalumab administered q3w or q4w is to be used for all patients with a body weight greater than 30 kg. Currently, the use of a fixed dose of 1500 mg durvalumab, administered both in combination with chemotherapy and as monotherapy, is approved for treatment of extensive-stage small-cell lung cancer; additionally, the 1500 mg fixed dose is approved in the US as monotherapy for both unresectable stage III non-small cell lung cancer (following chemoradiation).

Rationale for proposed every 3 weeks fixed dosing

The proposed dosing schedule is aligned with the standard fixed dosing of 1500 mg durvalumab for 4 cycles, which is supported by efficacy and safety as well as tolerability data across multiple studies in multiple tumor types. To conform to the chemotherapy schedule in the study, the Sponsor proposes to use standard durvalumab dose and ratio at a q3w dosing interval for the first 4 cycles rather than the standard q4w schedule.

The safety of a q3w dosing schedule in combination with chemotherapy has been explored in the ongoing Study D419SC00001, where durvalumab is administered at 1120 mg q3w in combination with 75 mg of the anti-CTLA-4 antibody tremelimumab followed by 1120 mg

durvalumab q3w. The combination has been declared tolerable and manageable. The 1120 mg dose of durvalumab is the q3w equivalent of the standard 1500 mg q4w dose. The q3w regimen is also being administered in the ongoing Study D9106C00001 (AEGEAN), in which durvalumab 1500 mg q3w is administered in combination with platinum-based chemotherapy regimens as neoadjuvant therapy in patients with resectable NSCLC.

In this study, AstraZeneca proposes to use the Phase III fixed dose of durvalumab, so this study will use 1500 mg durvalumab q3w in combination with chemotherapy as adjuvant therapy. The relative increase in dose density of durvalumab (ie, 1500 mg q3w instead of q4w) is supported by the fact that toxicities attributable to durvalumab do not appear dose-dependent, and PK modeling reveals no meaningful differences in drug levels between q3w and q4w dosing. After completion of SoC chemotherapy, the dose will be 1500 mg durvalumab q4w.

4.3.4 Rationale for standard of care adjuvant chemotherapy regimens

In this study, patients will receive 4 cycles of a SoC platinum-based adjuvant chemotherapy regimen, based on squamous or non-squamous histology, either in combination with durvalumab or with placebo (specific options are outlined in Table 8). This is in alignment with the NCCN guidelines (NCCN 2019), which recommend 4 cycles of chemotherapy in the adjuvant setting.

4.3.5 Rationale for Placebo

In this study patients will receive either durvalumab or placebo in combination with SoC chemotherapy and then afterwards as monotherapy. The continued use of placebo in this study is justified owing to limited global availability of adjuvant anti-PD-(L)1 immunotherapy, to determine potential risks and benefits of durvalumab in combination with chemotherapy, rigid timescales for commencing anti-PD-(L)1 therapies in Phase III studies leading to approval (relevant to patients already established on study treatment), and uncertain risks and benefits of anti-PD-(L)1 therapies in MRD- and MRD+ populations. These data are important for determining optimal future registrational clinical trial designs aimed at optimising patient outcomes. Given potential changes in SoC treatments available to patients, Investigators should continue to assess, and discuss with patients, the potential risks and benefits associated with ongoing study participation and ensure the nature and outcomes of these discussions are recorded in the source documentation.

4.4 End of study definition

The end of study is defined as the date of the last visit of the last patient in the study, which is approximately 12 months following last patient randomized. The DCO for primary DFS analysis will follow last patient last visit. No further visits or assessments will be conducted

thereafter. No additional data will be collected, except for mandatory safety reporting as outlined in Section 8.3.13.

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.

See section 8.3.13 for details regarding data collection on randomized patients (including patients in follow-up) and patients in observation following DCO for primary DFS analysis.

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

5 STUDY POPULATION

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who sign ICF1 and enter first screening. **Note that enrollment has closed for this study.** The first screening includes the period before, during, and after surgery but before second screening and determination of final eligibility for randomization in this study. The primary purpose of the first screening period is to determine the patient's MRD status.

The procedures during the second screening (initiated by the signing of ICF2) include final assessment of eligibility for randomization into the study. "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled patients, see Section 7.3.

5.1 Inclusion criteria

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

Patients must be capable of giving signed informed consent, which includes a **mandatory** genetic informed consent and compliance with the requirements and restrictions listed in the informed consent forms (ICFs) and in this protocol. Provision of signed and dated, written ICFs must occur prior to any mandatory study-specific procedures, sampling, and analyses.

This study will use a 2-tiered informed consent and screening process such that initial inclusion criteria are assessed during the first screening period (initiated by the signing of ICF1; Section 5.1.1) and additional inclusion/exclusion criteria are assessed during the second screening period (initiated by the signing of ICF2; Section 5.1.2); **all eligibility criteria must be assessed prior randomization**.

In addition to ICF1 and ICF2, patients will provide signed and dated written **optional** genetic informed consent prior to collection of a sample for optional genetic analysis at the time of second screening (Table 2). This is different from the genetic samples and testing covered by ICF1, which are mandatory for participation in this study.

The ICF process is described in Appendix A 3.

See Table 4 for a summary of the timings of inclusion criteria assessments relative to ICF1 (Section 5.1.1) and ICF2 (Section 5.1.2).

5.1.1 Criteria and procedures initiated with the signing of ICF1

1 ICF1 must be signed and dated prior to any study procedures and prior to the planned surgical resection of the primary NSCLC, with the exceptions noted below. This consent will cover the study-specific first screening procedures outlined in Table 1.

Exception: Patients will be permitted to sign ICF1 up to Week 3 (Day 21) post-surgery. Patients identified after Week 3 post-surgery but prior to Week 5 (Day 35) post-surgery may be allowed to sign ICF1 depending on the outcome of the discussion with the study physician. In these cases, a whole blood sample and resected tumor tissue must be collected and sent to the diagnostic lab as soon as possible after ICF1 is signed for development of the personalized panel. A plasma sample must still be collected at Week 3-5 (Day 21-35) post-surgery, even if creation of the personalized panel for MRD detection is delayed.

Age

2 Age ≥18 years at the time of screening.

Sex

3 Male and/or female.

Type of patient and disease characteristics

4 Individuals who have diagnosis of histologically confirmed NSCLC (WHO 2015 classification) with resectable (stage II-III) disease (according to IASLC Staging Manual in Thoracic Oncology v8.0).

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

5 A contrast-enhanced CT or MRI scan of the chest 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 (contrast-enhanced or low-dose CT component) in order to rule out detectable extrathoracic, extracranial metastasis and to assess for potential mediastinal lymph node involvement prior to surgery. In the absence of pre-operative FDG-PET CT imaging, pre-operative contrast-enhanced CT imaging or MRI scan must cover liver and adrenal glands. If only CT is available, or FDG-PET reveals suspicious lymph node mediastinal involvement, it is recommended that invasive pre-operative mediastinal staging is performed according to the algorithm of the European Society of Thoracic Surgeons guidelines (algorithm to follow for primary mediastinal staging if only pre-operative CT is available [De Leyn et al 2007], algorithm to follow for primary mediastinal staging when PET-CT is available [De Leyn et al 2014]). It is preferred that imaging occurs within 6 weeks prior to surgery. Brain MRI (preferred) or brain CT with IV contrast is required for complete staging of the tumor.

6 Complete resection of the primary NSCLC is mandatory. The primary tumor must be deemed resectable by a multidisciplinary evaluation that must include a thoracic surgeon certified or trained according to local standards and who performs lung cancer surgery as a significant part of their practice. 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: Patients undergoing segmentectomy must have tumors less than 2 cm in maximum diameter. 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.

At a minimum, the following parameters should be met for a tumor to be declared completely resected:

(a) The surgeon performing the resection should remove all gross disease by the end of surgery. All surgical margins of resection must be macroscopically negative for tumor.

(b) Pathology and/or operative reports must include the examination of at least 2 different mediastinal lymph node (N2) levels, one of which is the subcarinal node-group (level 7) and the second of which is lobe-specific (defined below).

Note: In the uncommon clinical situation where the surgeon thoroughly examines a mediastinal lymph node level and does not find any lymph nodes, that mediastinal lymph node level may be counted among the minimum 2 required levels. However, the surgeon must clearly document in the operative report or in a separate written statement that the lymph node level was explored and no lymph nodes were present. Normal appearing lymph nodes, if present, must be biopsied or removed. Exploration of nodes must clearly be documented in medical file if not recorded in operative report.

Note: Lobe-specific lymph node stations are classified based on the location of the primary tumor as follows (based on IASLC 2009 lymph node map terminology [Rusch et al 2009]): Stations 2R and 4R for right upper lobe or middle lobe tumors, stations 4L, 5, and 6 for left upper lobe tumors, stations 8 and 9 for lower lobe tumors of both sides (Adachi et al 2017, Rami-Porta et al 2005).

(c) No extracapsular nodal extension of the tumor is observed in resected mediastinal N2 lymph nodes.

Note: Extracapsular nodal extension in resected N1 nodes is permitted.
Note: The highest mediastinal node resected can be positive for malignancy.
Note: Carcinoma-in-situ can be present at the bronchial margin.

7 All patients who enrol in the study prior to surgery must have a pre-surgical plasma sample collected for MRD evaluation. Patients will not be excluded from randomization based on the results of analysing the pre-surgical plasma samples.

The following criteria must be met prior to signing ICF2:

8 Confirmation of suitable samples of resected tumor tissue and whole blood for WES of tumor and germline DNA, respectively, and creation of Sponsor-approved personalized panel for MRD detection. Tumor tissue and whole blood samples must be provided to the diagnostic laboratory for development of the personalized panel as soon as possible. Germline sequencing of whole blood is **mandatory**.

Note: If a patient's tumor has less than the requisite 50 tumor-specific variants, a panel cannot be built and the patient will no longer be able to participate in the study.

9 Established MRD status (MRD+ or MRD-) based on Sponsor-approved personalized assay of a plasma sample collected at Week 3-5 (Day 21-35) post-surgery.

10 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.

5.1.2 Criteria and procedures initiated with the signing of ICF2

11 Post-operative CT scan of the chest (including liver and adrenal glands) performed within 28 days + 7 days **prior to randomization**. If clinically indicated, additional scans (such as brain MRI [preferred] or brain CT with IV contrast) should be performed to confirm no evidence of metastasis.

12 ICF2 must be signed and dated after MRD status is determined and prior to initiation of any study-specific procedures, sampling, and analyses outlined in SoAs in Table 2 and Table 3. Randomization must occur within the 12 weeks (+ 7 days) following surgery.

13 WHO/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

14 Complete postoperative 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 or chemotherapy according to the Investigator's judgment.

15 Eligible to tolerate 4 cycles of platinum-based adjuvant chemotherapy

16 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.
- ALT and AST ≤2.5 × ULN
- Measured creatinine clearance (CL) ≥40 mL/min or Calculated creatinine CL ≥40 mL/min as determined by Cockcroft-Gault (using actual body weight)

  Males:

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

  Females:

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

17 Must have a life expectancy of at least 12 weeks

Weight

18 Body weight >30 kg

5.2 Exclusion criteria

All exclusion criteria must be checked prior to randomization. If a patient meets an exclusion criterion, the patient is ineligible to continue in the study.

Diagnostic assessments

1 Post-operative imaging demonstrating unequivocal evidence of disease recurrence or tissue biopsy-proven disease recurrence. 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.

2 *EGFR*-mutant and/or *ALK*-translocation-positive, as assessed either from a pre-surgical biopsy sample (preferred) or the resected tumor tissue (if biopsy was not evaluable or available). Any of the following scenarios are acceptable for this study:

Where *EGFR/ALK* results are obtained from a pre-surgical tissue biopsy as part of standard local practice, the patient must be confirmed *EGFR/ALK* wild-type prior to enrolling in the study.

Results obtained from testing the patient's primary tumor tissue during screening for another AstraZeneca study may be used in this study.

Results from local testing of a pre-surgical biopsy.

All local *EGFR/ALK* testing performed locally must be performed using a well-validated, local regulatory-approved test.

EGFR/ALK may be tested centrally if local testing is unavailable. Patients will still be allowed to continue with first screening procedures while testing is ongoing but will not be able to continue into second screening if their tumor tests positive for *EGFR* mutations and/or *ALK* translocations.

3 Mixed small cell and NSCLC histology.

4 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.

5 Patients who are candidates to undergo only wedge resections.

Medical conditions

6 History of allogeneic organ or bone marrow transplantation.

7 Non-leukocyte-depleted whole blood transfusion within 120 days of genetic sample collection. **Note:** This exclusion criterion only relates to whole blood and does not include other blood products (eg, packed red blood cells).

8 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

9 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 requirements, substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent.

10 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

11 History of active primary immunodeficiency

12 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** (HBV; known positive HBV surface antigen [HBsAg] result), **hepatitis C (HCV)**, or **human immunodeficiency virus infection** (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.

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

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

Prior/concomitant therapy

15 Received any prior adjuvant therapy for NSCLC or any prior exposure to durvalumab.

16 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.

17 Radiotherapy treatment for NSCLC in the neoadjuvant setting. 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.

18 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.

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

20 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab/placebo. 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

21 Participation in another clinical study with an IP administered since completion of surgery.

22 Previous IP assignment in the present study.

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

24 Prior randomization or treatment in a previous durvalumab clinical study regardless of treatment group assignment.

Other exclusions

25 Patients who are never-smokers; defined as no more than 100 cigarettes or its equivalent in his/her lifetime.

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

27 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

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

1 Patients must follow the contraception requirements outlined in Appendix H.
2 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/placebo or until alternate anticancer therapy is started.
3 Restrictions relating to concomitant medications are described in Section 6.4.

5.4 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. Screen failed patients should be recorded in the IWRS as soon as possible. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required eligibility criteria). "Eligibility criteria not fulfilled" as a reason for study withdrawal is only valid for screen failures (ie, not randomized patients). The reason for screen failures will be captured in the appropriate section of the electronic case report form (eCRF).

Please note that the patient may screen fail during either first or second screening. Screen failure may occur before a patient's MRD status can be determined. If a patient's tumor is found to have less than 50 tumor-specific variants required to build the MRD personalized panel, then the panel cannot be created, the MRD status will not be determined and the patient will not be able to continue to participate in the study.

Patients may be rescreened, following discussion with the study team and provided adjuvant therapy can be initiated within 12 weeks (+ 7 days) from surgery. Patients cannot be re-randomized in this study.

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 (Table 7).

Table 7 Minimum requirements for data entry for screen-failed patients

All patients	Patients with MRD result
• Demographics (age, gender, ethnicity, race, region)[a] • Smoking history • Stage (post-surgery) • Local *EGFR/ALK* status[b] • Central *EGFR/ALK* and PD-L1 results[b] • Date of surgery[b] • Date(s) of sample collection[b] • Reason(s) for screen failure (if applicable) • Any SAE related to study procedures	• Pre-surgical details (including imaging, if available) • Histology, pre- and post-surgery • Surgical details, including: o Extent of resection o Pleural invasion status o Nodal disease/Confirmation of node-negative disease o Extracapsular disease o Medistinal lymph node examination/dissection o Confirmation of complete resection • Post-surgical scan data[b]

[a] Where allowed by local laws and regulations.
[b] If available.

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 clinical study protocol (CSP). Study treatment in this study refers to durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy.

6.1 Treatments administered

AstraZeneca will supply durvalumab and placebo. SoC chemotherapy will be supplied locally. Under certain circumstances when local sourcing is not feasible, SoC chemotherapy may be supplied centrally through AstraZeneca. Study treatments are described in Table 8.

Table 8 Study treatments

Study treatment name	Durvalumab	Placebo	Standard of Care[a]		
			Squamous histology	Non-squamous histology	
			Carboplatin/Paclitaxel	Cisplatin[b,c/] Pemetrexed	Carboplatin[c]/ Pemetrexed
Dosage formulation	500-mg vial solution for infusion after dilution, 50 mg/mL	Vial solution for infusion after dilution	As sourced locally[a]	As sourced locally[a]	As sourced locally[a]
Route of administration	IV	IV	IV	IV	IV
Dosing instructions[d]	1500 mg infusion over 60 min q3w x 4 cycles followed by 1500 mg over 60 min q4w x 10 cycles up to a total of 12 months (14 cycles) of treatment[d,e]	Infusion over 60 min q3w x 4 cycles followed by infusion over 60 min q4w x 10 cycles up to a total of 12 months (14 cycles) of treatment[d,e]	Paclitaxel (200 mg/m^2) and carboplatin (AUC 6) Day 1 of each 3-week cycle for 4 cycles	Pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) Day 1 of each 3-week cycle for 4 cycles[f]	Pemetrexed (500 mg/m^2) with carboplatin (AUC 5) Day 1 of each 3-week cycle for 4 cycles[f]
Packaging and labeling	Study treatment will be provided in 500 mg vials. Each 500 mg vial will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.[e,g]	Study treatment will be provided in vials. Each vial will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.[e]	Sourced locally by site[a]	Sourced locally by site[a]	Sourced locally by site[a]
Provider	AstraZeneca	AstraZeneca	Sourced locally by site[a]	Sourced locally by site[a]	Sourced locally by site[a]

[a] Patients will receive one of the specified SoC regimens, depending on histology and per Investigator's decision. Regimens listed are according to NCCN guidelines (NCCN 2019, Version 3.2019). Under certain circumstances when local sourcing is not feasible, a chemotherapy treatment may be supplied centrally through AstraZeneca.

[b] In the event of unfavorable tolerability, non-squamous patients can switch from cisplatin to carboplatin therapy at any point during the study. However, it is preferred that all non-squamous patients receive at least 1 cycle of cisplatin.

[c] Patients with non-squamous NSCLC only: Administer vitamin B12 and folic acid in line with local practice.

[d] See Sections 6.1.2.1for specific instructions for preparing and storing durvalumab and placebo.

[e] If a patient's weight falls to 30 kg or below, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q3w or q4w after consultation between Investigator and Study Physician until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q3w or q4w. Durvalumab will be administered q3w in combination with SoC chemotherapy for the first 4 cycles of the study and q4w as monotherapy for an additional 10 cycles.

[f] Prepared in accordance with local labeling.

[g] 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.

AUC Area under the serum drug concentration-time curve; IV Intravenous; min Minutes; NCCN National Comprehensive Cancer Network; NSCLC Non-small cell lung cancer; q3w Every 3 weeks; q4w Every 4 weeks; SoC Standard of care.

6.1.1 Order of administration

On Day 1 of each cycle, patients will receive durvalumab 1500 mg or placebo via IV infusion over 1 hour. For the combination portion of the study, SoC chemotherapy via IV infusion will start approximately 1 hour (maximum 2 hours) after the end of the durvalumab or placebo infusion. The time between administration of durvalumab/placebo and SoC chemotherapy should be as short as possible.

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.

6.1.2 Investigational products

6.1.2.1 Durvalumab/placebo

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, CCI histidine/histidine hydrochloride, CCI trehalose dihydrate, and CCI 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 durvalumab/placebo doses for administration with an IV bag

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

6.1.2.2 Standard of care chemotherapy

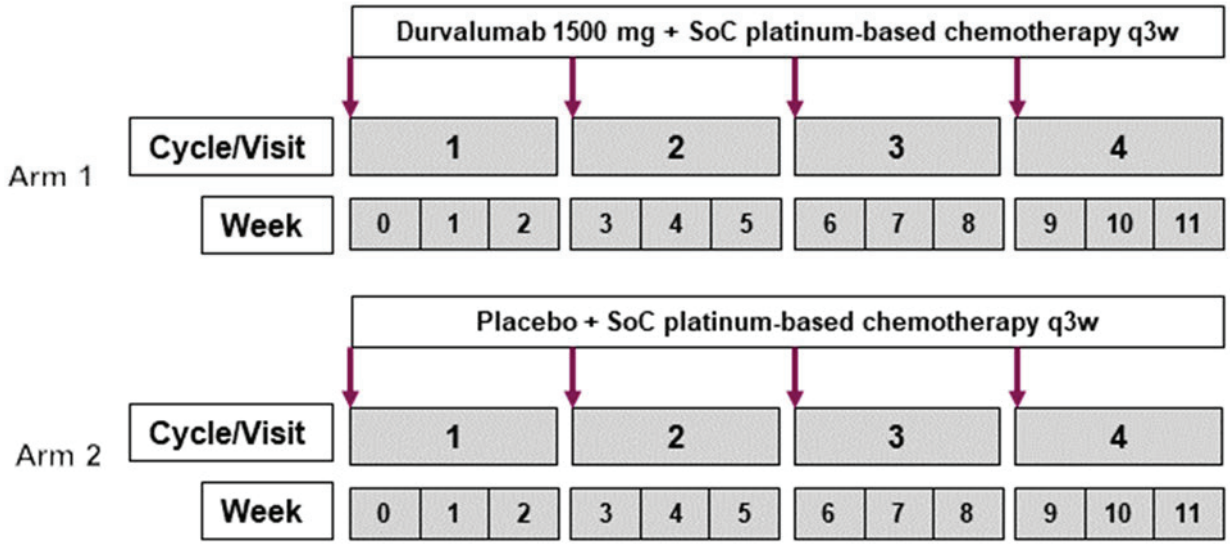
The SoC agent(s) will either be locally sourced or centrally supplied by AstraZeneca and will be administered according to prescribing information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug and it will be labeled with local language translated text in accordance with regulatory guidelines.

6.1.3 Dosage and treatment regimens

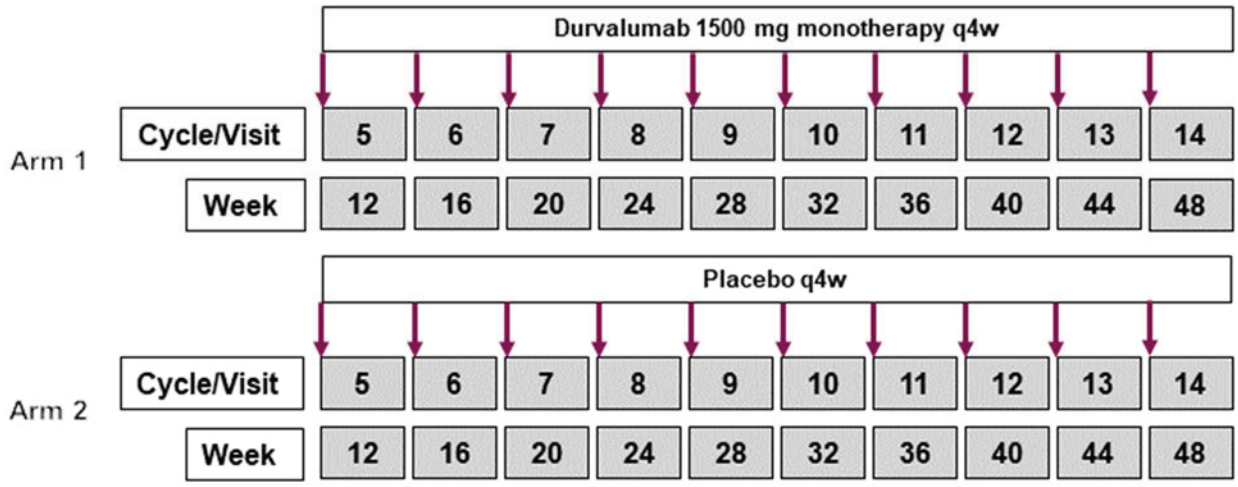
The full dosing scheme by treatment arm throughout the 12-month treatment period is shown in Figure 3 and described in the following sections.

Figure 3 Dosing scheme

q3w x 4 cycles



q4w x 10 cycles[a]



[a] At the discretion of the Investigator, eligible patients may receive PORT during the durvalumab/placebo monotherapy phase (see Section 6.4.1).

Note: Each treatment will be administered on Day 1 of each cycle, as indicated by the arrows.
IP Investigational product; PORT Postoperative radiation therapy; q3w Every 3 weeks; q4w Every 4 weeks; SoC Standard of care.

6.1.3.1 Durvalumab or placebo

Patients in the durvalumab or placebo arm will receive 1500 mg durvalumab or placebo via IV infusion q3w for 4 cycles then q4w for 10 cycles (for a total of 12 months of treatment) with the last administration on Week 48 or until disease recurrence (whichever occurs first) 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], the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo q3w or q4w after consultation between Investigator and Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg or placebo q3w or q4w).

6.1.3.2 Standard of care

SoC chemotherapy will consist of 4 cycles of carboplatin + paclitaxel or cisplatin/carboplatin + pemetrexed administered q3w, depending on tumor histology (per NCCN guidelines; NCCN 2019) and Investigator's discretion, as summarized in Table 8 and Figure 3.

6.1.4 Duration of treatment

All treatment will be administered beginning on Day 1 for up to 4 cycles (q3w) of durvalumab or placebo plus SoC chemotherapy, then continuing q4w for up to 10 additional cycles (for a total of 12 months of treatment) of durvalumab monotherapy or placebo, 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 12 months of therapy (14 cycles of treatment) or upon evidence of RECIST 1.1-defined disease recurrence, whichever occurs first.

Crossover within the study will not be permitted.

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 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, until death, or until DCO (whichever occurs first). The DCO for the primary DFS analysis will follow last patient last visit. See Section 4.1.1 for the order of events following last patient last visit.

Patients may not receive retreatment in this study.

6.1.5 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.

The IP label on the pack/bottle/carton for SoC specifies the appropriate storage for these agents.

6.2 Measures to minimize bias: randomization and blinding

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 patients will not be replaced.

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

This study will use a 2-tiered consent process. The signing of ICF1 will initiate the first screening, which includes procedures conducted prior to surgery and/or post-surgery through determination of MRD status, as outlined in Table 1. The signing of ICF2 will initiate the second screening procedures required for randomization and will also include the treatment and follow-up periods, as outlined in Table 2 and Table 3.

After confirmation of NSCLC diagnosis and prior to surgery, the Investigators or suitably trained delegate will:

- Obtain signed ICF1 before any study-specific first screening procedures are performed.
- Obtain a unique 7-digit enrollment number (E-code), via the IWRS in the following format: ECCNNXXX (with 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 eligibility based on the criteria outlined in the SoAs in Table 1, Table 4, and Table 5, and Sections 5.1 and 5.2.
  - This will include *EGFR/ALK* and PD-L1 testing, obtaining a whole blood sample and resected tumor tissue for development of the personalized panel, and obtaining a post-surgical plasma sample to assess MRD status.
  - NOTE: Surgery is **not** a study-specific procedure. However, patients will need to sign ICF1 to give the Sponsor access to complete surgical information and obtain resected tumor tissue for this study.

After determination of MRD status, patients will sign ICF2 and enter the second screening period (Days -28 to 0 relative to randomization). Randomization is allowed up to 12 weeks (+7 days) following surgery. If randomization cannot occur within this timeframe, the patient is ineligible for the study. During the second screening, the Investigator or suitably trained delegate will:

- Obtain signed ICF2 before any study-specific procedures outlined in the SoAs 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 based on study procedures conducted during second screening (see Table 2 and Sections 5.1 and 5.2)
- Obtain signed informed consent for **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 as soon as possible to screen fail the patient and terminate the patient in the system. Screen failures can occur at any time during first or second screening, including prior to determination of a patient's MRD status (see Section 5.4).

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.

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 not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn (ie, screen-failed) 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 Study Physician immediately, and a discussion should occur between the Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The Study Physician

must ensure all decisions are appropriately documented and that the potential benefit:risk profile remains positive for the patient.

Patients may not be re-randomized into the study.

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, study team, and Sponsor will be fully blinded to all treatment.

The IWRS will provide to the Investigator(s) or pharmacist(s) (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 patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the patient to 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 patient have been made and documented.

The IWRS will provide to the Investigator and pharmacist(s) 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 patient's assigned study treatment throughout the course of the study.

In the event that the treatment allocation for a patient 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. In addition to blinding to treatment, Investigators will be blinded to the patient's PD-L1 status.

Please note that Investigators will not be notified of the patient's MRD status to limit potential bias upon interpreting the scans. If an Investigator becomes unblinded to treatment allocation, it is not necessary to also notify the Investigator regarding the patient's MRD status, as this information is not necessary to inform treatment decisions.

6.2.5 Methods for unblinding

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.

If the Investigator requests to be unblinded to the patient's study treatment assignment, they will also be automatically unblinded to the patient's PD-L1 status. The patient's MRD status will not be unblinded at the time of treatment unblinding.

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

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.

6.3 Treatment compliance

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

Any dose reductions (applicable for SoC chemotherapy only), change from the dosing schedule, dose delays/interruptions, and dose discontinuations should be recorded in the eCRF.

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.

6.4 Concomitant therapy

Concomitant medications should only be recorded during the first screening period in the eCRF if an SAE has been reported (Table 1). **Note:** During first screening, only SAEs related to study procedures (ie, blood draws and [if performed during first screening] the post-surgical scan) must be reported.

The Investigator must be informed as soon as possible about any medication taken from the time of the second screening until the end of the clinical treatment phase of the study, including the 90-day follow-up period following the last dose of IP (Table 2 and Table 3).

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

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

Patients must be instructed not to take any medications, including herbal medication and 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). For agents in the SoC chemotherapy group, please refer to the local prescribing information with regard to warnings, precautions, and contraindications.

Table 9 Prohibited concomitant medications for all treatment arms

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Exception is made for patients who are eligible for PORT therapy, provided the radiotherapy is given after chemotherapy has been completed (Section 6.4.1)

Table 9 Prohibited concomitant medications for all treatment arms

Prohibited medication/class of drug:	Usage:
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 • Short-term premedication for patients receiving chemotherapy[a] where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • 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
EGFR TKIs	Should not be given concomitantly while the patient is on study treatment Should be used with caution in the 90 days post last dose of durvalumab Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies, which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor
Antibiotics	Should not be used within 30 days prior to randomization[b]

[a] Note: Alternative anti-emetic pre-medication should be prioritised in place of steroids (eg, 5-HT3 inhibitors, neurokinin inhibitors). Where steroid pre-medication is utilised, steroid doses should be administered in line with the Multinational Association of Supportive Care in Cancer (MASCC) guidelines (Rolia et al 2016).

[b] Pinato et al 2019

AE Adverse event; CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4; IO Immuno-oncologic therapy; IP Investigational product; mAbs Monoclonal antibodies; PD-1 Programmed cell death 1; PD-L1 Programmed cell death-ligand 1; PORT Postoperative radiation therapy; TKI Tyrosine kinase inhibitor.

Table 10 Supportive medications

Supportive medication/class of drug:	Usage:
Post-operative radiation therapy (PORT) for pathologically confirmed N2 lesions following adjuvant chemotherapy; concurrent chemo-radiation is not permitted	To be administered at the discretion of the Investigator, only after chemotherapy has been completed, but permitted during durvalumab/placebo maintenance. Please refer to Section 6.4.1
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 Please note restrictions in Table 9 regarding antibiotic usage prior to randomization
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.4.1 Postoperative radiotherapy standardized guidance

Patients with **pathologically confirmed N2 disease or positive pleural margins** may receive adjuvant postoperative radiation therapy (PORT) at the discretion of the Investigator, provided that PORT is given sequential to chemotherapy (ie, during durvalumab or placebo monotherapy) but not concurrent to chemotherapy.

Either intensity-modulated radiation therapy (IMRT) or 3D-conformal radiotherapy is allowed, though IMRT is preferred.

Motion assessment is required, with motion management depending on the results of the motion assessment. Four-dimensional CT simulation is the preferred method for motion assessment. Motion management acceptable forms require that the motion management method employed by the participating institution reduces the effective motion of the target to ≤10 mm.

Daily image-guided radiotherapy is strongly recommended.

Some form of immobilization is required, with attention to patient comfort to prevent intra-fraction motion. Patients must be immobilized in a stable position using the participating institution's standard of practice.

The treatment planning CT is required for defining target volumes and organs-at-risk.

6.4.2 Other concomitant treatment

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

Note: For all patients with non-squamous tumor histology scheduled to receive pemetrexed, folic acid and vitamin B12 should commence prior to treatment initiation for up to 7 days, in line with local practice. This is to ensure treatment can begin on Day 1.

6.4.3 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab, either nonclinically or in patients. As durvalumab is a 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.

6.4.4 Rescue medication

As a result of imAEs that could potentially be experienced by patients on durvalumab, steroids and other immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy-related toxicities. These rescue medications must be receipted, controlled, and dispensed by the pharmacist and stored according to the labeled storage conditions, with temperature excursions reported accordingly by the pharmacist. If required for use as a result of an imAE, the IWRS will provide to the pharmacists the kit identification number to be allocated to the patient at the time. Blinded and unblinded access and notifications will be controlled using the IWRS.

6.5 Dose modification

Dose delays are permitted for durvalumab (see Section 8.4.5.1). The patient should receive up to 14 cycles of therapy, even if a dose delay causes the treatment period to extend beyond 12 months.
However, **dose reduction is not permitted for IO therapy.**

Investigators should follow local standard clinical practice regarding dose modifications (dose delay and/or dose reductions) for the SoC treatments (chemotherapy).

6.6 Treatment after the end of study

No further treatment will be offered after the end of study.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

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

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1) or as defined in the local prescribing information for the SoC agents
- Pregnancy or intent to become pregnant
- Non-compliance with the CSP 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 disease recurrence (refer to Section 8.1.1.1 and Appendix G) and Investigator determination that the patient is no longer benefiting from treatment with IP
- Completion of 12 months (14 cycles) of treatment

In the event that durvalumab/placebo is permanently discontinued due to treatment-related toxicity, chemotherapy may still be administered as scheduled. In the event that chemotherapy is permanently discontinued due to treatment-related toxicity, durvalumab/placebo may still be administered as scheduled. Treatment decisions should be made at the Investigator's discretion and AstraZeneca should be consulted.

7.1.1 Procedures for discontinuation of study treatment

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

Patients can discontinue durvalumab/placebo and continue with SoC chemotherapy through the planned 4 cycles. Patients can discontinue SoC chemotherapy and still continue with durvalumab/placebo. In both cases, patients will still be considered on study treatment while they receive either SoC chemotherapy or durvalumab/placebo.

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

Patients who are permanently discontinued from further receipt of any 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 12 months (14 cycles) of treatment for reasons other than disease recurrence should continue to have scans performed every 12 weeks (q12w) ± 1week (relative to the date of randomization) until primary DFS analysis or until RECIST 1.1-defined disease recurrence or death (whichever occurs first) as defined in the SoAs.

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

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is

re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

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."

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

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

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

7.3 Withdrawal from the study

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

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

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

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

- All further participation in the study, including any further follow up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples (see Section 8.7.3).

Given potential changes in SoC treatments available to patients, Investigators should continue to assess, and discuss with patients, the potential risks and benefits associated with ongoing study participation and ensure the nature and outcomes of these discussions are recorded in the source documentation.

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of ICF1 and/or ICF2 may be utilized for screening or baseline

purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoAs.

8.1 Efficacy assessments

The primary endpoint of DFS in the FAS will be derived using Investigator assessments according to the RECIST 1.1 definition of new lesions.

Secondary efficacy endpoints will include DFS in the MRD+ analysis set, also using Investigator assessments according to RECIST 1.1; DFS in both MRD+ patients and the FAS; and OS in MRD+ analysis set and the FAS. See Section 8.1.1 for details on assessment of DFS. In addition, PFS, CCI , and CCI are included as exploratory endpoints.

Radiological assessment of scans will be according to RECIST 1.1 guidelines for new lesions (Appendix G). To limit potential bias in reading the scans, Investigators will not be notified of the patient's MRD status.

A "baseline" scan must be performed within 28 days + 7 days **prior to randomization** (Table 2). Subsequent scans are to be performed q12w ± 1 week (relative to the date of randomization) until disease recurrence is recorded or until primary DFS analysis (whichever occurs first). If an unscheduled assessment is performed and the patient has not had 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 radiological disease recurrence, disease assessments should continue according to the SoAs.

8.1.1 Disease-free survival

DFS 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. Further details of the CT and MRI acquisition parameters are documented in the Image Acquisition Guidelines; 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 assessment.

The "baseline" scan must be performed within 28 days + 7 days **prior to randomization** (Table 2). It is also required that the scan is collected before PORT, as applicable. Subsequent assessments are to be performed q12w until RECIST 1.1-defined disease recurrence is recorded or until primary DFS analysis (whichever occurs first). If a patient discontinues treatment prior to disease recurrence or receives other anticancer treatment, the patient should continue to be imaged in accordance with this schedule until disease recurrence is recorded. 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 disease recurrence on CT or MRI scan (which may or may not be confirmed as pathological disease on biopsy by investigational site assessment).

NOTE: 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 truly represents new disease. If repeat scans (scheduled or unscheduled per Investigator discretion [if unscheduled, a minimum of 6 weeks between scans is recommended]) 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.

NOTE: Please refer to Appendix G for further guidance on defining disease recurrence.

NOTE: 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 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 (ie, the first time the lesion was observed, even if it was marked as equivocal at the initial observation), even if this is determined in retrospect or tissue confirmation occurs subsequent to the initial appearance of a suspicious area/lesion on a scan (see Appendix G for additional details).

If there is equivocal progression, and the site 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. Date of the first subsequent progression as indicated in the SoAs (Table 2 and Table 3) will be collected per local practice, assessed by the Investigator, 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, may be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (iCRO) for quality control, storage, and for 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. Image collection will occur for all patients until the last patient last visit. A BICR of images may 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 schedule in Table 3 following treatment discontinuation. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician.

The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

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

8.1.4 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. PROs are a type of COA. 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, and CCI (see Appendix I). Each is described below.

PRO assessments will no longer be performed under CSP V4.0. Analyses of PRO data will be performed on data collected up to and including CSP V3.0.

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 (GHS/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 GHS/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 EORTC 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 [redacted]

8.1.4.3 CCI

[redacted]

CCI

8.1.4.4 CCI

8.1.4.5 Administration of patient-reported outcome questionnaires (not applicable from CSP V4.0)

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 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.

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 and 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 instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the 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 with 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. If technical or other device-related issues prohibit completion on the device, an appropriate back-up option may be considered with prior approval from AstraZeneca.
- 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 the eCRF.

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 HBsAg, HCV antibodies, and HIV antibodies. If negative HIV and hepatitis serology was determined during the first screening period, re-testing during the second screening period is not necessary, provided the patient is not at high risk for infection.

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, and magnesium testing are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.
[d] 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, 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 F for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

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

Medical history information will be obtained only in the event of a reported SAE during the first screening period (Table 1).

A complete medical history will be obtained at the second screening (Table 2); findings from current medical history will be assigned a baseline grade according to NCI CTCAE Version 5.0 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, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at the second screening only (initiated by the signing of ICF2). 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 (blood pressure [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/placebo

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

BP and pulse will be collected 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 (±5 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/placebo

BP, pulse, and other vital signs should be measured, collected/recorded in the eCRF ≤30 minutes prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard

and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF page.

Infusion of SoC agents

During administration of SoC agents, patients should be monitored predose and as clinically indicated before every infusion or administration. SoC agents should always be administered after completion of the observation period following the durvalumab/placebo infusions.

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 eCRF.

8.2.5 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study (see the SoAs, Table 2 and Table 3). 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 (Cycle 1 Day 14, Cycle 2 Day 14, and Cycle 3 Day 14) IP(s) to ensure early identification and management of toxicities (Table 2).

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, Table 2 and Table 3) 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, pyrexia, etc), including auscultation for lung field will be assessed.
- Saturation of peripheral oxygen
- 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 that are related to disease progression
    - Additional Clinical chemistry: C-reactive protein, lactate dehydrogenase

8.3 Collection of adverse events

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

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

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

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

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

During the first screening period (ie, from the time the patient signs ICF1 but before signing ICF2), only SAEs related to study procedures (ie, study-specific blood draws and [if performed during first screening] the post-surgical scan) will be collected. All AEs and SAEs will be collected from the time that the patient signed ICF2 until the follow-up period is completed (90 days after the last dose of IP) (see Table 1 and Sections 6.4 and 8.2.2). 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 reported as an AE or SAE as applicable.

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

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

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

8.3.3 Follow up of adverse events and serious adverse events

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

Any AEs that are unresolved at the patient's last visit in the study 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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

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

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment 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 can be 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 CSP-mandated laboratory tests and vital signs will be summarized in the Clinical Study 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 recurrence, should not be reported as an AE/SAE.

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

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix F 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 disease recurrence, should not be reported as AEs 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

During first screening (that is, from the time a patient signs ICF1 until they sign ICF2), only deaths related to study procedures (i.e. study-specific blood draws and [if performed during first screening] the post-surgery scan) must be reported.

All deaths that occur after the patient has signed ICF2, including 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 recurrence or 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 disease recurrence/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 in the eCRF. 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 nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab 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 alternative etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

AESIs/imAEs observed with PD-L/PD-L1 agents such as durvalumab include pneumonitis, hepatitis, diarrhea/colitis, 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-Barré 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 Section 8.4.5.1). These guidelines have been prepared by the Sponsor to assist the Investigator

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

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

For patients who received the last dose of study treatment <90 days prior to the final DCO, AEs and SAEs will be collected at least 90 days after the last dose, 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 8.4.5.1).

All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

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

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

During first screening (ie, after a patient has signed ICF1 but before they have signed ICF2), only SAEs related to study procedures (ie, study-specific blood draws and [if performed during first screening] the post-surgical scan) must be reported.

Following the signature of ICF2, 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 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

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

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

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

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

8.4.1.1 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of patients 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 (IRBs)/Independent Ethics Committees (IECs), 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 an 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 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 patient has received any IP.

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

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

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, 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 and the time limit for such precautions for SoC agents.

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 IECs/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 and will enter follow-up (see the SoAs [Table 3]).

8.4.3 Overdose

8.4.3.1 Durvalumab

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 inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

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

8.4.3.2 Standard of care

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

8.4.4 Medication error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (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

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

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

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

8.4.5.1 Specific toxicity management and dose modification information for durvalumab

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 the 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: In the event that durvalumab/placebo is delayed due to a treatment-related toxicity during the first 4 cycles of treatment, SoC chemotherapy should still be administered as scheduled; every effort should be made to ensure patients receive all scheduled cycles of SoC chemotherapy across all arms in the study, if conditions allow.

When it is feasible to restart durvalumab/placebo treatment, durvalumab/placebo should be administered with SoC chemotherapy on Day 1 of the next cycle to ensure treatment visits continue to coincide.

The patient should still receive up to 14 cycles of therapy, even if a dose delay causes the treatment period to extend beyond 12 months.

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

8.4.5.2 Specific toxicity management and dose modification information – standard of care

Chemotherapies are associated with a number of unwanted effects. SoC chemotherapy-related toxicity management and/or dose adjustments (including dose delays and reductions) should be performed as indicated in the local prescribing information for the relevant agent. In the event of unfavorable tolerability, patients can switch from cisplatin to carboplatin at any point in the study. Note: It is preferred that patients begin the chemotherapy regimen with cisplatin and receive at least 1 cycle of cisplatin.

Dose reduction is permitted for chemotherapy.

Dose Delays: SoC chemotherapy-related toxicity management, dose adjustment, including dose delays and reductions should be performed as indicated in the local prescribing information for the relevant agent. In the event of unfavorable tolerability, patients can switch between cisplatin and carboplatin therapy at any point on study (at the discretion of the Investigator).

If toxicities can reasonably be attributed to SoC chemotherapy, dose adjustment should be attempted before modifying the administration of durvalumab. In the event that SoC chemotherapy is delayed, durvalumab/placebo should also be delayed and should resume as soon as feasible. Every effort should be made to ensure patients receive all scheduled cycles of SoC chemotherapy across all treatment arms in the study, if conditions allow. 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 methods related to on-study evaluation of plasma samples for ctDNA. No other pharmacodynamic parameters will be 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 via signature of ICF1. See Section 8.7.1.2 for details on sample collection, analysis performed, and data storage. This **mandatory** genetic testing is conducted for detection of MRD. As part of this mandatory genetic testing, germline and tumor DNA (exome only) is analyzed to enable the design of the personalized panel for MRD determination and subsequent testing for ctDNA.

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

8.6.2 CCI

[redacted]

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, 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 itself 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.

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 therapy 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* status

A sample of a pre-surgical tumor biopsy (preferred) or resected tumor tissue is required for assessing *EGFR* mutation and *ALK* translocation status. *EGFR/ALK* wild-type patients will be eligible for the study. If a pre-surgery biopsy is not available or evaluable, testing will be conducted as soon as possible on the resected tumor tissue while the personalized panel is in development; patients will still be allowed to continue with first screening procedures while testing is ongoing, but will be ineligible to enter second screening if their tumor tissue tests positive for *EGFR* mutations and/or *ALK* translocations.

Testing must be performed using a well-validated, local regulatory approved kit. *EGFR/ALK* may be tested centrally if local testing is unavailable.

Note: Where *EGFR/ALK* results are obtained from pre-surgical tissue biopsy as part of standard local practice, the patient should be confirmed as *EGFR/ALK* wild-type prior to signing ICF1 and enrolling in the study.

8.7.1.2 Minimal residual disease

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

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 is performed on DNA extracted from the patient's resected tumor tissue and controlled for germline mutations by WES of the patient's whole blood (as indicated in the SoAs, Table 1). A Sponsor-approved personalized panel is then developed, comprised of 50 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 tumor variants. This personalized approach allows detection of the patient's tumor variants in DNA extracted from their plasma 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.

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 (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 between Week 3-5 (Day 21-35) post-surgery for determination of MRD status using the personalized assay, as described in the SoAs (Table 1).

A pre-surgical plasma sample will be collected from all patients who sign ICF1 prior to surgery. Patients will not be excluded from randomization based on the results from analysing the pre-surgical sample.

Pre-surgical, on-treatment, and post-treatment plasma samples will be collected longitudinally for 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. PD-L1 TC expression must be known for randomization. Data will be compared between arms to determine if baseline PD-L1 status is prognostic and/or predictive of outcomes associated with durvalumab plus SoC chemotherapy versus placebo plus SoC chemotherapy. Baseline tumor requirements are described in Section 5.1.

Based on availability of tissue, additional exploratory biomarkers may be evaluated as described in Section 8.7.2. Also, descriptions of exploratory, peripheral measures are described in this section. Samples will be obtained according to the assessment schedules provided in the SoAs (Table 1 and Table 2).

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).

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

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

A brief description of exploratory tumor markers to be explored is provided in Section 8.7.2.

8.7.2 Exploratory biomarkers

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, and Table 3). Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Measurements at baseline, on treatment, and/or at recurrence may 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 plus SoC chemotherapy versus placebo plus SoC chemotherapy, 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 potential 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 status may be analyzed for additional markers, including PD-L1 immune cell (IC) expression. 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 may 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 evaluate study association with response and clinical outcome.

OPTIONAL: Provision of tumor tissue upon recurrence, formalin fixed and embedded in paraffin, for exploratory analyses to compare biomarker changes compared to baseline/surgery and to identify mechanisms of recurrence. If the patient refuses to provide this sample, the reason for this refusal must be captured.

8.7.2.3 Whole blood gene expression (PaxGene RNA)

Whole blood samples will be collected in PaxGene RNA tubes and stored frozen for nucleic acid preparation. Total RNA may be prepared for quantification of RNA, micro-RNA, and/or non-coding RNA using reverse transcription quantitative polymerase chain reaction, microarray, sequencing, or other technology. The focus will be on genes linked to target expression, mechanism of action, and immunomodulatory genes linked to pharmacodynamic activity. RNA expression signatures may be defined, before and after treatment, and correlated with other exploratory biomarkers and clinical outcomes.

8.7.2.4 Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results other than MRD status 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 CSP.

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.

8.7.2.5 Optional Genomic Initiative samples

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

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 or other IO therapies to generate hypotheses to be tested in future research.

8.7.4 Labeling and shipment of biological samples

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

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

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered 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 Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patient's 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

8.8 Medical resource utilization and health economics

Medical resource utilization and health economics will not be evaluated in this study.

8.9 Study Participant Feedback Questionnaire (SPFQ)

This study will include an option for patients to complete an anonymized questionnaire, 'Study Participant Feedback Questionnaire' for patients to provide feedback on their clinical trial experience (Appendix J). Individual patient level responses will not be reviewed by

investigators. Responses would be used by the Sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the patient's disease, symptoms, treatment effect, or AEs and therefore would not be study data.

9 STATISTICAL CONSIDERATIONS

The primary objective of the study is to compare the efficacy and safety of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS (using Investigator assessments according to RECIST 1.1), in all patients with a diagnosis of stage II-III NSCLC with complete resection.

- All personnel involved with the analysis of the study will remain blinded until DBL and CSP deviations are identified.
- Analyses will be performed by AstraZeneca or its representatives.
- A SAP will be written to provide further details and will be finalized in advance of database lock.

9.1 Statistical hypotheses

Prior to CSP V4.0, a formal statistical analysis was to be performed to test the main hypotheses:

- H0: No difference between durvalumab plus SoC chemotherapy and placebo plus SoC chemotherapy
- H1: Difference between durvalumab plus SoC chemotherapy and placebo plus SoC chemotherapy

Under CSP V4.0 no formal statistical analyses will be performed, and all analyses will be exploratory. Further details will be included in the SAP.

Prior to CSP V4.0, the primary objective of this study was to compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the MRD+ analysis set. A secondary objective was to compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the FAS. Under CSP V4.0 as a result of the decision to close study enrollment, the intended patient numbers will not be reached. The primary objective of this study will now compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the FAS rather than in the MRD+ analysis set. A secondary objective will compare the efficacy of durvalumab plus SoC chemotherapy to placebo plus SoC chemotherapy in terms of DFS in the MRD+ analysis set. The details on the multiple testing procedure for controlling the type I error rate can be found in Section 9.5.4.

9.2 Sample size determination

Prior to CSP V4.0, approximately CCI patients with stage II-III NSCLC were planned to be randomized 1:1 to durvalumab plus SoC chemotherapy or placebo plus SoC chemotherapy. Of the patients randomized into the study, approximately CCI patients were required to be MRD+, as determined by the result from their post-surgical plasma sample. The number of MRD- patients was to be capped at 100 (See Section 4.2.1 for the caveat to this cap).

The study was sized for the primary endpoint of DFS in the MRD+ analysis set and for the secondary endpoint of DFS in the CCI.

The analysis of the primary endpoint (DFS) was to occur when approximately CCI DFS events had occurred (CCI % maturity) in the MRD+ analysis set. If the true DFS HR is CCI in the MRD+ analysis set, the study would have provided at least CCI power to demonstrate a statistically significant difference for DFS with an overall 2-sided significance level of CCI; this translates to a CCI-month benefit in median DFS over CCI months on placebo plus SoC chemotherapy, or CCI difference in CCI-year DFS rate over CCI on placebo plus SoC chemotherapy, if DFS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of CCI. It was estimated that this analysis would occur approximately 51 months after the first patient has been randomized, assuming a 3-month lag before the first MRD+ patient is randomized, 44-month recruitment period, and a minimum follow-up of 4-months.

The study was also sized to provide at least CCI power for the DFS endpoint in the CCI. The analysis will be performed at the same time as the primary analysis, when it was expected that approximately CCI events had occurred (CCI) in the FAS. If the true DFS HR is CCI in this population, this would have provided at least CCI power to demonstrate a statistically significant difference for DFS, assuming an overall CCI 2-sided significance level; this translates to a CCI-month benefit in median DFS over CCI months on placebo plus SoC chemotherapy, or CCI difference in CCI year DFS rate over CCI on placebo plus SoC chemotherapy, if DFS is exponentially distributed.

Under CSP v4.0, the planned number of randomized patients will not be met. This is a result of the decision by AstraZeneca to close study enrollment early. There will be one analysis (i.e. primary DFS analysis) which will occur after DCO (see Section 4.4).

OS will also be analyzed in the MRD+ analysis set and in the CCI at the time of the DFS analysis. Prior to CSP V4.0, in the MRD+ analysis set, if the true HR is CCI, then it was anticipated that approximately CCI events CCI maturity) would have occurred. This translates to an CCI month benefit in median OS over CCI months on placebo plus SoC chemotherapy. In the CCI, if the true HR is CCI, then it was anticipated that approximately CCI events (CCI maturity) would have occurred. This translates to a CCI month benefit in median OS over

CCI months on placebo plus SoC chemotherapy. Under CSP V4.0 these events will not be reached.

Prior to CSP V4.0, a further analysis of OS was to be performed at approximately CCI events (CCI maturity) in the MRD+ analysis set. At this time there was also expected to be approximately CCI events (CCI maturity) in the CCI. It was anticipated that this analysis would occur approximately CCI months after the first patient was randomized. If events were accruing slower than expected, then the DCO would have occurred CCI months after the first patient was randomized, regardless of number of events accrued. Under CSP V4.0 this further analysis will not be performed and the primary DFS analysis will be the final analysis.

9.3 Populations for analyses

The populations for analyses are summarized in Table 14 per outcome variable.

Table 14 Summary of outcome variables and analysis populations

Outcome	Population
Efficacy data	
DFS	MRD+ analysis set
	Full analysis set
OS	MRD+ analysis set
	Full analysis set
PROs	MRD+ analysis set
	Full analysis set
Demography	Full analysis set
	MRD+ 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 survival; MRD+ Minimal residual disease-positive; OS Overall survival; PROs Patient-reported outcomes.

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 MRD+ analysis set

The MRD+ analysis set will include all patients in the FAS who are MRD+, as determined by results from the post-surgical plasma sample.

9.3.3 Safety analysis set

The SAS will consist of all randomized patients who received at least 1 dose of study treatment (durvalumab/placebo and/or SoC chemotherapy). 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, with or without SoC chemotherapy, they will be summarized in the durvalumab plus SoC chemotherapy treatment group. If a patient only receives placebo, with or without SoC chemotherapy, they will be summarized in the placebo plus SoC chemotherapy treatment group. Patients who only received SoC chemotherapy and did not receive any doses of either the durvalumab or placebo 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

An analysis of DFS may be performed based on data assessed by a BICR for all patients.

Where BICR is performed, 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 and secondary endpoints: 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 RECIST 1.1 assessments or date of death due to any cause, whichever occurs first.

Patients who are disease-free, ie, have not experienced disease recurrence and are 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 derived based on scan/assessment dates and not visit dates.

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

- For Investigator assessments, the date of disease recurrence will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates disease recurrence.
- Where BICR assessments are performed, date of recurrence will be determined based on the earliest of the dates of the component that triggered the recurrence on the first set of scans that indicates recurrence for the adjudicated reviewer selecting recurrence, or of either reviewer where both reviewers select recurrence as a timepoint response, and there is no adjudication for central review (BICR) data.
- When censoring a patient for DFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

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 post 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 Exploratory 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 they are 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.

9.4.1.5 Exploratory efficacy endpoint: CCI

CCI

[redacted]

9.4.1.6 Exploratory efficacy endpoint: CCI

CCI

[redacted]

9.4.1.7 Exploratory efficacy endpoint: ctDNA clearance or changes

The efficacy of durvalumab treatment on ctDNA clearance will be evaluated as an exploratory objective, and endpoints will include:

- 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 following treatment

The relationship between treatment effect on DFS and on ctDNA endpoints will also be evaluated.

Details on these exploratory analyses will be presented in a SAP.

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 the date of start dose and 90 days following discontinuation of IP (ie, the last dose of durvalumab/placebo or SoC agents). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsen 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 IP (ie, the last dose of durvalumab/placebo/SoC agent) 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/SoC agent 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/SoC agent (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 predose and at least 1 postdose value recorded.
- If a CTCAE criterion does not consider changes from baseline to be evaluable, the patient need only have 1 postdose 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 modules (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 the FAS and MRD+ analysis sets.

9.4.3.1 Calculation or derivation of 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 GHS/QoL scale according to the EORTC QLQ-C30 Scoring Manual CCI and EORTC QLQ-LC13 instructions.

Higher scores on the GHS/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 CCI . 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, predose) 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 GHS/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

The 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 visual analog scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

9.4.4 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 prespecified criteria that will be detailed in a SAP.

9.4.5 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 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 D).

9.5 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and CSP deviations are identified.

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

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment 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 group.

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

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the MRD+ analysis set and FAS. Safety data will be summarized on the SAS.

All outputs will be summarized by treatment group for all randomized patients (FAS), and all randomized patients in the MRD+ analysis set.

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 plus SoC chemotherapy versus placebo plus SoC chemotherapy in terms of DFS, using Investigator assessments according to RECIST 1.1, in the FAS. DFS, using Investigator assessments according to RECIST 1.1, in the MRD+ analysis set is a secondary endpoint.

Under CSP V4.0, all analyses will be exploratory.

Table 16 details the statistical analysis planned for each endpoint, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint. Note: All endpoints compare durvalumab plus SoC chemotherapy versus placebo plus SoC chemotherapy in the MRD+ 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
Disease-free survival	Primary analysis using stratified log-rank test using Investigator assessments (RECIST 1.1) for FAS. Secondary analysis using stratified log-rank test using Investigator assessments (RECIST 1.1) for MRD+ analysis set Estimate of DFS rates at 6 and 12 months based on the Kaplan-Meier curve

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

Endpoints analyzed	Notes
Overall survival	Stratified log-rank test, Kaplan-Meier plots
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, Kaplan-Meier plots

DFS Disease-free survival; EORTC-QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; EORTC QLQ-LC13 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items; FAS Full analysis set; MRD+ Minimal residual disease-positive; RECIST Response Evaluation Criteria in Solid Tumors.

9.5.1.1 Primary endpoint: disease-free survival

DFS, using Investigator assessment according to RECIST 1.1, will be analyzed using the log-rank test stratified by disease stage (stage II or III), PD-L1 TC expression (<1% versus ≥1%) and MRD status (MRD+ or MRD-) on the FAS.

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 disease stage and PD-L1 TC expression.

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 time to 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.

The assumption of proportionality will be assessed firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct timeperiods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of

treatment-by-covariate interactions, which will be investigated. In addition, the Kaplan-Meier curve along with landmark analyses (eg, 1-year DFS rate) will also help in understanding the treatment benefit.

Subgroup analyses may be conducted comparing DFS between durvalumab plus SoC chemotherapy versus placebo plus SoC chemotherapy in the following subgroups of the 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 at randomization (<65 versus ≥65 years of age)
- Smoking status (current smoker versus former non-smoker vs never smoker)
- 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 (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 and will include 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, using Investigator assessments according to RECIST 1.1, will be performed on the MRD+ analysis set using the same methodology as for the primary analysis described above, excluding the strata of MRD status (MRD+ or MRD).

Overall survival

OS will be analyzed similarly to DFS for the MRD+ 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 still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median time to OS for each treatment.

9.5.1.3 Exploratory efficacy endpoints

Progression-free survival

PFS (using local standard practice) will be analyzed similarly to DFS for the MRD+ 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.

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CCI and CCI will be analyzed similarly to DFS for the MRD+ 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.

9.5.1.4 Patient-reported outcomes

EORTC QLQ-C30 and QLQ-LC13

The primary PRO measures will be patient-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 GHS/QoL domains of the EORTC-CT30 are further prespecified endpoints of interest.

Summaries of original and change from baseline values of each symptom scale/item, the GHS/QoL 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.

Changes from baseline will be analyzed using a linear mixed model for repeated measures analysis for each assessment timepoint (for primary PRO measures only).

Time to deterioration will be analyzed for each of the symptom scales/items, function scales, and GHS/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 GHS/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.

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

CCI [redacted]

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

9.5.2 Safety analyses

All safety and tolerability data will be presented by treatment group 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 group 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 plus SoC chemotherapy and placebo plus SoC chemotherapy will be summarized. Time on study, time on durvalumab, and SoC dose delays and dose reductions for the SoC regimen will also be summarized. At the time of the analysis, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.5.3 Biomarker data

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

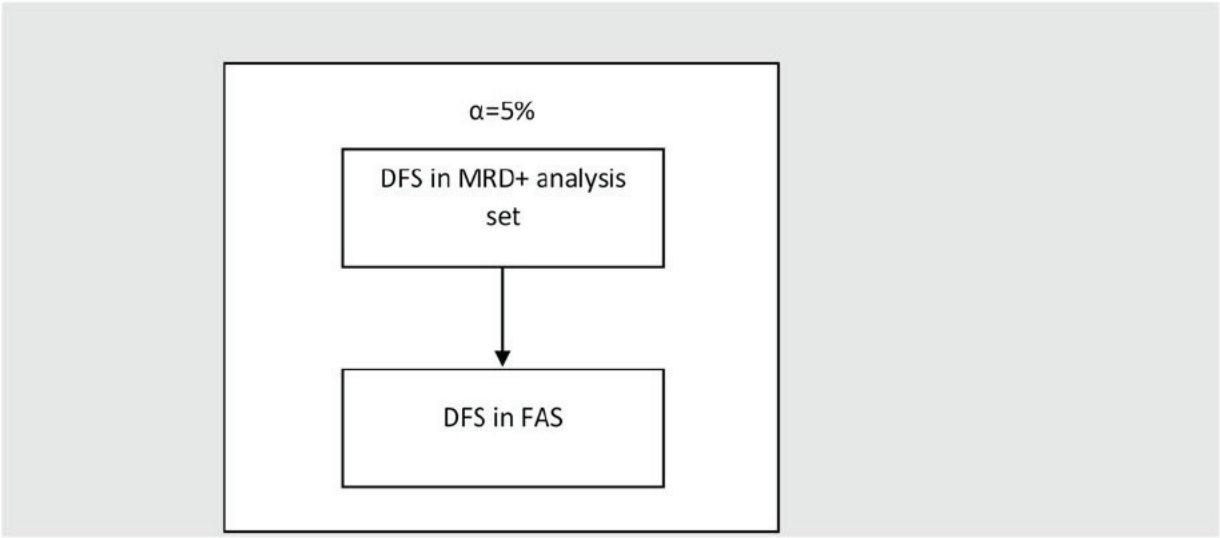
PD-L1 TC expression determined by IHC will be reported in the CSR. Summaries and analyses for exploratory biomarkers, including the correlation between ctDNA and DFS, will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.5.4 Methods for multiplicity control

Prior to CSP V4.0, in order to provide strong control of the type I error rate, α=5% (2-sided), a multiple testing procedure with gatekeeping strategy was to be used across the primary endpoint of DFS in the MRD+ analysis set and the secondary endpoint of DFS in the FAS. The first 2 layers of the multiple testing procedure are shown in Figure 4. If DFS was significant in the FAS, the alpha was to be recycled to other endpoints. The recycle scheme of these additional endpoints, if included in the multiple testing procedure, was to be specified in the SAP prior to database lock.

The overall 5% type I error rate was to be allocated to the DFS analysis on the MRD+ analysis set. If this analysis was statistically significant, 5% alpha (2-sided) was to 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; MRD+ Minimal residual disease-positive.

Under CSP v4.0, no methods for multiplicity control will be performed and the analyses of all endpoints will be considered exploratory.

9.6 Interim analyses

Prior to CSP v4.0, an interim analysis of OS was to be performed at the time of the DFS analysis. At this time it was expected that approximately 87 events (38% maturity) would have occurred in the MRD+ analysis set and approximately 112 events (34% maturity) would have occurred in the FAS.

A further analysis of OS was to be performed at approximately 155 events (67% maturity) in the MRD+ analysis set. At this time there was also expected to be approximately 190 events (57% maturity) in the FAS. It was anticipated that this analysis would occur approximately 72 months after first patient was randomized. If events were accruing slower than expected, then the DCO would have occurred 72 months after the first patient was randomized, regardless of number of events accrued. An alpha spending function was to be used to control the overall type I error for the interim and final analyses of OS at the 5% level. Details of the OS testing plan were to be provided in the SAP.

Under CSP V4.0, the further analysis of OS at approximately 155 events will not be performed and there will be no interim analysis. There will be one analysis of OS at the time of the DFS (i.e. primary DFS analysis) which will be the final analysis.

9.7 Data monitoring committee

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

An IDMC comprised of independent experts will meet to assess the safety and tolerability of durvalumab and report back to the Sponsor. The first data cutoff for the IDMC will be 12 months after the first subject has received IP or after the first 50 subjects have received IP, whichever occurs first. 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.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

The investigator will be responsible for the following:

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

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

A 2 Financial disclosure

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

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally 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/placebo, 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 on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

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

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

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

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

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

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

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

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study 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 recurrence of 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-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.
- Adverse Events (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 tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant 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 (eg, 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 patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical 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 an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another 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 patients 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 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:

Patients 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 enrollment/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 Genomics Initiative 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 Genomics Initiative subsection of the main consent form for 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 analyses 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 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 90% of targeted bases covered at 20X or greater, whereas tumour 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 genetics 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 patient 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 patient 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 patient 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 patient 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 patient meets PHL criteria (see Section 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 patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient 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 patient 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 patients 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 patient's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. 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 patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

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 an 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 laboratory 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)

Hy's Law laboratory kit for central laboratories

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 new lesions using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

The RECIST 1.1 guidelines are typically used in the context of patients who have measurable and/or non-measurable disease at baseline. However in thist study, patients will be randomized once there is confirmation that there are no lesions at baseline. In the setting of early stage disease, new lesions may be difficult to detect. This appendix details the implementation of (RECIST 1.1) guidelines (Eisenhauer et al 2009) for the assessment of new lesions Additional special guidance is provided for evaluation of scans collected after equivocal radiological progression.

Imaging modalities and acquisition specifications for RECIST 1.1

The preferred imaging modality and coverage for radiological assessments of disease recurrence (new lesions, NLs) is contrast CT of the chest and abdomen including liver and adrenal glands. A summary of all the imaging modalities that can be used (under specific circumstances) for assessment of new lesions Table 17 and detailed in the paragraphs below.

Table 17 Summary of imaging modalities for tumor assessment

New Lesions
CT
MRI
Plain 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 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 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 at the pre-surgery baseline (screening) and follow-up visits the timepoints are specified in the SoA (Table 2). Examples of the preferred modalities include the following:

- IV contrast-enhanced CT of chest and 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 for consideration when patients have sensitivity to IV contrast or have compromised renal function:

- Chest-abdomen CT with IV CT contrast (most preferred)

- 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
- 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.

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.

Chest X-ray

Chest X-ray can, be used 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 to identify the presence of new bone lesions.

Isotopic bone scan

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.

The low-dose or attenuation correction CT portions of a combined FDG-PET/CT scan may be 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

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.

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.

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.

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 (e.g. pseudoprogression related to edema or infiltration of immune cells). 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.

If equivocal lesions are present at baseline, they will not be documented on the baseline CRF. Therefore, such lesions would not be recorded as new until the timepoint they are determined to be unequivocal, if applicable, and will not be backdated to baseline. However, they can be backdated to post-baseline follow-up scans in instances where the equivocal lesion converts to unequivocal without an intervening period of lesion absence.

Pleural effusions, when present at baseline, should not be recorded at baseline and therefore would not be recorded as new lesions until the timepoint they are determined to be unequivocal, if applicable.

New or pleural enlarging effusions will be considered new equivocal lesions unless there are corresponding soft tissue changes suggestive of metastatic disease in which case they will be documented as new unequivocal lesions. Only significant and unequivocally new pleural effusions will be recorded as new unequivocal lesions and be indicative of disease relapse.

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.

If the site 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.

Central imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization (CRO) for QC and storage. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A blinded independent central review (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 not be based upon the results of theBICR. 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

Contraception requirements for this study are as follows.

H 1 Female Pateints

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 18). 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 durvalumab/placebo or 180 days after the last dose of chemotherapy, whichever is longer).

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 patients should refrain from breastfeeding throughout this period.

H 2 Male Pateints with a Female Partner of Childbearing Potential

Non-sterilized male patients (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 durvalumab/placebo or 180 days after the last dose of chemotherapy, whichever is longer) to prevent pregnancy in a partner.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients 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 patients 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 patients must also use a highly effective method of contraception throughout this period (Table 18).

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 18. 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 18 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

[a] Hormonal methods not prone to drug-drug interactions.

Appendix I Patient-Reported Outcomes

This appendix includes example copies of the following patient-reported outcome (PRO) 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 [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

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

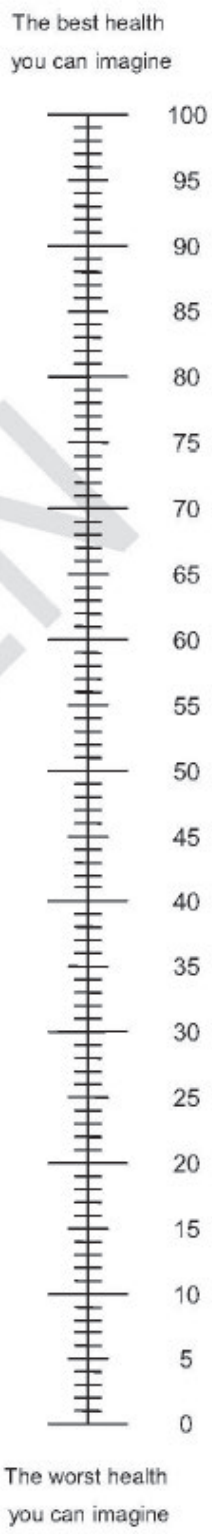
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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

CCI

Study Number: D0000C00000		Site Number:
Subject Number:	Visit Number:	Assessment Date:

CCI

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 20 September 2019

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
3.	In the last 7 days, did you have any RASH?				
	○ Yes		○ No		
4.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Appendix J Study Participant Feedback Questionnaire Template

Patient Experience Initiative

Study Participant Feedback Questionnaire (SPFQ)

Version 1.0

Prepared by:

TransCelerate Patient Experience Initiative Team

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YOUR EXPERIENCE BEFORE YOU STARTED THE STUDY

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1. I understand the treatment process in this trial (for example: when and how to take or use a treatment)	0	1	2	3	4
2. The information given to me before I joined the trial was everything I wanted to know (for example: visits and procedures, time commitment, who to contact with questions)					
3 The information given to me before I joined the trial was easy for me to understand (for example: visits and procedures, time commitment, who to contact with questions)					
4 I felt comfortable that I could ask any questions before I joined the trial					

YOUR EXPERIENCE DURING THE TRIAL

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1. Overall I am satisfied with the trial site (for example: comfort and privacy of treatment area, waiting area, parking, ease of access to the site)	0	1	2	3	4
2. My trial visits have been well organized					
3. My trial visits are scheduled at a convenient time for me					
4. The staff treats me with respect					
5. I feel comfortable that I can ask questions during the trial					
6. I am satisfied with the answers I have received to my questions during the trial					
	No		Yes		
7. The time taken to collect data is acceptable to me (for example: in person visits, questionnaires, forms)					
8. The impact the trial has on my daily activities is acceptable (for example: household chores, work commitments, eating)					

YOUR EXPERIENCE AT THE END OF THE TRIAL

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 15 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.

	No		Yes		
1 . I was informed when I had completed the trial					
2 . I was informed of any future opportunities to access the overall trial results if I wanted to					
	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
3 . Overall, I was satisfied with the information I received about future support after the trial (for example: future treatment, follow-up contact details)	0	1	2	3	4
4 . Overall, I was satisfied with my trial experience					
	Much less than expected	Somewhat less than expected	Same as expected	Somewhat more than expected	Much more than expected
5 . Compared to when the trial started, the overall commitment required was similar to what I expected	0	1	2	3	4

Appendix K Abbreviations

Abbreviation or special term	Explanation
ABCP	atezolizumab, bevacizumab, carboplatin, and paclitaxel
ADA	antidrug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum drug concentration-time curve
BCP	bevacizumab, carboplatin, and paclitaxel
BICR	blinded independent central review
BP	blood pressure
CCTG	Canadian Cancer Trials Group
CD	cluster of differentiation
CI	confidence interval
CL	clearance
COA	clinical outcome assessment
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 Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items

Abbreviation or special term	Explanation
ePRO	electronic patient-reported outcomes
CCI [redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	^{18}F-Fluoro-deoxyglucose positron emission tomography
GCP	Good Clinical Practice
GHS	global health status
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hy's law
HR	hazard ratio
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure
IC	immune cells
ICF	informed consent form
ICF1	informed consent form 1
ICF2	informed consent form 2
ICH	International Council for Harmonisation
iCRO	imaging Contract Research Organization
IDMC	independent data monitoring committee
IEC	independent ethics committee, synonymous with institutional review board (IRB)
IHC	immunohistochemistry
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IMRT	intensity-modulated radiation therapy
IP	investigational product
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.
IO	immuno-oncologic
IRB	institutional review board

Abbreviation or special term	Explanation
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
LIMS	Laboratory Information Management System
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRD+	MRD-positive
MRD-	MRD-negative
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NTL	non-target lesion
ORR	objective response rate
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
CCI	[redacted]
CCI	[redacted]
PK	pharmacokinetic(s)
PORT	postoperative radiation therapy
PR	partial response
PRO	patient-reported outcome
CCI [redacted]	CCI [redacted]
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q12w	every 12 weeks

Abbreviation or special term	Explanation
CCI [redacted]	[redacted]
[redacted]	[redacted]
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
TC	tumor cell
CCI [redacted]	[redacted]
TL	target lesion
TMB	tumor mutational burden
TMG	toxicity management guidelines
TPS	tumor proportion score
CCI [redacted]	[redacted]
UICC	Union for International Cancer Control
ULN	upper limit of normal
VATS	video-assisted thoracoscopic surgery
WBDC	Web Based Data Capture
WES	whole exome sequencing
WHO	World Health Organization
w/v	weight per volume

SIGNATURE PAGE

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