Clinical Study Protocol	
Drug Substance	Durvalumab and tremelimumab
Study Code	D933QC00001
Version	5.0
Date	10 January 2023

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Local sponsor in Japan: AstraZeneca K.K., 3-1, Ofuka cho, Kita-ku Osaka 530-0011, Japan

Regulatory Agency Identifying Number(s):

EudraCT: 2018-000867-10

VERSION HISTORY

Version 5.0, 10 January 2023

The primary purpose of the current amendment is to include an interim analysis for the primary endpoint of progression free survival (PFS-IA) per BICR. ADRIATIC was initially designed to include an interim analysis for the dual PFS primary endpoints (durvalumab monotherapy vs placebo and durvalumab + tremelimumab vs placebo comparisons). This was removed during the CSP V4 amendment in November 2020 due to the anticipated proximity to PFS FA. Review of blinded event predictions show a potential shift in study timelines which has afforded an opportunity to introduce an IA for the primary endpoint PFS analysis.

Additional clarifications on OS interim analyses and primary PFS analysis are also included in Amendment 5 in the following sections: **Sections 1.2, 9.2, 9.5 and 9.6**.

Other changes in this amendment include the following:

Description of the collection schedule of EORTC QLQ-LC13 and PRO-CTCAE after IP discontinuation, corrected to align with **Table 1**. **Sections updated: Section 1.1, Table 2**.

Update to the description of the patient-reported outcome derivations (**Section 9.4.3**) and planned statistical analyses to align with the SAP (**Sections 9.5.1, 9.5.1.3, 9.5.1.9, 9.5.2 & Table 13**). Update to the categories for subgroup analyses (**Section 9.5.1.1**).

Further clarifications are added per updated protocol template. **Sections updated: Sections 4.4, 6.6, 8.4.4 and Appendices A1, A6, A7, B8 and E8**.

Removal of **Appendix C3** as it was redundant with **Appendix G.**

Updated risk language and consolidated list of rare/miscellaneous AESIs. **Sections updated: Section 2.3.2 and Section 8.3.12**

Version 4.0, 13 November 2020

The primary objective of the current amendment is to revise the primary efficacy endpoint. Specifically, the analysis of OS for the comparison of durvalumab monotherapy versus placebo has been promoted, and PFS and OS will now be analyzed as dual primary efficacy endpoints. In addition, emerging data indicate the need to modify previous assumptions relating to treatment effect. Thus, the total sample size has been increased from 600 to approximately 724 randomized patients, with the number of patients in each of the durvalumab monotherapy and placebo groups increased from 200 to approximately 262 patients. As recently published data also indicate that the additional efficacy benefit of combining an anti-CTLA-4-mAb with PD-1/PD-L1 inhibition over PD-1/PD-L1 inhibition alone is ambiguous, but not conclusive, thus the comparison of durvalumab plus tremelimumab versus placebo has been moved to a secondary endpoint and the number of patients will remain unchanged at approximately 200 patients. The following sections are affected:

1. OS for the comparison of durvalumab monotherapy versus placebo has been added to the primary endpoint, ie, the study now has dual primary endpoints of PFS and OS for the comparison of durvalumab monotherapy versus placebo; the comparison of durvalumab plus tremelimumab versus placebo in terms of PFS and OS are now secondary endpoints. **Sections updated: Section 1.2, Section 2.1.3, Section 3, Table 3, Section 4.2.1, Section 9.1, Section 9.5.1, Table 13, Section 9.5.7.**
2. The amendment incorporates new and updated published clinical data that support the decision to revise the study design with respect to both the primary endpoint analysis/efficacy endpoints and the treatment effect assumptions. **Sections updated: Section 1.2, Section 2.1.3, Section 2.3.1.1, Section 10.**
3. Text relating to the planned number of patients and to the sample size calculation has been updated to increase the total sample size from 600 to approximately 724 patients, with additional patients in each of the durvalumab and placebo groups (approximately 262 patients each). The number of patients in the durvalumab plus tremelimumab group is unchanged (approximately 200 patients). **Sections updated: Section 1.2, Section 2.1.3, Section 4.1, Section 9.2.**
4. As the number of patients in the durvalumab plus tremelimumab group is unchanged, the amendment clarifies that once 600 patients have been randomized, randomization will continue 1:1 in the durvalumab monotherapy and placebo groups. **Sections updated: Section 1.1, Table 1, Section 1.2, Section 2.1.3, Section 6.1.2, Section 6.2.1, Section 9.2.**
5. Change to the study design to indicate that once 600 patients have been randomized, no further PK or ADA samples relevant to tremelimumab are required. **Section updated: Section 1.1, Table 2.**
6. Provision for enrolment in China to continue after global enrolment is closed to allow inclusion of a total of approximately 108 patients. **Sections updated: Section 1.2, Section 4.1, Section 9.2.**
7. The statistical sections have been updated to accommodate the changes described above. **Sections affected: Section 1.2, Section 2.1.3, Section 9.1** (updated null hypotheses regarding the efficacy endpoints), **Section 9.2** (sample size determination and updated timing of interim and final analyses), **Section 9.3.2** (clarification of patients included in the analyses of the combination analysis set), **Section 9.3.4** (definition of the combination safety analysis set), **Section 9.4.1** (calculation or derivation of efficacy variables), **Section 9.5.1** (updated analyses of PFS, OS, and duration of response [DoR]), **Section 9.5.7** (updated description of methods for multiplicity control reflecting the updated analyses), **Section 9.6** (updated details of the interim analyses of OS and their anticipated timing).
8. The benefit-risk assessment has been updated for durvalumab and overall. **Sections updated: Section 1.2, Section 2.3.1.1, Section 2.3.3**.

Other changes included in this amendment:

9. Clarification of the timing of the baseline tumor assessment, **Section updated: Section 1.1, Table 1.**
10. Based on current enrollment trends and given the increased sample size, the study is now expected to provide adequate representation of patients with Stage I/II disease.

Therefore, the requirement to limit the percentage of patients with TNM Stage III disease to 85% of the total has been removed. **Sections updated: Section 1.2, Section 4.1, Section 6.2.1.**

11. Consistent with the results of recent analyses, the exploratory endpoint, PD-L1 expression in tumor and/or immune cells relative to response/efficacy outcomes, has been promoted to a secondary endpoint and the secondary endpoint, TMB relative to response/efficacy outcomes, has been changed to an exploratory endpoint. Text relating to other tissue-based biomarkers has been updated. **Sections updated: Section 1.2, Section 2.1.3, Section 3, Table 3, Section 8.8.**
12. The Schedule of Activities has been updated to clarify that tumor assessments will continue to be collected until the end of the study, regardless of the scheduled interim analyses. **Sections updated: Section 1.1, Table 1 and Table 2, Section 8.1.**
13. The timing of the following clinical outcome assessments has been changed from "Every 4 weeks (±3 days) relative to randomization until study termination or death" to "Every 4 weeks (±3 days) relative to randomization until study termination or PFS2 or death": EORTC QLQ-LC13, EORTC QLQ-C30, PRO-CTCAE, PGIS, and EQ-5D-5L. The visit window for completion of these assessments by e-device has been corrected in the protocol (ie, changed from ±1 day to ±3 days for the EORTC QLQ-LC13 at Weeks 4 and 8 and for the PRO-CTCAE at Weeks 4, 8, and 12) so that the window is consistent with that correctly employed in the e-device; additional guidance is provided regarding use of e-devices. The timing of the HOSPAD assessment has been changed from "Every 24 weeks (±3 days) relative to randomization until study termination or death" to "Every 24 weeks (±3 days) relative to randomization until treatment discontinuation" and the timing of HOSPAD after treatment discontinuation has been changed from "Health resource use assessment should be performed every 24 weeks (±2 weeks), after 48 weeks following study treatment discontinuation" to "Health resource use assessment should be performed every 24 weeks (±2 weeks) after treatment discontinuation and until PFS2 or study termination or death, which ever occurs first." **Sections updated: Section 1.1, Table 1 and Table 2, Section 8.1.3.5.**
14. Updates to the treatments admininstered to show the latest information. **Sections updated: Section 1.2, Section 6.1.1, Section 6.1.1.1 (durvalumab), Section 6.1.1.2 (tremelimumab), Section 6.1.1.3 (placebo).**
15. Estimated date of last patient completed has been updated to Q2 2025 in line with latest calculations. **Section updated: Section 1.2.**
16. Figure 1 amended to show the expanded sample size and the associated provisions for randomization, and to include disease stage. **Section updated: Section 1.3, Figure 1.**
17. Removal of obsolete text following decommissioning of the Toxicity Management Guidelines WebPortal. **Section updated: Section 8.4.5.1.**

Version 3.0, 13 January 2020

1. Addition of options to continue recruitment in China, following achievement of the global recruitment target of 600 randomized patients, as required by the National Medical Products Administration and addition of China specific language into Study Objectives, Endpoints, Statistics and the collection/analysis of patient samples. **Sections updated: Section 1.1, Table 1 and Table 2, Section 1.2, Section 3, Section**

4, Section 8.5, Section 8.7, Section 8.8, Section 9.4, Section 9.5, Appendix A, Appendix D.

2. Clarifications made to the collection timepoints for PK and ADA samples for tremelimumab: **Sections updated: Section 1.1, Table 1, Section 1.1, Table 2.**
3. Reduction in the number of stool samples collected and clarification that these samples are optional and will only be collected in the EU and North America. **Sections updated: Section 1.1, Table 1, Section 8.8.**
4. Clarification of the timing of brain imaging and PCI, including addition of new footnote "v" to Table 1 and amending of Figure 1;. **Section updated: Section 1.1, Table 1, Section 1.3, Section 6.4.**
5. Update to cover most up to date safety information related to IPs and adverse events of special interest. **Sections updated: 2.3.2, Section 8.3.12.**
6. Inclusion criterion 11 and Exclusion criterion 17 amended for clarity. **Sections updated: Section 5.2.**
7. Addition of possibility to use translucent infusion bag sleeves and details regarding securing the bag. Clarifications regarding IP specificity and treatment schedule. **Sections updated: Section 6.1.1, Section 6.1.2, Section 6.2.4.**
8. Appendix E (Actions required in cases of increases in liver biochemistry and evaluation of Hy's law) updated due to implementation of new process - **Sections updated: Appendix E.**
9. Appendix H removed due to implementation of Toxicity Management Guidelines as the standalone document together with dedicated process. **Sections updated: Appendix H (removal), Section 6.5, Section 8.4.5.1.**
10. Minor editorial changes were made throughout the protocol for consistency and clarity.

Version 2.0, 28 January 2019

1. Alignment on Small-Cell Lung Cancer disease terminology from ED/LD (Extensive Disease / Limited Disease) to ES/LS (Extensive Stage / Limited Stage) in the Clinical Study Protocol's title and content.
2. Removed TMB as biomarker exploratory objective as already included as secondary objective. **Sections updated: Section 1.2, Section 3.**
3. Clarification on objectives of exploratory objectives on samples collected. **Sections updated: Section 1.2, Section 3.**
4. Removed variables from PD-L1 exploratory objective's endpoints. **Sections updated: Section 1.2, Section 3.**
5. Introduction – data updated **Section updated: Section 2**
6. Removed "image-guided" and "at least 18-gauge" specifications from optional tumor biopsy procedure description. **Section updated: Section 8.8.**
7. Addition of the stool samples collection for microbiome analysis procedure description and rationale to secondary and exploratory biomarkers section. **Section updated: Section 8.8**
8. Inclusion criterion 3 amended to state that provision of signed and dated written genetic informed consent prior to collection of sample for genetic analysis is optional. **Sections updated: Section 5.1.**
9. Inclusion criterion 4 amended to remove age cap of 75 years. **Sections updated: Section 5.1.**

10. Inclusion criterion 5 amended to state that status of medically inoperable for patients who are Stage I or II is determined by investigator. **Sections updated: Section 5.1.**
11. Inclusion criterion 7 amended to address prior chemoradiotherapy, including radiotherapy treatment (previously inclusion criterion 9) and moved PCI to inclusion criterion 9 **Sections updated: Section 5.1.**
12. Inclusion criterion 10 amended to mandatory availability of tumor samples, and detailed guidance on acceptance of samples, procedures, and order of preferences updated. **Sections updated: Section 5.1, Section 8.8.**
13. Exclusion criterion 3 amended to "any history of Grade ≥2 pneumonitis" - exclusion criterion now broadened to ensure patient safety. **Sections updated: Section 5.2**
14. Removed criterion 20 – "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 study drug" not applicable to the early disease setting in this study. **Sections updated: Section 5.2.**
15. Exclusion criterion 29 updated for consistency with study Master ICF and most recent guidance for timelines of using effective birth control for durvalumab monotherapy and durvalumab + tremelimumab combination therapy. **Sections updated: Section 5.2.**
16. ADA samples added to Schedule of Assessments (Table 1) for durvalumab at cycle 13 and 20 and for tremelimumab at cycle 7 and 10. **Sections updated: Section 1.1, Table 1.**
17. The procedure of stool samples collection for microbiome analysis added to Schedule of Assessments Table 1 and Table 2 **Sections updated: Section 1.1, Table 1 and Table 2.**
18. Frequency of second progression assessment changed in Schedule of Assessments (Table 2) from "every 12 weeks" to "every 8 weeks". **Sections updated: Section 1.1, Table 2.**
19. Section 6.2.1 amended to state and clarify that all screening laboratory and imaging results must have been obtained after completion of chemoradiotherapy and within 42 days of randomization and the first dose of IP. **Sections updated: Section 6.2.1.**
20. Clarification of screening and baseline examinations **Sections updated: Section 8.**
21. Table 1 Footnotes updated to provide clarity **Section updated: Section 1.1, Table 1**
22. Lifestyle restrictions section and Informed Consent section updated for consistency with study Master ICF and most recent guidance for timelines of using effective birth control for durvalumab monotherapy and durvalumab + tremelimumab combination therapy. **Sections updated: Section 5.3, Appendix A subsection 3**
23. Sample size determination clarified **Sections updated: Section 9.2**
24. Appendix F updated - **Sections updated: Appendix F - tables 15, 16, 17.**
25. Minor editorial changes were made throughout the protocol for consistency and clarity.

Version 1.0, 27 June 2018

Initial creation

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Schedule of activities (SoA)

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

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, pharmacokinetic [PK] blood sample) to occur at the time points indicated in the schedules 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 (eg, PK blood sample) to occur at the time points indicated in the SoAs.

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, 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 tumor efficacy (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-lives of durvalumab and tremelimumab (see current Investigator Brochures [IBs] for durvalumab and tremelimumab).

Table 1 Schedule of assessments for durvalumab ± tremelimumab therapy or placebo treatment

	Screening[a]	C1	C2	C3	C4	C5 to C25	C26/ Final Dosing Visit	For details, see Section
Week	**-6 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				**100**	
Day	**-42 to -1**	**1[b]**	**q28days ±3 days unless dosing needs to be held for toxicity reasons**				**701**	
Informed consent								
Informed consent: study procedures[c]	X							6.2.1
Consent: genetic sample and analysis (optional, not applicable for China)[d]	X							8.7.1
Study procedures								
Physical exam (full)	X							8.2.2
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	8.2.2
Vital signs[e]	X	X	X	X	X	X	X	8.2.3
ECG[f]	X	As clinically indicated						8.2.4
Concomitant medications	<----------						---------->	6.4
Demography, including baseline characteristics and tobacco use	X							
Eligibility criteria	X							5.1, 5.2
Brain MRI (preferred) or high-quality brain CT with IV contrast[g]	X	As clinically indicated						5.2
Laboratory assessments								
Clinical chemistry[h]	X	X[i]	X	X	X	X	X	Table 8
Hematology[h]	X	X[i]	X	X	X	X	X	Table 9
TSH (reflex free T3 or free T4[j])	X	X[k]	X	X	X	X	X	Table 8
Urinalysis	X	As clinically indicated						Table 10
Hepatitis B and C and HIV	X							8.2.1

	Screening[a]	C1	C2	C3	C4	C5 to C25	C26/ Final Dosing Visit	For details, see Section
Week	**-6 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				**100**	
Day	**-42 to -1**	**1[b]**	**q28days ±3 days unless dosing needs to be held for toxicity reasons**				**701**	
Pregnancy test[l]	X	X	X	X	X	X	X	8.2.1
Pharmacokinetics								
Durvalumab PK sample (serum)		X[m]	X[n]			Cycle 5 only[n]	X[n,o]	8.5
Tremelimumab PK sample (serum)[p]		X[m]	X[n]			Cycle 5 and 7 only[n]		8.5
Monitoring								
WHO/ECOG performance status	X	X	X	X	X	X	X	8.2.5
AE/SAE assessment[q]	<----------						---------->	8.3
IP administration								
Durvalumab or placebo[r,s]		X	X	X	X	X	X	6.1.1.1, 6.1.1.3
Tremelimumab or placebo[r,s]		X	X	X	X			6.1.1.2, 6.1.1.3
Drug accountability		All visits						6.3
Other assessments and assays								
Durvalumab immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)		X[n]				Cycle 5, 13 and 20 only[n]	X[n,o]	8.5
Tremelimumab immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)[p]		X[n]				Cycle 5, 7 and 10 only[n]		8.5
Whole blood for genotyping (not applicable for China)		X[n]						8.8

	Screening[a]	C1	C2	C3	C4	C5 to C25	C26/ Final Dosing Visit	For details, see Section
Week	**-6 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				**100**	
Day	**-42 to -1**	**1[b]**	**q28days ±3 days unless dosing needs to be held for toxicity reasons**				**701**	
Whole blood for gene expression (PaxGene-RNA tubes, not applicable for China)		X^{n}	X^{n}		X^{n}			8.8
Circulating soluble factors (plasma, not applicable for China)		X^{n}	X^{n}	X^{n}	X^{n}	$X^{n,t}$		8.8
Stool sample collection for microbiome analysis (optional, applicable in North America and Europe only)[u]		X		X				8.8
EORTC QLQ-LC13 (by e-device)[v]		X	Weekly (±1 day on weeks 1, 2, 3, 5, 6, and 7, and ±3 days on weeks 4 and 8) for the first 8 weeks from randomization and then every 4 weeks (±3 days) relative to randomization until study termination or PFS2 or death					8.1.3
EORTC QLQ-C30 (by e-device)[v]		X	Every 4 weeks (±3 days) relative to randomization until study termination or PFS2 or death					8.1.3
PRO-CTCAE (by e-device)[v]		X	Weekly (±1 day on weeks 1, 2, 3, 5, 6, 7, 9, 10, and 11, and ±3 days on weeks 4, 8, and 12) for the first 12 weeks from randomization and then every 4 weeks (±3 days) relative to randomization until study termination or PFS2 or death					8.1.3
PGIS (by e-device)[v]		X	Every 8 weeks (±3 days) relative to randomization until study termination or PFS2 or death					8.1.3
EQ-5D-5L (by e-device)[v]		X	Every 8 weeks (±3 days) relative to randomization until study termination or PFS2 or death					8.1.3
Health resource use module (HOSPAD)	X	Every 24 weeks (±3 days) relative to randomization until treatment discontinuation						8.9
Mandatory tumor tissue sample[c]	X							5.1, 8.8
Optional newly acquired tumor biopsy[c]	X							5.1, 8.8
Genetic sample (optional DNA element for long-term storage/future use, not applicable for China)[w]		X						8.7

	Screening[a]	C1	C2	C3	C4	C5 to C25	C26/ Final Dosing Visit	For details, see Section
Week	**-6 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				**100**	
Day	**-42 to -1**	**1[b]**	**q28days ±3 days unless dosing needs to be held for toxicity reasons**				**701**	
Efficacy evaluations								
Tumor assessments (CT or MRI) (RECIST 1.1)[y]	X[z]	On-study tumor assessments occur q8w ± 1w for the first 72 weeks (relative to the date of randomization), followed by q12w ±1w until up to 96 weeks relative to the date of randomization, and then q24w ±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological progression, plus one follow-up scan no earlier than 4 weeks later and no later than the next regularly scheduled imaging visit. This on-study schedule MUST be followed regardless of any delays in dosing. Tumor assessments up to progression may continue after the PFS analysis and up to the end of the study						8.1

[a] The screening period starts from the last day of the final cycle of chemotherapy (eg, C4D21) or the last day of radiotherapy (whichever occurs later) and may last 1 to 42 days prior to randomization and the first dose of IP.

[b] Every effort should be made to minimize the time between randomization and starting treatment. CRT treatment, and PCI treatment if received per local standard of care, must be completed within 1 to 42 days prior to randomization and the first dose of IP.

[c] Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply a tumor tissue sample for entry into this study. This consent is included in the main patient ICF. The collection of additional biopsies upon progression is encouraged where technically and clinically feasible (not applicable for China). If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 42 days prior to randomization and the first dose of IP.

[d] Consent for the optional genetic sample and analysis is included in the main patient ICF.

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

[f] Triplicate ECGs required.

[g] Brain MRI (preferred) or high-quality brain CT with IV contrast should be conducted after completion of CRT and within 1 to 42 days before randomization and first dose of IP (screening period). This scan should also be performed before commencing PCI (if PCI is indicated as per local standard of care).

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

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

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

[m] Within 10 minutes of the end of infusion.

[n] Pre-dose, within 60 minutes prior to start of infusion; before tremelimumab infusion in C1 to C4; before durvalumab infusion in C5 and subsequent cycles. Once 600 patients have been randomized, PK and ADA assessments related to tremelimumab will not be required for any newly randomized patients.

[o] PK and ADA samples should be collected on the last scheduled cycle of IP (ie, the last cycle of IP that is within the maximum 24 months from the first dose of IP).

[p] Samples should **not** be collected for newly-randomized patients once 600 patients have been randomized.

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

[r] During the combination portion of treatment, tremelimumab or placebo will be administered first; the durvalumab or placebo infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab or placebo infusion. If there are no clinically significant infusion reactions with the first cycle, and at the discretion of the Investigator, then for all other cycles, the durvalumab or placebo can be given immediately after the tremelimumab or placebo infusion has finished. Once 600 patients have been randomized, patients newly randomized to durvalumab monotherapy or to placebo will receive 1 infusion only. Patients randomized before 600 patients have been randomized will continue to receive infusions as per schedule.

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

[t] Samples for soluble factors (plasma) should be collected on Cycles 5, 7, 9, 11, 13, 15, 17, 19, 22, and 25.

[u] Optional stool samples will be requested from sites in North America and Europe only. Kits for collecting stool samples should be given to patients at a previous visit and samples may be collected from consenting patients, in a home setting or in the clinic, up to 3 days before the scheduled Cycle 1 or Cycle 3 visit and the sample brought (to the site as appropriate) at the next scheduled visit.

[v] ePRO LogPads must be assigned to patients only on the day of randomization; baseline ePROs should be completed by patients prior to dosing and prior to any other assessments while they are still in the clinic on Cycle 1 Day 1 to ensure that the device is correctly set up and working properly. Thereafter, ePROs should be completed by the patients at home. PRO-CTCAE will be administered only in the languages where a linguistically validated version exists.

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

[y] See Section 8.1 and Appendix F for additional details relevant to the imaging schedule. The follow-up scan after a RECIST 1.1-defined PD is also evaluated according to RECIST 1.1 criteria (Appendix F).

[z] The baseline tumor assessment must be performed post-CRT as part of the screening procedures within 42 days before randomization and the first dose of IP.

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

ADA Anti-drug antibody; AE Adverse event; C Cycle; CRT Chemoradiation therapy; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; ePRO Electronic patient-reported outcome; EQ-5D-5L EuroQoL 5 dimension, 5 level health state utility index; HIV Human immunodeficiency virus; ICF Informed consent form; IP Investigational product (ie, durvalumab, tremelimumab, or placebo); LFT Liver function test; MRI Magnetic resonance imaging; PCI Prophylactic cranial irradiation; PD Progressive disease; PGIS Patient's Global Impression of Severity; PK Pharmacokinetic; PRO Patient-reported outcome; QLQ C30 30 Item core quality of life questionnaire; QLQ LC13 Lung cancer module; qXdays Every X days; qXw Every X weeks; RECIST Response Evaluation Criteria In Solid Tumors; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 2 Schedule of assessments for patients who have completed/discontinued treatment with durvalumab ± tremelimumab therapy or placebo

	Time since last dose of IP								
	Day (±3)	Week (±1 week)						48 weeks and every 8 weeks (±2 weeks) until study termination or death	For details, see Section
Evaluation	**30**	**8**	**12**	**16**	**24**	**32**	**40**		
Physical examination (full)	X								8.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								8.2.3
Weight	X	X	X						8.2.3
Pregnancy test[a]	X	As clinically indicated							8.2.1
AE/SAE assessment	X	X	X						8.3
Concomitant medications	X	X	X						6.4
WHO/ECOG performance status	At time points consistent with tumor assessments; at Day 30 (±3), Week 8 (±1 week), and Week 12 (±1 week); and then at initiation of subsequent anticancer therapy[b]								8.2.5
Second progression assessment[c]	Patients who discontinue study drug following progression will be assessed every 8 weeks for a second progression (using the patient's status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death.								8.1.2
Subsequent anticancer therapy[d] and survival status[e]		X	X	X	X	X	X	X	8.1.2
Hematology	X	X	X						Table 9
Clinical chemistry	X	X	X						Table 8
TSH (reflex free T3 or free T4[f])	X	X	X						Table 8
Durvalumab PK assessment[g]			X						8.5
Tremelimumab PK assessment[h]			X						8.5
Durvalumab immunogenicity assessment (ADA sampling) to identify ADA responses[i]			X		X				8.5
Tremelimumab immunogenicity assessment (ADA sampling) to identify ADA responses[j]			X		X				8.5

	Time since last dose of IP								
	Day (±3)	**Week (±1 week)**						**48 weeks and every 8 weeks (±2 weeks) until study termination or death**	**For details, see Section**
Evaluation	**30**	**8**	**12**	**16**	**24**	**32**	**40**		
Whole blood for gene expression (PaxGene-RNA tubes, not applicable for China)	X	X							8.8
Circulating soluble factors (including TMB; plasma, not applicable for China)	X	X							8.8
EORTC QLQ-LC13 (by e-device)[k]	Weekly (±1 day on weeks 1, 2, 3, 5, 6 and 7, and ±3 days on weeks 4 and 8) for the first 8 weeks from randomization and then every 4 weeks (±3 days) relative to randomization until study termination or PFS2 or death								8.1.3
EORTC QLQ-C30 (by e-device)[k]	Every 4 weeks (±3 days) relative to randomization until study termination or PFS2 or death								8.1.3
PRO-CTCAE (by e-device)[k]	Weekly (±1 day on weeks 1, 2, 3, 5, 6, 7, 9, 10 and 11, and ±3 days on weeks 4, 8 and 12) for the first 12 weeks from randomization, then every 4 weeks (±3 days) relative to randomization until study termination or PFS2 or death								8.1.3
PGIS (by e-device)[k]	Every 8 weeks (±3 days) relative to randomization until study termination or PFS2 or death								8.1.3
EQ-5D-5L (by e-device)[k]	Every 8 weeks (±3 days) relative to randomization until study termination or PFS2 or death								8.1.3
Health resource use module (HOSPAD)					X			X[m]	8.9
Tumor assessment (CT or MRI) (RECIST 1.1)[l]	On-study tumor assessments occur q8w ±1w for the first 72 weeks (relative to the date of randomization), followed by q12w ±1w until up to 96 weeks relative to the date of randomization, and then q24w ±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological progression, plus one follow-up scan no earlier than 4 weeks later and no later than the next regularly scheduled imaging visit. This on-study schedule MUST be followed regardless of any delays in dosing. Additional scans to be completed per standard practice post-progression. Tumor assessments up to progression may continue after the PFS analysis and up to the end of the study								8.1

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

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

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

[d] Details of any treatment for LS-SCLC (including surgery and hospitalizations) after the last dose of IP must be recorded in the eCRF. At minimum, the start date and description of the subsequent anticancer therapy must be collected.

[e] Patients may be contacted in the week following DCOs to confirm survival status. Details of any treatment for LS-SCLC (including surgery and hospitalizations) after the last dose of IP must be recorded in the eCRF.

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

[g] PK samples for durvalumab and its placebo are to be collected 12 weeks (±7 days) after treatment with durvalumab/placebo ends.

[h] PK samples for tremelimumab and its placebo are to be collected 12 weeks (±7 days) after treatment with tremelimumab/placebo ends. If tremelimumab/placebo PK samples were taken at Cycle 7 as per Table 1, then the 12-week tremelimumab/placebo PK sample does not need to be collected again. Once 600 patients have been randomized, PK samples related to tremelimumab should **not** be collected for any newly randomized patients.

[i] Immunogenicity samples for durvalumab and its placebo are to be collected 12 weeks (±7 days) and 24 weeks (±7 days) after treatment with the durvalumab/placebo ends.

[j] Immunogenicity samples for tremelimumab and its placebo are to be collected 12 weeks (±7 days) and 24 weeks (±7 days) after treatment with tremelimumab/placebo ends. If tremelimumab/placebo ADA samples were taken at Cycle 7 and 10 as per Table 1, then these tremelimumab/placebo ADA samples do not need to be collected again. Once 600 patients have been randomized, ADA samples related to tremelimumab should **not** be collected for any newly randomized patients.

[k] ePRO LogPads assigned at randomization will be used.

[l] See Section 8.1 and Appendix F for additional details relevant to the imaging schedule. The follow-up scan after a RECIST 1.1-defined PD is also evaluated according to RECIST 1.1 criteria (Appendix F).

[m] Health resource use assessment should be performed every 24 weeks (±2 weeks) after treatment discontinuation and until PFS2 or study termination or death, whichever occurs first.

ADA Anti-drug antibody; AE Adverse event; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC European Organisation for Research and Treatment of Cancer; ePRO Electronic patient reported outcome; EQ-5D-5L EuroQoL 5 dimension, 5 level health state utility index; IP Investigational product (ie, durvalumab, tremelimumab, or placebo); LS-SCLC Limited stage small-cell lung cancer; MRI Magnetic resonance imaging; PFS2 Time from randomization to second progression; PGIS Patient's Global Impression of Severity; PK Pharmacokinetic; PRO Patient-reported outcome; QLQ-C30 30 Item core quality of life questionnaire; QLQ LC13 Lung cancer module; qXw Every X weeks; RECIST Response Evaluation Criteria In Solid Tumors; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

1.2 Synopsis

International Co-ordinating Investigator

[redacted]
Department of Radiation Oncology, Cancer Center Amsterdam
Locatie VUmc
PK –1, 150
De Boelelaan 1117, Postbus 7057, 1007 MB Amsterdam
Tel: [redacted]

Protocol Title: A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC)

Rationale:

Small-cell lung cancer (SCLC), which accounts for approximately 14% of newly diagnosed lung cancers, is an aggressive disease characterized by rapid growth and early metastases. For limited stage (LS)-SCLC, which accounts for approximately 30% of SCLC diagnoses, the prognosis remains poor despite curative-intent concurrent chemoradiation therapy (CRT) with median overall survival (OS) around two years; no new systemic treatment has become available for LS-SCLC in several decades. Immunotherapy in particular checkpoint inhibitors targeting both programmed cell death 1 (PD-1) and cytotoxic T-lymphocytes-associated antigen-4 (CTLA-4) has been in development in SCLC for several years now. At the time of study inception in 2018, data were available from several key AstraZeneca-sponsored studies suggesting that durvalumab monotherapy is efficacious in the post-CRT setting in locally advanced non-small cell lung cancer (NSCLC) and is also active in pre-treated extensive stage (ES)-SCLC. The PACIFIC study (D4191C00001 [NCT02125461]) demonstrated that the addition of durvalumab as consolidation treatment post platinum-based CRT significantly improves progression-free survival (PFS; improved median PFS from 5.6 to 16.8 months, hazard ratio [HR] of 0.52, 95% confidence interval [CI]: 0.42, 0.65, p<0.0001) (Antonia et al 2017) and subsequently the study also demonstrated a statistically significant improvement in OS; (HR of 0.68; 99.73% CI: 0.47, 0.997, p=0.00251 (Antonia et al 2018) with manageable toxicities in patients with locally advanced NSCLC. In the Phase I/IB Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108 [NCT01693562]), durvalumab monotherapy showed encouraging activity in patients with pre-treated ES-SCLC, with an objective response rate (ORR) of 9.5%, a median OS of 4.8 months (95% CI: 1.3, 10.8), and a 1-year survival rate of 27.6% (95% CI: 10.2%, 48.4%). Additional data from later line studies in patients with ES-SCLC suggest that treatment with durvalumab in combination with tremelimumab may provide additional benefits to durvalumab alone in pretreated ES-SCLC patients. Similar data were published in other drugs of the same class (ie, nivolumab in combination with ipilimumab). In a Phase I/II study (D4190C00010; hereafter referred to as Study 10 [NCT02261220]), durvalumab in combination with tremelimumab demonstrated clinical activity in heavily pre-treated ES-SCLC with ORR of 13.3% and median OS of 7.9 months (95% CI: 3.2, NR) and a 1-year survival rate of 41.7% (95% CI: 23.3%, 59.2%). The CHECKMATE-032 study (NCT01928394), conducted in patients

with recurrent SCLC, reported ORRs of 10% and 23% in patients with monotherapy and combination therapy, respectively, a median PFS of 1.4 months (95% CI: 1.2, 2.2 months) and 2.6 months (95% CI: 1.4, 4.1 months) with monotherapy and combination therapy, respectively, and a median OS of 4.1 months (95% CI: 3.1, 9.1 months) and 7.9 months (95% CI: 3.6, 14.2 months), respectively (Antonia 2016). These data warrant further development of durvalumab, an anti-programmed cell death ligand 1 (PD-L1) monoclonal antibody (mAb), alone or in combination with tremelimumab, an antiCTLA-4 -mAb, in patients with LS-SCLC who have not progressed following platinum-based chemotherapy concurrent with radiotherapy (cCRT).

Study Design Change – Rationale and Impact

Since study inception in 2018, new clinical data have emerged regarding the management of SCLC and the role of immunotherapy:

CASPIAN

In the first-line ES-SCLC setting, the Phase III CASPIAN study (D419QC00001 [NCT03043872]) demonstrated that addition of durvalumab to etoposide-platinum (EP) chemotherapy significantly improved OS (HR 0.73, 95% CI 0.59, 0.91; p = 0.0 47) (Paz-Ares et al 2019), confirming the role of immunotherapy (PD-L1 inhibition) in the management of ES-SCLC.

In the same study, the treatment group investigating the combination of durvalumab and tremelimumab plus EP showed a numerical improvement in OS, but did not reach statistical significance ($p \leq 0.0418$) per the prespecified statistical plan (HR 0.82, 95% CI 0.68, 1.00; p = 0.0451). However, safety and tolerability were consistent with known safety profiles of these medicines (Paz-Ares et al 2020).

CHECKMATE-451

In the Phase III CHECKMATE-451 study (NCT02538666), which investigated the role of maintenance nivolumab monotherapy or nivolumab plus ipiliumumab after first-line platinum based chemotherapy in patients with extensive disease SCLC, the combination treatment did not reach statistical significance in terms of OS compared with placebo (HR 0.92, 95% CI: 0.8, 1.1; p = 0.37) (Owonikoko et al 2019).

CHECKMATE-032

The Phase I/II CHECKMATE-032 study (NCT01928394) published its recurrent SCLC cohort results in 2020, showing a higher ORR in the combination ipilimumab and nivolumab group compared to the nivolumab monotherapy group; however, overall efficacy results were similar in both groups (Ready et al 2020).

STIMULI

Data from the Phase II STIMULI study (NCT02046733) presented in 2020 indicated that patients with LS-SCLC who received nivolumab and ipilimumab after standard treatment

(chemotherapy and radiotherapy) showed no difference in PFS when compared with patients who received observation after standard treatment (HR 1.02, 95% CI: 0.66, 1.58; p = 0.93). This finding may possibly be due to the short period on active treatment observed in the study (Peters et al 2020).

The accumulated evidence from the comparative trials suggests that the role of CTLA-4 inhibition in combination with PD-1/PD-L1 inhibition remains ambiguous but not conclusive and that efficacy gains through the addition of CTLA4-inhibition to PD-L1 blockade may be limited. However, monthly blinded review of safety data from ADRIATIC has not detected a safety signal, hence continued evaluation of this combination therapy as a secondary objective remains warranted.

In view of the updated data, the sponsor has reconsidered the study hypothesis and modified the study design accordingly in the Version 4 Amendment:

- OS for the comparison of durvalumab monotherapy versus placebo has been added to the primary endpoint, ie, the study now has dual primary endpoints of PFS and OS for the comparison of durvalumab monotherapy versus placebo; the comparison of durvalumab plus tremelimumab vs placebo in terms of PFS and OS are now secondary endpoints (Section 3).
- Due to revision of the anticipated treatment effects on PFS and OS, the total sample size for the study has been increased from 600 to approximately 724 patients: the durvalumab monotherapy and placebo groups have both been increased to approximately 262 patients and the durvalumab plus tremelimumab combination treatment group has remained unchanged (approximately 200 patients).

The following aspects of study design are also impacted:

- As the number of patients in the durvalumab plus tremelimumab group is unchanged, once 600 patients have been randomized, randomization will continue 1:1 in the durvalumab monotherapy and placebo groups.
- Once 600 patients have been randomized, no further PK or ADA samples relevant to tremelimumab are required.
- Enrolment in China may continue after global enrolment is closed to allow inclusion of a total of approximately 108 patients.
- Several statistical sections have been updated to describe changes to the null hypotheses for the efficacy endpoints, the sample size determination, timing of the interim and final analyses, clarification of patients included in the analyses of the combination analysis set, the calculation or derivation of efficacy variables, the analyses of PFS, OS, and DoR, the description of methods for multiplicity control, and the updated details of the interim analyses of OS and their anticipated timing.
- The benefit-risk assessment has been updated for durvalumab and overall.

Objectives and Endpoints

Dual primary objectives:	Endpoints/variables:
To assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS	PFS using BICR assessments according to RECIST 1.1
To assess the efficacy of durvalumab monotherapy compared to placebo in terms of OS	OS

Secondary objectives:	Endpoints/variables:
To assess the efficacy of durvalumab and tremelimumab combination therapy compared to placebo in terms of PFS and OS	PFS using BICR assessments according to RECIST 1.1 OS
To further assess the efficacy of durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo in terms of ORR, PFS18[a], PFS24[a], TTDM, OS24, OS36, and PFS2	ORR, PFS18[a], PFS24[a], and TTDM using BICR assessments according to RECIST 1.1 OS24 and OS36 PFS2
To assess the efficacy of durvalumab and tremelimumab combination therapy compared to durvalumab monotherapy in terms of PFS, OS, and ORR	PFS and ORR using BICR assessments according to RECIST 1.1 OS
To assess disease-related symptoms and HRQoL in patients treated with durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo using the EORTC QLQ-C30 v3 and QLQ-LC13	EORTC QLQ-C30 and QLQ-LC13: change in symptoms, functioning, and global health status/QoL
To assess the PK of durvalumab monotherapy and durvalumab and tremelimumab combination therapy	Concentration of durvalumab and tremelimumab in serum (such as peak concentration and trough; sparse sampling)
To investigate the immunogenicity of durvalumab monotherapy and durvalumab and tremelimumab combination therapy	Presence of ADA for durvalumab and tremelimumab (confirmatory results: positive or negative)

To investigate the relationship between PD-L1 expression and spatial distribution within the tumor microenvironment and clinical outcomes with durvalumab monotherapy or durvalumab and tremelimumab combination therapy	PD-L1 expression in tumor and/or immune cells (cutoff ≥ 1%) relative to response/efficacy outcomes (PFS, OS, and ORR). Other PD-L1 cutoffs may also be analyzed
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability profile of durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo in patients with LS-SCLC	AEs; laboratory findings including clinical chemistry, hematology, and urinalysis; physical examinations; vital signs including blood pressure and pulse; and electrocardiograms
Exploratory objectives:	**Endpoints/variables:**
To assess treatment-related side effects in patients treated with durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo using PRO-CTCAE	Change in the 9 treatment-related symptoms evaluated in this study
To assess the patients' overall impression of the severity of their cancer symptoms using PGIS	PGIS: Proportion of patients assessing current symptom severity
To describe and evaluate health resource use associated with durvalumab monotherapy and durvalumab and tremelimumab combination therapy and underlying disease	Health resource utilization measures including hospitalization, outpatient visits, or emergency department visits
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
To collect blood and tissue samples, or leverage residual samples, for analysis of peripheral and tumoral biomarkers (not applicable for China)	Exploratory biomarkers, which may include but are not limited to, DNA, RNA, and protein-based assessment within the tumor microenvironment and/or in the periphery. Evaluation of tumor-cell and/or immune-cell gene expression profiles, tumor or ctDNA derived mutational analyses, PD-L1 expression, SCLC molecular subtypes, tumor-immue spatial profiling, etc., and association of each biomarker with response and/or resistance
To investigate the relationship between TMB measured in tumor and/or blood and efficacy outcomes with durvalumab monotherapy and durvalumab and tremelimumab combination therapy (not applicable for China)	TMB relative to response/efficacy outcomes (ORR, PFS, and OS)

To explore the relationship(s) between patient biomarker status and durvalumab PK exposure and clinical outcomes before and after treatment (TMB related testing or analysis will not be conducted on Chinese samples)	Biomarker status before and after treatment, durvalumab PK exposure, and relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate
To explore irRECIST as assessment methodologies for clinical benefit of durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo with assessment by BICR	PFS and ORR using BICR assessment according to irRECIST
To collect and store DNA from tissue and/or blood according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to IPs and/or susceptibility to disease (optional, not applicable for China)	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety, or response parameters observed in patients treated with durvalumab and/or susceptibility to disease
To investigate the effect of baseline colonic microbiome on response to treatment and the effect of treatment on the microbiome over time (applicable for EU and North America only)	Microbiome analysis of stool sample

[a] Progression-free survival at 18 and 24 months following randomization (PFS18 and PFS24) is equivalent to the proportion of patients alive and progression-free at 18 and 24 months following randomization (APF18 and APF24), respectively.

ADA Anti-drug antibody; AE Adverse event; BICR Blinded Independent Central Review; CTCAE Common Terminology Criteria for Adverse Events; ctDNA Circulating tumor DNA; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5 dimension, 5-level health state utility index; HRQoL Health-related quality of life; IP Investigational product; irRECIST Immune-related Response Evaluation Criteria In Solid Tumors; LS-SCLC Limited stage small cell lung cancer; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomization; OS36 Proportion of patients alive at 36 months from randomization; PDL1 Programmed death ligand 1; PFS Progression-free survival; PFS2 Time from randomization to second progression; PFS18 Progression-free survival at 18 months following randomization; PFS24 Progression-free survival at 24 months following randomization; PGIS Patient's Global Impression of Severity; PK Pharmacokinetic(s); PRO Patient-reported outcome; QLQ-C30 30-item core quality of life questionnaire; QLQ-LC13 Lung cancer module; QoL Quality of life; RECIST Response Evaluation Criteria In Solid Tumors; TMB Tumor mutational burden; TTDM Time to death or distant metastasis.

Overall design:

This is a Phase III, randomized, double-blind, placebo-controlled, multi-center study assessing the efficacy and safety of durvalumab or durvalumab and tremelimumab combination therapy versus placebo as consolidation treatment in patients with LS-SCLC who have not progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy (cCRT).

In order to be eligible for this study, patients must have achieved complete response (CR), partial response (PR), or stable disease (SD) and have not progressed following definitive, platinum-based chemotherapy, concurrent with radiotherapy (cCRT). This cCRT treatment, and prophylactic cranial irradiation (PCI) treatment if received per local standard of care, must be completed within 1 to 42 days prior to randomization and the first dose of investigational product (IP; ie, durvalumab, tremelimumab, or placebo) in this study. In addition, the baseline efficacy assessment must be performed post-CRT as part of the screening procedures within 42 days before randomization and the first dose of IP.

Initially, patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups: durvalumab monotherapy, durvalumab and tremelimumab combination therapy, or placebo. Once 600 patients have been randomized, subsequent patients will be randomized 1:1 to durvalumab monotherapy or placebo. Randomization will be stratified by stage (I/II versus III) based on tumor, node, and metastatic classification (TNM) and receipt of PCI (yes versus no).

Study Period:

Estimated date of first patient enrolled: Q3 2018

Estimated date of last patient completed: Q2 2025.

Number of patients:

Approximately 965 patients will be enrolled in order to randomize 724 patients. This includes approximately 524 patients randomized to the durvalumab monotherapy and placebo treatment groups (approximately 262 patients per treatment group), and approximately 200 patients to the durvalumab and tremelimumab combination treatment group.

Enrolment in China may continue after global enrolment is closed to allow inclusion of a total of approximately 108 patients randomized from sites in China (approximately 15% of the global sample size). Patients enrolled in China prior to the closure of global enrolment will be included in both the Global Cohort and the China Cohort. Patients enrolled in China after closure of global enrolment will only be analyzed in the China Cohort.

Treatments and treatment duration:

Patients will receive 1 of the following treatments, based on treatment group assignment:

- Durvalumab monotherapy: Durvalumab (1500 mg intravenous [IV]) every 4 weeks (q4w) in combination with placebo (IV) q4w for 4 doses/cycles each, followed by durvalumab 1500 mg q4w. The first durvalumab monotherapy 1500 mg dose q4w will be 4 weeks after the final dose of durvalumab in combination with placebo . Following completion of enrollment in the durvalumab and tremelimumab combination therapy group, all patients newly randomized to durvalumab monotherapy will receive 1 infusion only (durvalumab) from Cycle 1. Patients randomized prior to completion of enrolment to the durvalumab and tremelimumab treatment group will receive 2 infusions (durvalumab and placebo) for the first 4 cycles, followed by 1 durvaluamb infusion from Cycle 5 onwards.

- Placebo: Placebo (IV) q4w in combination with a second placebo (IV) q4w for 4 doses/cycles each, followed by placebo monotherapy (IV) q4w from Cycle 5. The first placebo monotherapy dose q4w will be 4 weeks after the final dose of the 2 placebo combination. Following completion of enrollment in the durvalumab and tremelimumab combination therapy group, all patients newly randomized to placebo will receive 1 infusion only (placebo) from Cycle 1. Patients randomized prior to completion of enrolment to the durvalumab and tremelimumab treatment group will receive 2 infusions (placebo + placebo) for the first 4 cycles, followed by 1 placebo infusion from Cycle 5 onwards.

- Durvalumab in combination with tremelimumab: Durvalumab (1500 mg IV) q4w in combination with tremelimumab (75 mg IV) q4w for 4 doses/cycles each, followed by durvalumab 1500 mg q4w. The first durvalumab monotherapy 1500 mg dose q4w will be 4 weeks after the final dose of durvalumab in combination with tremelimumab. Once 600 patients have been randomized, subsequent patients will be randomized 1:1 to the durvalumab monotherapy and placebo groups only.

Treatment in all treatment groups will continue until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurs first.

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 q4w and 1 mg/kg tremelimumab or placebo q4w after consultation between the 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 plus tremelimumab 75 mg or placebo q4w.

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients will continue therapy until clinical/RECIST 1.1-defined progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurs first.

Follow-up of patients post discontinuation of study drug

Patients who have discontinued treatment due to toxicity, symptomatic deterioration, or clinical progression will be followed up with tumor assessments until RECIST 1.1-defined radiological progression plus one follow-up scan or until death (whichever comes first) and followed for survival.

Survival

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

Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) comprised of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule and for the interim analyses. The safety review will take place after the first 20 patients have been

randomized into each of the 3 treatment groups (i.e. after a total of 60 patients have been randomized to the study). In addition, the IDMC will review planned interim analyses and inform the Sponsor whether the interim boundaries specified in Section 9.5.2 are met.

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

Statistical methods

The dual primary objectives of this study are to assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS and OS. PFS (per RECIST 1.1 as assessed by Blinded Independent Central Review [BICR]) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression. OS is defined as the time from the date of randomization until death due to any cause.

Efficacy data will be summarized and analyzed based on the full analysis set (FAS), and the treatment groups will be compared on the basis of randomized treatment, regardless of the treatment actually received. However, for efficacy analyses involving the durvalumab plus tremelimumab combination treatment group, only those patients randomized up to and including the date of the 600th patient will be included in the analyses. Patients who were randomized but did not subsequently go on to receive IP are included in the FAS.

The study will be considered positive (ie, a success) if either of the null hypotheses outlined in Section 9.1 are rejected based on the dual primary analysis of PFS and/or OS in the FAS (durvalumab monotherapy versus placebo).

A multiple testing procedure will be used to strongly control the family-wise type I error rate (alpha) at 5% (2-sided) for the dual primary endpoints of PFS and OS. The alpha will be split with 0.5% allocated to PFS and 4.5% allocated to OS for the comparisons of durvalumab monotherapy versus placebo. If both are found to be significant, then OS and then PFS for the durvalumab plus tremelimumab combination versus placebo will be tested sequentially at 5%.

Three interim analyses are planned, 1 for PFS and 2 for OS.

The interim analysis of PFS (PFS-IA) will occur when approximately 308 PFS BICR events have cumulated with 58.8% maturity in the durvalumab monotherapy and placebo treatment groups.

The first interim analysis of OS (OS-IA1) will occur at the time of the PFS interim analysis. It is anticipated that approximately 242 death events in the durvalumab monotherapy and placebo treatment groups with 46.2% maturity will have cumulated at this interim OS analysis.

The second interim analysis of OS (OS-IA2) will occur when approximately 299 death events have cumulated with 57.1% maturity in the durvalumab monotherapy and placebo treatment groups.

The primary PFS analysis will occur at the earliest of:

1. When approximately 370 PFS BICR events have occurred (70.6% maturity) in the durvalumab monotherapy and placebo treatment groups
2. At OS-IA2, if OS-IA2 is statistically significant (durvalumab monotherapy vs placebo)
3. 36 months after the last patient randomized

With 370 PFS BICR events, the study will have 90% power to detect a PFS HR = 0.65 (median PFS of 15.4 months versus 10 months) at the 2-sided 0.5% alpha level. A recruitment period of approximately 38 months are expected for the primary PFS analysis.

The primary OS analysis will occur when approximately 348 death events have occurred (66.4% maturity) in the durvalumab monotherapy and placebo treatment groups. With 348 death events, the study will have 80% power to detect a HR = 0.73 (median OS of 32.9 months versus 24 months).

The interim and primary PFS analysis will be based on the programmatically derived RECIST 1.1 using BICR tumor assessments. PFS and OS analyses will be performed in the FAS using a stratified log-rank test adjusting for TNM stage (I/II versus III) and receipt of PCI (yes versus no). The effect of treatment will be estimated by the HR together with its corresponding CI from a Cox proportional hazards model.

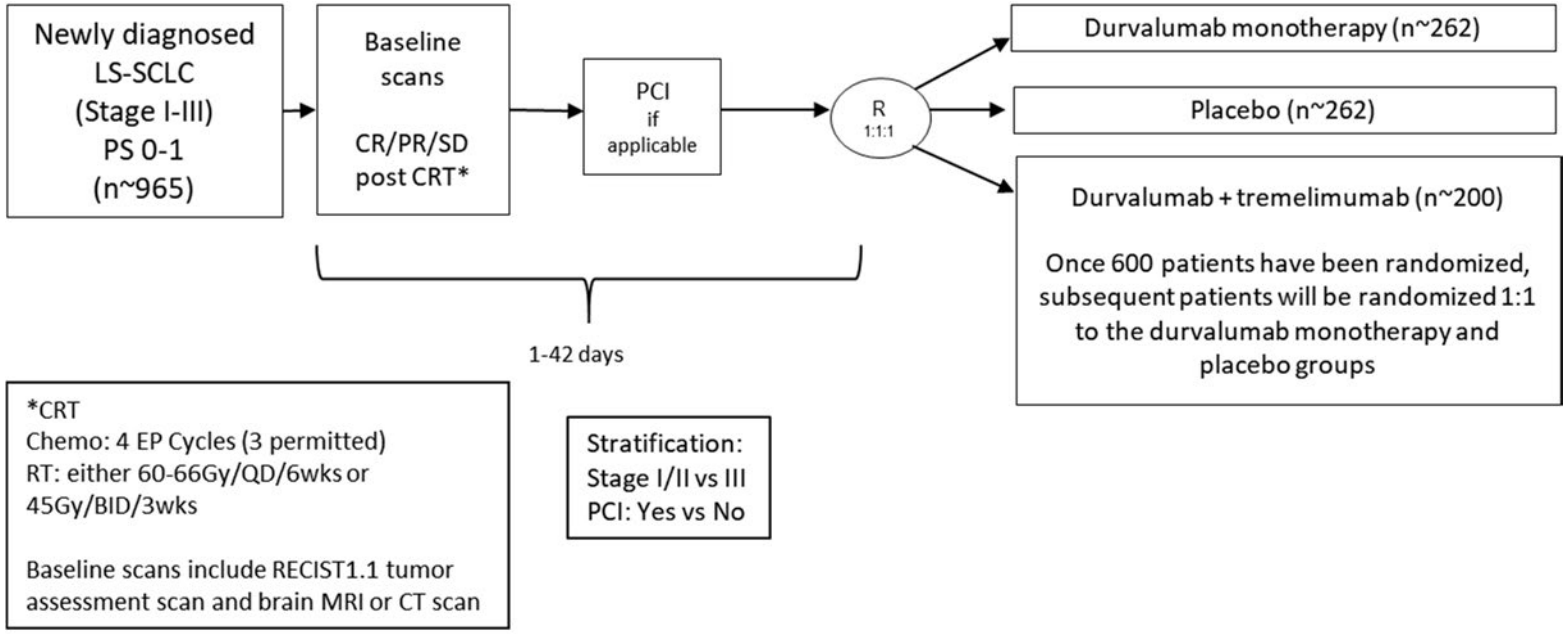
Safety data will be summarized descriptively and will not be formally analyzed.

Details of China subgroup analysis on efficacy and safety will be covered in the Statistical Analysis Plan (SAP).

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



BID Twice daily; CR Complete response; CRT Chemoradiation therapy; D Durvalumab; EP Etoposide and cisplatin chemotherapy; LS-SCLC Limited stage small-cell lung; PCI Prophylactic cranial irradiation; PD Progressive disease; PR Partial response; PS Performance status; QD Once daily; R Randomization; RT Radiotherapy; SD Stable disease; T Tremelimumab.

2. INTRODUCTION

Lung cancer has been among the most common cancers in the world for several decades, with an estimated 2.1 million new cases in 2018 (11.6% of all new cancers), and was also the most common cause of death from cancer in 2018, with 1.76 million deaths (18.4% of the total cancer deaths; GLOBOCAN 2018).

Small-cell lung cancer (SCLC) represents approximately 14% of all newly diagnosed lung cancers (Howlander et al 2016). In the United States (US), over 56,000 new cases of SCLC were diagnosed between 1983 and 2012 (Wang et al 2017). SCLC is distinguishable from non-small-cell lung cancer (NSCLC) by its more aggressive characteristics that include rapid doubling time, high growth fraction, and early dissemination. It is also strongly associated with tobacco smoking and high tumor mutation rate (Peifer et al 2012). While the incidence of SCLC is declining for most age groups (Riaz et al 2012, Wang et al 2017), there has been little improvement in the median overall survival (OS) over the last 3 decades and this remains at 7 months (Wang et al 2017).

A 2-stage system dividing patients into limited and extensive stage or disease was developed in 1973 by the US Veteran's Administration Lung Cancer Study Group (Zelen M 1973). Limited Stage (LS) was defined as tumor tissue that could be encompassed in a single radiation port, and Extensive Stage (ES) was defined as any tumor that extended beyond the boundaries of a single radiation port. At present, LS is diagnosed in ~30% of patients presenting with SCLC, and ES is diagnosed in ~70% of patients.

The standard-of-care treatment for LS-SCLC is thoracic radiotherapy (once daily with a total dose of 60 to 66 Gy or twice daily with a total dose of 45 Gy) combined with 4 cycles of either cisplatin or carboplatin and etoposide chemotherapy (Früh et al 2013, NCCN 2017). In addition, data suggest that prophylactic cranial irradiation (PCI; for patients that respond to initial therapy) may increase the OS and PFS in LS-SCLC patients (Aupérin et al 1999). Response rates for concurrent CRT in LS-SCLC are approximately 90%, but the majority of patients eventually progress, with median PFS of 10 to 15 months and median OS of 15 to 30 months (Faivre-Finn et al 2017, Grønberg et al 2016, Seckl et al 2017). Therefore, there is still a significant unmet medical need for additional treatment options for this patient population to improve PFS and OS.

2.1 Study rationale

SCLC may be particularly susceptible to immune checkpoint inhibitor therapy given the high mutational burden of this disease. Several recent studies analyzing data from different tumor types have demonstrated a correlation between mutational burden and response to checkpoint inhibitors targeting both PD-1 (Rizvi 2015) and CTLA-4 (Snyder et al 2014, Van Allen et al 2015).

2.1.1 Durvalumab monotherapy

Data from 2 key AstraZeneca-sponsored studies and 1 non-AstraZeneca sponsored study suggest that durvalumab monotherapy may provide benefit to patients with LS-SCLC who have not progressed following CRT.

- The AstraZeneca-sponsored PACIFIC study (D4191C00001 [NCT02125461]) evaluated sequential treatment with durvalumab versus placebo in patients with locally advanced, unresectable, Stage III NSCLC whose disease had not progressed following platinum-based concurrent CRT. The study demonstrated that the addition of durvalumab as sequential therapy to platinum-based CRT significantly improves PFS (improved median PFS from 5.6 to 16.8 months, HR of 0.52, 95% CI: 0.42, 0.65, p<0.0001; Antonia et al 2017) and subsequently the study also demonstrated statistical significant improvement in overall survival (OS) (HR of 0.68; 99.73% CI, 0.47 to 0.997, p=0.00251); Antonia et al 2018), with well tolerated safety profile in patients with locally advanced NSCLC.

- In the AstraZeneca-sponsored, Phase I/IB study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108 [NCT01693562]), durvalumab monotherapy showed encouraging activity in 21 patients with pretreated ES-SCLC after a median followup of 36.4 months (range: 1.4 to 37.9 months), with an objective response rate (ORR) of 9.5% and median OS of 4.8 months (95% CI: 1.3, 10.8). The 1-year OS rate was 27.6% (95% CI: 10.2%, 48.4%). This is in contrast to a 9% 1-year OS observed with topotecan in refractory and resistant ES-SCLC, the only approved single agent in second-line treatment of ES-SCLC (Horita et al 2015). The safety profile of durvalumab monotherapy in Study 1108 was manageable and generally consistent with the known safety profile of the antiPDL1/PD1 drug class; immune-mediated AEs (imAEs) were manageable and generally reversible.

- The CHECKMATE-032 study (NCT01928394), conducted in patients with recurrent SCLC, evaluated treatment with nivolumab (OPDIVO®; an antiPD-1 mAb) as monotherapy or in combination with ipilimumab (YERVOY®; an antiCTLA-4 mAb) in patients with relapsed ES-SCLC or LS-SCLC with progressive disease (PD) after at least 1 prior platinum-containing regimen. This has shown that nivolumab is active as monotherapy. Previously presented results for patients receiving nivolumab monotherapy included an ORR of 10%, a median PFS of 1.4 months (95% CI: 1.2, 2.2 months), and a median OS of 4.1 months (95% CI: 3.1, 9.1 months), with manageable toxicity (Antonia 2016, CheckMate-032 WCLC Presentation 2016).

Based on these data, Study D933QC00001 will evaluate the efficacy and safety of durvalumab monotherapy in patients with LS-SCLC who have not progressed following platinum-based chemotherapy concurrent with radiotherapy (cCRT).

2.1.2 Durvalumab in combination with tremelimumab

Additional data from later-line studies in patients with ES-SCLC suggest that treatment with durvalumab in combination with tremelimumab may provide synergistic antitumor activity in patients with LS-SCLC who have not progressed following CRT.

- In the AstraZeneca-sponsored, Phase I/II study (D4190C00010; hereafter referred to as Study 10 [NCT02261220]), durvalumab in combination with tremelimumab demonstrated clinical activity in heavily pretreated ES-SCLC, with an ORR of 13.3%, median OS of 7.9 months (95% CI: 3.2, NR), and 1-year OS rate of 41.7% (95% CI:

23.3%, 59.2%). The safety profile of durvalumab in combination with tremelimumab was manageable and generally consistent with the known safety profile of the antiPD-L1/PD-1 and CTLA-4 drug classes. Immune-mediated AEs were manageable and generally reversible.

- The CHECKMATE-032 study (NCT01928394), conducted in patients with recurrent SCLC, evaluated treatment with nivolumab (OPDIVO®) as monotherapy or in combination with ipilimumab (YERVOY®) in patients with relapsed ES-SCLC or LS-SCLC with PD after at least 1 prior platinum-containing regimen. Previously presented results for patients receiving combination therapy with nivolumab and ipilimumab included an ORR of 23%, a median PFS of 2.6 months (95% CI: 1.4, 4.1 months), and a median OS of 7.9 months (95% CI: 3.6, 14.2 months), with manageable toxicity (Antonia 2016, CheckMate-032 WCLC Presentation 2016).

Based on these data, Study D933QC00001 will evaluate the efficacy and safety of durvalumab in combination with tremelimumab in patients with LS-SCLC who have not progressed following platinum-based chemotherapy concurrent with radiotherapy (cCRT) as secondary analyses.

In addition to safety and efficacy, the relationship between patient biomarker status (eg, PD-L1, tumor mutational burden, etc.) and efficacy outcomes will be evaluated as secondary or exploratory endpoints in this study; such data may indicate improved efficacy with either durvalumab monotherapy or durvalumab in combination with tremelimumab based on biomarker status.

2.1.3 Study Design Change – Rationale and Impact

Since study inception in 2018, clinical data have emerged regarding the management of SCLC and the role of immunotherapy. These data include:

- In the first-line ES-SCLC setting, the Phase III CASPIAN study (D419QC00001 [NCT03043872]) demonstrated that addition of durvalumab to etoposide-platinum (EP) chemotherapy significantly improved median OS from 10.3 to 13.0 months (HR 0.73, 95% CI: 0.59, 0.91, p = 0.047), with 34% (95% CI: 26.9, 41.0) versus 25% (95% CI: 18.4, 31.6) of patients alive at 18 months in the durvalumab plus EP vs EP treatment groups at a pre-planned interim analysis (Paz-Ares et al 2019). The OS benefit was sustained at final analysis with over 2 years' follow up: median OS was 12.9 vs 10.5 months (HR 0.75, 95% CI: 0.62, 0.91, p = 0.0032), with 22.2% versus 14.4% of patients alive at 2 years in the durvalumab plus EP vs EP treatment groups (Paz-Ares et al 2020).
- In the same study, the treatment group investigating the combination of durvalumab and tremelimumab plus EP showed a numerical improvement in OS, but did not reach statistical significance compared to chemotherapy alone (EP) per the prespecified statistical plan ($p \leq 0.0418$). Median OS was 10.4 vs 10.5 months (HR 0.85, 95% CI: 0.68, 1.00, p = 0.0451), with 23.4% versus 14.4% of patients alive at 2 years in the durvalumab and tremelimumab plus EP vs EP treatment groups. However, safety and tolerability were consistent with known safety profiles of these medicines (Paz-Ares et al 2020). Additionally, PD-L1 correction analyses using a $\geq$ 1% cutoff in tumor and/or

immune cells suggest a potentially greater treatment effect with the combination of durvalumab and tremelimumab plus EP vs EP in patients in the PD-L1 ≥ 1% subgroups compared to those with PD-L1 < 1% (Data on file). TMB correlation analyses showed that TMB was not predictive of an improvement in OS for the durvalumab and tremelimumab plus EP combination vs EP (Goldman et al 2020).

Furthermore, there has been emerging new and updated clinical data regarding CTLA-4 inhibitors in ES-SCLC.

- As indicated above, in the Phase III CASPIAN study (NCT03043872) patients receiving first-line ES-SCLC treatment with the combination of durvalumab and tremelimumab plus EP showed numerical improvement in OS vs EP alone, but this did not reach statistical significance per the prespecified statistical plan (Paz-Ares et al 2020).
- The Phase III CHECKMATE-451 (NCT02538666) study investigated the role of maintenance nivolumab monotherapy or nivolumab plus ipiliumumab after first-line chemotherapy in patients with extensive disease SCLC. The combination treatment group did not reach statistical significance compared with placebo, with a HR of 0.92 (95% CI: 0.8, 1.1; p = 0.37), median OS of 9.2 months (95% CI: 8.2, 10.2 months) vs placebo group median OS of 9.6 months (95% CI: 8.2, 11.0 months). Nivolumab monotherapy has shown HR of 0.84 (95% CI: 0.7, 1.0) vs placebo with median OS of 10.4 months vs 9.6 months (Owonikoko et al 2019).
- The Phase I/II CHECKMATE-032 study (NCT01928394) included a cohort of patients with recurrent SCLC who were randomized to receive nivolumab vs nivolumab plus ipilimumab. Updated results published in 2020 reported ORRs of 11.6% and 21.9% in patients receiving nivolumab monotherapy and nivolumab in combination with ipilimumab, respectively. However, there were no differences in survival outcomes: median PFS was 1.4 months (95% CI: 1.3, 1.4 months) and 1.5 months (95% CI: 1.4, 2.2 months) and median OS was 5.7 months (95% CI: 3.8, 7.6 months) and 4.7 months (95% CI: 3.1, 8.3 months) for monotherapy and combination therapy, respectively (Ready et al 2020).
- The Phase II STIMULI (NCT02046733) study investigated the efficacy and tolerability of standard treatment (chemotherapy and radiotherapy) alone compared with standard treatment followed by nivolumab and ipilimumab in patients with LS-SCLC. Results presented in 2020 indicated that there is no difference in PFS with an HR of 1.02 (95% CI: 0.66, 1.58; p = 0.93) in patients who received nivolumab and ipilimumab after standard treatment versus observation, with a median PFS of 10.7 months vs 14.5 months. There was also no difference in OS, although OS data are immature (HR 1.06, 95% CI: 0.61, 1.86; p = 0.83). Grade ≥ 3 AEs were reported for 62% of patients in the nivolumab and ipilimumab treatment arm vs 25% in the observation arm. Median time on active treatment was 1.7 months and the rate of discontinuations due to AEs was 55%. It was interpreted that the short duration of treatment due to the high rate of discontinuations may have impacted efficacy (Peters et al 2020).

The accumulated evidence from comparative trials suggests that the role of CTLA-4 inhibition in combination with PD-1/PD-L1 inhibition remains ambiguous but not conclusive and that efficacy gains through the addition of CTLA4-inhibition to PD-L1 blockade may be limited. However, monthly blinded review of safety data from ADRIATIC has not detected a safety signal, hence continued evaluation of this combination therapy as a secondary objective remains warranted.

In view of the updated data, the sponsor has reconsidered the study hypothesis and modified the study design accordingly in the Version 4 amendment:

- OS for the comparison of durvalumab monotherapy versus placebo has been added to the primary endpoint, ie, the study now has dual primary endpoints of PFS and OS for the comparison of durvalumab monotherapy versus placebo; the comparison of durvalumab plus tremelimumab versus placebo in terms of PFS and OS are now secondary endpoints (Section 3).
- Due to revision of the anticipated treatment effects on PFS and OS, the total sample size for the study has been increased from 600 to approximately 724 patients: the durvalumab monotherapy and placebo groups have both been increased to approximately 262 patients and the durvalumab plus tremelimumab combination treatment group has remained unchanged (approximately 200 patients).

The following aspects of study design are also impacted:

- As the number of patients in the durvalumab plus tremelimumab group is unchanged, once 600 patients have been randomized, randomization will continue 1:1 in the durvalumab monotherapy and placebo groups.
- Once 600 patients have been randomized, no further PK or ADA samples relevant to tremelimumab are required.
- Enrolment in China may continue after global enrolment is closed to allow inclusion of a total of approximately 108 patients.
- Several statistical sections have been updated to describe changes to the null hypotheses for the efficacy endpoints, the sample size determination, timing of the interim and final analyses, clarification of patients included in the analyses of the combination analysis set, the calculation or derivation of efficacy variables, the analyses of PFS, OS, and DoR, the description of methods for multiplicity control, and the updated details of the interim analyses of OS and their anticipated timing.
- The benefit-risk assessment has been updated for durvalumab and overall.

2.2 Background

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

2.2.1 Immunotherapies

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

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T lymphocyte (T-cell) activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). 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 PD1, 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 overexpressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells, leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous antitumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and cluster of differentiation (CD)80 receptors expressed on immune cells (ICs). 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 (MOA) is different from direct agonism of a stimulatory receptor such as CD28.

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

Pre-clinical 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 US Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell NSCLC, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD1 on T cells and CD80 (B7.1) on ICs. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The MOA for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (IFN-γ). 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 PDL1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Sections 4.3.1 and 8.3.12. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

2.2.3 Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and IFN-γ) from human T cells, peripheral blood mononuclear cells, and whole blood (Tarhini and Kirkwood 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

Details on the safety profile of tremelimumab monotherapy are summarized in Section 2.3.2.3. Refer to the current tremelimumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

2.2.4 Durvalumab in combination with tremelimumab

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant, targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012); therefore, AstraZeneca is also investigating the use of durvalumab and tremelimumab combination therapy for the treatment of cancer. In view of recent trial results, this will be undertaken as a secondary objective (see Section 2.1.3).

To date, more than 3000 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab and tremelimumab combination therapy are summarized in Sections 4.3.1 and 2.3.2.4. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

2.3 Benefit/risk assessment

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

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

2.3.1 Potential benefits

2.3.1.1 Durvalumab

Durvalumab monotherapy was evaluated in an SCLC cohort expansion of Study 1108 (NCT01693562). A total of 21 patients with pre-treated ES-SCLC were enrolled; the ORR was 9.5%, median PFS was 1.5 months, OS was 4.8 months (95% CI: 1.3, 10.8), and the 1-year survival rate was 27.6% (95% CI: 10.2%, 48.4%) with a median follow-up of 36.4 months (Goldman et al 2018).

The PACIFIC study (D4191C00001 [NCT02125461]) compared sequential treatment with durvalumab versus placebo in patients with locally advanced, unresectable, Stage III NSCLC whose disease had not progressed following platinum-based chemotherapy concurrent with radiotherapy. The results of the PACIFIC study demonstrated that durvalumab as consolidation treatment after definitive CRT provides statistically significant prolongation of PFS, which translates to a 48% reduction of risk of relapse. The median PFS from randomization was 16.8 months (95% CI: 13.0, 18.1 months) with durvalumab versus 5.6 months (95% CI: 4.6, 7.8 months) with placebo (HR 0.52; 95% CI: 0.42, 0.65; p <0.0001) (Antonia et al 2017). Subsequently the study also demonstrated statistical significant improvement in OS with HR of 0.68; 99.73% CI, 0.47 to 0.997, p=0.00251 (Antonia et al 2018).

The Phase III CASPIAN study (D419QC00001 [NCT03043872]) investigated durvalumab as part of combination therapy in the first-line ES-SCLC setting. The study demonstrated that the addition of durvalumab to EP chemotherapy significantly improved median OS from 10.3 to

13.0 months (HR 0.73, 95% CI: 0.59, 0.91; p = 0.047). In addition, in the durvalumab plus EP treatment group, 34% (95% CI: 26.9, 41.0) of patients were alive at 18 months compared with 25% (95% CI: 18.4, 31.6) of patients in the EP treatment group (Paz-Ares et al 2019). This confirmed the role of durvalumab in addition to standard of care chemotherapy, followed by ongoing durvalumab treatment in the first line ES-SCLC setting. Final analysis confirmed that the improvement in OS was sustained over 2 years' follow-up, with HR of 0.75 (Paz-Ares et al 2020).

2.3.1.2 Durvalumab in combination with tremelimumab

The efficacy of durvalumab and tremelimumab combination therapy was initially evaluated in an ongoing dose escalation and dose expansion study in patients with NSCLC (Study D4190C00006). As of 15 April 2015, 63 patients with at least 16 weeks of follow-up were evaluable for response across various durvalumab + tremelimumab dose regimens. Of these, 17 patients (27%) had a best objective response (BoR) of PR, 14 patients (22%) had a BoR of SD, 22 patients (35%) had PD, and 10 patients (16%) were Not Evaluable (NE). The ORR (confirmed and unconfirmed CR or PR) was 27%, and the disease control rate (CR, PR, or SD) was 49% as assessed by RECIST 1.1 (Eisenhauer et al 2009). In the 20-mg/kg durvalumab and 1-mg/kg tremelimumab q4w cohort, a total of 5 of 11 patients were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with PR, 1 patient (20%) with SD, and 1 patient (20%) with PD.

Durvalumab in combination with tremelimumab was evaluated in 30 patients with heavily pre-treated ES-SCLC in Study 10 (NCT02261220): the ORR was 13.3%, the median PFS was 1.8 months, the median OS was 7.9 months (95% CI: 3.2, NR), and the 1-year survival rate was 41.7% (95% CI: 23.3%, 59.2%) (Cho et al 2018).

2.3.2 Overall risks

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

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and that may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal (GI) 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 (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, encephalitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g. Guillain Barre syndrome, myasthenia gravis).

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

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

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

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

2.3.2.2 Durvalumab after completion of CRT

In the PACIFIC study (D4191C00001 [NCT02125461]), durvalumab treatment in patients with locally advanced, unresectable Stage III NSCLC who had recently completed CRT demonstrated a well-tolerated and manageable safety profile that was consistent with the established safety profile to date, with the exception of the events of pneumonitis/radiation pneumonitis (Antonia et al 2017, Antonia et al 2018). AEs were reported in 96.8% of patients who received durvalumab and 94.9% who received placebo; Grade 3 or 4 AEs were reported in 30.5% of patients who received durvalumab and 26.1% who received placebo. The most frequently reported Grade 3 or 4 AE was pneumonia (4.4% and 3.8%, respectively). SAEs were reported in 28.6% and 22.6% of patients, respectively, and deaths due to AEs occurred in 4.4% and 6.0% of patients, respectively. Pneumonitis and radiation pneumonitis were notable events in multiple AE categories. There was a numerical increase in these events in the durvalumab group over placebo (32.8% vs 23.5%, respectively, patients with pneumonitis or radiation pneumonitis of any grade), but most of these events were low grade and manageable. Grade 3 or 4 pneumonitis was reported in 3.4% and 2.1% of patients in the durvalumab and placebo groups, respectively. Clinically important CTCAE Grade 3 and above events were infrequent and balanced between the 2 groups. In addition to pneumonitis, the other adverse events of special interest (AESIs) and immune-mediated adverse events (imAEs) reported in the study were typical of the PD-1/PD-L1 class of immunotherapies and were generally manageable and/or reversible with appropriate treatment guidelines, which included the use of steroids or endocrine therapy, withholding durvalumab until the event resolved, or permanent discontinuation of durvalumab.

2.3.2.3 Tremelimumab

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhea, enterocolitis, and intestinal perforation); endocrine disorders (hypo- and

hyperthyroidism, hypophysitis, and adrenal insufficiency); skin effects (rash and pruritus); clinical manifestations of pancreatitis (elevations in lipase and amylase); hepatic events (including immune mediated hepatitis and liver enzyme elevations); pneumonitis and ILD; neurotoxicity (including encephalitis, encephalopathy, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome); thrombocytopenia, anemia, and neutropenia; infusion-related reactions and hypersensitivity/anaphylactic reactions; renal events (including tubulointerstitial nephritis/autoimmune nephritis and acute kidney injury, autoimmune arthritis, Sjogren's syndrome, giant cell temporal arteritis and ulcerative colitis); hyperglycemia and diabetes mellitus.

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

In monotherapy clinical studies, AEs reported at an incidence of ≥ 20% include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting and dyspnea. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab, and approximately 45% of patients experienced an SAE. Please see the current version of the IB for a detailed summary of monotherapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the tremelimumab program.

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

2.3.2.4 Durvalumab and tremelimumab

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study D4190C00006 in patients with NSCLC, is being studied in a number of other ongoing clinical studies in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20 mg/kg and a tremelimumab dose of 1 mg/kg) are similar to those for durvalumab monotherapy with additional risks of intestinal perforation and large intestinal perforation, which are unique risks for the durvalumab and tremelimumab combination.

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

In durvalumab + tremelimumab combination studies at the dose of durvalumab 20 mg/kg and tremelimumab 1 mg/kg, AEs reported at an incidence of ≥ 20% included events such as fatigue, diarrhea, nausea, decreased appetite, pruritus, dyspnea, constipation and anemia. Please see the current version of the durvalumab IB for a detailed summary of combination therapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program, including durvalumab in combination with tremelimumab.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug, and approximately 16% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study Investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB

2.3.3 Overall benefit/risk

There remains a significant unmet medical need for additional treatment options for patients with LS-SCLC. Despite favorable initial responses with the current standard of care in this aggressive disease, the majority of LS-SCLC patients relapse with a median OS of 15 to 30 months (Faivre-Finn et al 2017, Grønberg et al 2016, Seckl et al 2017). The poor prognosis reflects the limited treatment options available, highlighting the need for the development of newer therapeutic options.

The efficacy of treatment with checkpoint inhibitor immunotherapies in patients with SCLC has been observed in multiple recent studies, including studies with durvalumab alone or in combination with tremelimumab (eg, Study 1108 [NCT01693562] and Study 10 [NCT02261220]). These data suggested that durvalumab is active in SCLC. The safety profile of durvalumab with or without tremelimumab is consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class.

Results from the PACIFIC study (D4191C00001 [NCT02125461]) further support the efficacy and safety of durvalumab as consolidation treatment post CRT. The results from the CASPIAN (D419QC00001 [NCT03043872]) study demonstrated statistical significant and sustained improvement in OS in patients with ES-SCLC when durvalumab was added to platinum based chemotherapy.

As indicated in Section 2.1.3, emerging data suggest that the efficacy of PD-L1 inhibition in combination with CTLA-4 inhibition in ES-SCLC is ambiguous, but not conclusive. However, the available data do still warrant the inclusion of a combination treatment group of durvalumab plus tremelimumab in the present study; the efficacy analyses for this combination will be considered as secondary endpoints only.

The overall benefit/risk assessment continues to support the proposed study to evaluate the efficacy and safety of durvalumab monotherapy and durvalumab in combination with tremelimumab when given as consolidation therapy in patients with LS-SCLC.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Dual primary objectives:	Endpoints/variables:
To assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS	PFS using BICR assessments according to RECIST 1.1
To assess the efficacy of durvalumab monotherapy compared to placebo in terms of OS	OS

Secondary objectives:	Endpoints/variables:
To assess the efficacy of durvalumab and tremelimumab combination compared to placebo in terms of PFS and OS	PFS using BICR assessments according to RECIST 1.1 OS
To further assess the efficacy of durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo in terms of ORR, PFS18[a], PFS24[a], TTDM, OS24, OS36, and PFS2	ORR, PFS18[a], PFS24[a], and TTDM using BICR assessments according to RECIST 1.1 OS24 and OS36 PFS2
To assess the efficacy of durvalumab and tremelimumab combination therapy compared to durvalumab monotherapy in terms of PFS, OS, and ORR	PFS and ORR using BICR assessments according to RECIST 1.1 OS
To assess disease-related symptoms and HRQoL in patients treated with durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo using the EORTC QLQ-C30 v3 and QLQ-LC13	EORTC QLQ-C30 and QLQ-LC13: change in symptoms, functioning, and global health status/QoL
To assess the PK of durvalumab monotherapy and durvalumab and tremelimumab combination therapy	Concentration of durvalumab and tremelimumab in serum (such as peak concentration and trough; sparse sampling)
To investigate the immunogenicity of durvalumab monotherapy and durvalumab and tremelimumab combination therapy	Presence of ADA for durvalumab and tremelimumab (confirmatory results: positive or negative)
To investigate the relationship between PD-L1 expression and spatial distribution within the tumor microenvironment and clinical outcomes with durvalumab monotherapy or durvalumab and tremelimumab combination therapy	PD-L1 expression in tumor and/or immune cells (cutoff ≥ 1%) relative to response/efficacy outcomes (PFS, OS, and ORR). Other PD-L1 cutoffs may also be analyzed
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability profile of durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo in patients with LS-SCLC	AEs; laboratory findings including clinical chemistry, hematology, and urinalysis; physical examinations; vital signs including blood pressure and pulse; and electrocardiograms

Exploratory objectives:	Endpoints/variables:
To assess treatment-related side effects in patients treated with durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo using PRO-CTCAE	Change in the 9 treatment-related symptoms evaluated in this study
To assess the patients' overall impression of the severity of their cancer symptoms using PGIS	PGIS: Proportion of patients assessing current symptom severity
To describe and evaluate health resource use associated with durvalumab monotherapy and durvalumab and tremelimumab combination therapy and underlying disease	Health resource utilization measures including hospitalization, outpatient visits, or emergency department visits
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
To collect blood and tissue samples, or leverage residual samples, for analysis of peripheral and tumoral biomarkers (not applicable for China)	Exploratory biomarkers, which may include but are not limited to, DNA, RNA, and protein-based assessment within the tumor microenvironment and/or in the periphery. Evaluation of tumor-cell and/or immune-cell gene expression profiles, tumor or ctDNA-derived mutational analyses, PD-L1 expression, SCLC molecular subtypes, tumor-immune spatial profiling, etc., and association of biomarkers with response and/or resistance
To investigate the relationship between TMB measured in tumor and/or blood and efficacy outcomes with durvalumab monotherapy and durvalumab and tremelimumab combination therapy (TMB-related testing or analysis will not be conducted on samples from China)	TMB relative to response/efficacy outcomes (ORR, PFS, and OS)
To explore the relationship(s) between patient biomarker status and durvalumab PK exposure and clinical outcomes before and after treatment (TMB related testing or analysis will not be conducted on samples from China)	Biomarker status before and after treatment, durvalumab PK exposure, and relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate

To explore irRECIST as assessment methodologies for clinical benefit of durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo with assessment by BICR	PFS and ORR using BICR assessment according to irRECIST
To collect and store DNA from tissue and/or blood according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to IPs and/or susceptibility to disease (optional, not applicable for China)	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety, or response parameters observed in patients treated with durvalumab and/or susceptibility to disease
To investigate the effect of baseline colonic microbiome on response to treatment and the effect of treatment on the microbiome over time (applicable for EU and North America only)	Microbiome analysis of stool sample

[a] Progression-free survival at 18 and 24 months following randomization (PFS18 and PFS24) is equivalent to the proportion of patients alive and progression free at 18 and 24 months following randomization (APF18 and APF24), respectively.

ADA Anti-drug antibody; AE Adverse event; BICR Blinded Independent Central Review; CTCAE Common Terminology Criteria for Adverse Events; ctDNA Circulating tumor DNA; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5 dimension, 5-level health state utility index; HRQoL Health-related quality of life; IP Investigational product; irRECIST Immune-related Response Evaluation Criteria In Solid Tumors; LS-SCLC Limited stage small cell lung cancer; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomization; OS36 Proportion of patients alive at 36 months from randomization; PD-L1 Programmed death ligand 1; PFS Progression-free survival; PFS2 Time from randomization to second progression; PFS18 Progression-free survival at 18 months following randomization; PFS24 Progression-free survival at 24 months following randomization; PGIS Patient's Global Impression of Severity; PK Pharmacokinetic(s); PRO Patient-reported outcome; QLQ-C30 30-item core quality of life questionnaire; QLQ-LC13 Lung cancer module; QoL Quality of life; RECIST Response Evaluation Criteria In Solid Tumors; TMB Tumor mutational burden; TTDM Time to death or distant metastasis.

4. STUDY DESIGN

4.1 Overall design

This is a Phase III, randomized, double-blind, placebo-controlled, multi-center study assessing the efficacy and safety of durvalumab or durvalumab and tremelimumab combination therapy versus placebo as consolidation treatment in patients with LS-SCLC who have not progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy (cCRT).

In order to be eligible for this study, patients must have achieved CR, PR, or SD and have not progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy (cCRT). This cCRT treatment, and PCI treatment if received per local standard of care, must be completed within 1 to 42 days prior to randomization and the first dose of investigational product

(IP; ie, durvalumab, tremelimumab, or placebo) in this study. (Additional details are provided in Sections 5.1 and 5.2.) In addition, the baseline efficacy assessment must be performed post-CRT as part of the screening procedures within 42 days before randomization and the first dose of IP.

Approximately 965 patients will be recruited and screened in order to enroll and randomize approximately 724 patients to 1 of 3 treatment groups: durvalumab monotherapy (approximately 262 patients), placebo (approximately 262 patients), and durvalumab and tremelimumab combination therapy (approximately 200 patients). (See Section 6.1.2 for descriptions of the dosing regimens.) Randomization will be stratified by stage (I/II versus III) based on TNM classification and receipt of PCI (yes versus no). Patients will receive their assigned treatment until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurs first (See Section 7.1 for additional details on discontinuation of study treatment).

To ensure that there is no significant over recruitment beyond the planned 724 patients randomization target, the AstraZeneca Study Team will actively manage study enrolment. The AstraZeneca Study Team may close global study enrolment to all sites apart from sites in China at an appropriate time to ensure approximately 724 patients are randomized to the global study population. If necessary, recruitment of patients from sites in China will continue until approximately 108 patients (approximately 15%) are randomized. Enrolment of patients from sites in China will be actively managed by the AstraZeneca Study Team to ensure there is no significant over recruitment of patients from sites in China. Patients enrolled in China prior to the closure of global study enrolment will be included in both the Global Cohort and the China Cohort. Patients enrolled in China after global enrolment closure will only be analyzed in the China Cohort. If approximately 108 patients are enrolled in the global cohort, then the additional China Cohort will not be created.

For an overview of the study design, see Figure 1 Study design

, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered. For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific rationale for study design

4.2.1 Rationale for study endpoints (efficacy)

The primary aim of this study is to assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS and OS.

PFS may serve as a surrogate for OS when differences between treatment groups are of sufficient magnitude and are clinically important (FDA Guidance 2011, Foster et al 2015, Mauguen et al 2013, Pazdur 2008). In particular, PFS has shown a strong surrogacy for OS in first-line ES SCLC studies (Foster et al 2015). In this study PFS and OS will be dual primary endpoints for durvalumab monotherapy versus placebo.

The secondary efficacy endpoints will be examined to further evaluate the antitumor effect of durvalumab monotherapy versus placebo. The combination of durvalumab and tremelimumab will be investigated versus placebo as secondary analyses. Antitumor activity will be assessed based on BICR assessments according to RECIST 1.1 guidelines.

Sensitivity analyses will also be performed using study site Investigator's tumor data from all scans based on RECIST 1.1.

Response to immunotherapy may differ from typical responses observed with cytotoxic chemotherapy, including the following differences (per Wolchok et al 2009):

1. Response to immunotherapy may be delayed.

2. Response to immunotherapy may occur after PD by conventional criteria.

3. SD while on immunotherapy may be durable and represent clinical benefit.

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

4.2.2 Rationale for study endpoints (other secondary and exploratory endpoints)

Biological samples will be used to explore potential biomarkers in tumor, plasma, and/or serum, which may influence the progression of cancer (and associated clinical characteristics) and/or response to durvalumab with or without tremelimumab. Blood samples will be taken to allow for research into PK and immunogenicity of durvalumab and tremelimumab.

SCLC is characterized by its high mutational burden. The exploratory analysis from CheckMate-032 [NCT01928394] have shown that, for patients treated with either nivolumab monotherapy or nivolumab plus ipilimumab, efficacy was enhanced among patients with a high tumor mutational burden (ie, high TMB). In the TMB high subgroup, the combination of nivolumab and ipilimumab appeared to provide greater clinical benefit compared with nivolumab monotherapy, with doubling 1-year survival rate (62.4% vs 35.2%, respectively; Hellmann et al 2018). To better understand the significance of this finding and any impact this may have on patients in the present study (ADRIATIC), we plan to assess tumor burden in both tumor and blood samples as secondary and exploratory endpoints (not applicable in China).

PD-L1 expression has also been shown to play a significant role in response to immunotherapy in late-stage NSCLC (Brody et al 2017, Reck et al 2016). Although such data remain sparse in SCLC, PD-L1 will also be evaluated as a potential predictive biomarker in this study.

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

4.2.3 Rationale for treatment duration

The median PFS for patients with LS-SCLC after cCRT is about 10 months, therefore continuation of treatment up to PD is justifiable. Treatment in this study will continue until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurs first (see Section 7.1). This guidance was supported by data from the CHECKMATE-153 study presented at the 2017 European Society for Medical Oncology Congress, which indicated that patients treated with nivolumab (an anti-PD-1 agent) until PD showed superior PFS when compared to treatment with nivolumab with a 1-year fixed duration (HR: 0.43; 95% CI: 0.25, 0.76), a trend toward improved OS, and no new safety signals after 1 year of treatment (Spigel et al 2017). In the PACIFIC study, the treatment duration was limited to 12 months; however, the safety data from the PACIFIC study (D4191C00001; NCT02125461) suggest that the risk of developing immune-modulated toxicities remains very low and that the cumulative probability of onset of new events was also very low beyond 6 months of treatment. Treatment will be discontinued following clinical progression or RECIST 1.1-defined radiological PD to allow the patient the opportunity to utilize an alternate anticancer treatment. Patients that do not experience disease progression will be treated for a maximum of 24 months, unless there is intolerable toxicity or withdrawal of consent, or another discontinuation criterion is met.

4.3 Justification for dose

4.3.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 (NCT01693562) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 (NCT01693562) with doses ranging from 0.1 to 10 mg/kg 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 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_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of anti-drug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

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

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.

4.3.1.1 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (NCT01693562; 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 (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-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 WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40 to 120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase I through Phase III (N=654; doses= 0.01 to 15 mg/kg q4w or q90d; metastatic melanoma) (Wang et al 2014). Population PK modeling indicated a minor impact of body WT on the PK of tremelimumab (coefficient of ≤0.5). The WT-based (1 mg/kg q4w) and fixed dosing (75 mg/kg q4w; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median, and 95th percentiles) using population PK model in a simulated population of 1000 patients with body WT distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and

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

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to 20 mg/kg q4w) and a fixed dose of 75 mg q4w tremelimumab (equivalent to 1 mg/kg q4w) is included in the current study.

4.3.2 Durvalumab and tremelimumab dose and treatment regimen justification

4.3.2.1 Durvalumab and tremelimumab combination therapy dose rationale

The durvalumab and tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetics/pharmacodynamics data

Study D4190C00006 included dose cohorts with both a q4w and an every 2 weeks (q2w) schedule of durvalumab in combination with a q4w schedule of tremelimumab. The q4w schedule was included to align with the q4w dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the serum drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed preclinically and in line with that seen in the first-time-in-human, single agent study (CD-ON-MEDI4736-1108 [NCT01693562]) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum serum concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing pre-clinical and clinical data.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented pharmacodynamic activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab, including both the 15 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Clinical data

In Study D4190C00006, various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to

20 mg/kg. Tremelimumab was given on a q4w schedule, while durvalumab was explored in both q4w and q2w schedules, with the goal of identifying the dose combination that best optimizes the risk:benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of AEs, including discontinuations due to AEs, SAEs, and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade ≥3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis, colitis, and other immune-mediated events were more commonly seen in cohorts using either 3 mg/kg or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3- or 10-mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab.

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities were reported in this cohort.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations.

Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information on the durvalumab and tremelimumab combination, including safety, efficacy, and PK.

4.3.2.2 Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up (Schadendorf et al 2013).

Data from Study D4190C00006 also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab q4w or q2w. (For further information on PK observations in Study D4190C00006, see the current durvalumab IB).

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

The durvalumab and tremelimumab combination regimen will be administered for 4 doses q4w followed by durvalumab monotherapy q4w until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurs first, or unless other specific discontinuation criteria are met.

4.4 End of study definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines 2 completion dates:

- Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

- Study Completion Date – is defined as the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit (including OS determination).

The study may be stopped if, in the judgment of AstraZeneca, study participants are placed at undue risk because of clinically significant findings.

Should the study meet the primary endpoint at any of the prescribed interim analyses, additional data cuts may be needed per local health authority requirements.

See Section 6.6 for details on management following the final DCO, as well as following study completion.

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 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 informed consent. "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled or randomized patients, see Section 6.2.2.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria apply:

Informed consent

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

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

3. Optional provision of signed and dated written genetic informed consent prior to collection of sample for genetic analysis (Not applicable for China)

The ICF process is described in Appendix A 3.

Age

4. ≥18 years at the time of screening. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.

Type of patient and disease characteristics

5. Histologically or cytologically documented limited-stage SCLC (Stage I-III SCLC [T any, N any, M0] according to the American Joint Committee on Cancer Staging Manual [AJCC Cancer Staging Manual, 8th Edition] or the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology 2016]), ie, patients whose disease can be encompassed within a radical radiation portal. Patients who are Stage I or II must be medically inoperable as determined by investigator.

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

7. Received an appropriate first line concurrent chemoradiotherapy regimen as defined below, unless after consultation with the global study medical team an alternative is acceptable

   - Received 4 cycles of platinum-based chemotherapy concurrent with RT, which must be completed within 1 to 42 days prior to randomization and the first dose of IP.
   - The chemotherapy regimen must contain platinum and IV etoposide, administered as per local standard-of-care regimens.
   - Received a total dose of radiation of 60 to 66 Gy over 6 weeks for standard QD radiation schedules or 45 Gy over 3 weeks for hyperfractionated BID radiation schedules. Sites are encouraged to adhere to mean organ radiation dosing as follows:
     - Mean lung dose <20 Gy and/or V20 <35%
     - Heart V50 <25%
   - Radiotherapy must have commenced no later than the end of Cycle 2 of chemotherapy.
   - Receipt of 3 cycles of platinum-based chemotherapy concurrent with RT will be permitted if the patient has achieved disease control and in the opinion of the Investigator, no additional benefit will be expected with additional cycle of chemotherapy.

8. Patients must have achieved CR, PR, or SD and not have progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy.

9. PCI may be delivered at the discretion of investigator and local standard of care, and must be conducted after the end of cCRT and completed between 1 to 42 days to first dose of IP.

10. Tumor sample requirements:

    – Mandatory availability of tumor sample, which may include a core needle biopsy, newly cut unstained slides, or fine needle aspirate (FNA) cell block samples. (refer to Section 8.8 for details on accepted tumor samples and order of preference). Tissue sample should be submitted before or within 60 days of randomization. However, patients may be enrolled into the study before the pre-treatment tumor tissue sample is submitted.

    – A newly acquired tumor biopsy (taken following completion of chemoradiotherapy) is optional, provided that a biopsy procedure is technically feasible, and the procedure is not associated with unacceptable clinical risk.

11. Adequate organ and marrow function (independent of transfusion, infusion, or growth factor support for at least 14 days prior to obtaining screening labs), defined as below:

    – Hemoglobin ≥9.0 g/dL

    – Absolute neutrophil count $\geq 1.5 \times 10^9$ /L

    – Platelet count $\geq 100 \times 10^9$/L

    – Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia [predominantly unconjugated bilirubin] in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician.

    – ALT and AST ≤2.5 × ULN

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

      Males:

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

      Females:

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

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

Weight

13. Body weight >30 kg

Sex

14. Male or female

5.2 Exclusion criteria

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

Medical conditions

1. Mixed SCLC and NSCLC histology

2. Extensive-stage SCLC

3. Any history of Grade ≥2 pneumonitis

4. History of allogeneic organ transplantation

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

   – 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

6. 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 GI 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

7. 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

8. History of leptomeningeal carcinomatosis

9. History of active primary immunodeficiency

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

11. Any unresolved toxicity NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 from previous CRT with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

    – Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

    – Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.

12. Brain metastases or spinal cord compression. All patients will have an MRI (preferred) or CT, preferably with IV contrast of the brain, prior to study entry.

13. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart)

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

15. Patients who received sequential CRT for LS-SCLC (no overlap of RT with chemotherapy)

16. Patients whose conditions have progressed while on concurrent CRT

Prior/concomitant therapy

17. Receipt of chemotherapy that exceeds 4 cycles in total. Chemotherapy regimens other than etoposide and platinum are not permitted.

18. Prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.

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

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

21. Major surgical procedure (as defined by the Investigator) within 42 days prior to the first dose of IP.

22. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. 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

23. Participation in another clinical study with an investigational product administered in the last 4 weeks

24. Previous IP assignment in the present study

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

26. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment group assignment.

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

Other exclusions

28. Female patients who are pregnant or breastfeeding and male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 3 months after the last dose of durvalumab monotherapy or 6 months after the last dose of durvalumab + tremelimumab combination therapy.

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

30. Genetics research study (optional, not applicable for China):

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

    – Previous allogeneic bone marrow transplant

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

5.3 Lifestyle restrictions

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

1. Female patient of child-bearing potential

    – Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized- male partner must use at least 1 **highly** effective method of contraception (Table 4) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy). Non-sterilized male partners of a female patient of childbearing potential must use a male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

    – Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy). Periodic abstinence, the rhythm method, and the

withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

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

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

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

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

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

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

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

[a] This is also considered a hormonal method
[b] Not approved for use in Japan

3. All patients: Patients should not donate blood or blood components while participating in this study and through 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy.

4. 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. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients may be rescreened a single time, but they may not be re-randomized.

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 serious adverse events (SAE).

6. STUDY TREATMENTS

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to durvalumab, tremelimumab, or placebo.

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca will supply durvalumab (MEDI4736) and tremelimumab. The 0.9% (w/v) saline or 5% (w/v) dextrose solution for the placebo will be supplied locally. See Table 5 for further details on the IPs.

Table 5 Study treatments

	Treatment 1	Treatment 2	Placebo
Study treatment name	Durvalumab (MEDI4736)	Tremelimumab	0.9% (w/v) saline solution or 5% (w/v) dextrose solution
Dosage formulation	500-mg vial solution for infusion after dilution, 50 mg/mL	400-mg or 25-mg vial solution for infusion after dilution, 20 mg/mL	Sterile solution of 0.9% (w/v) sodium chloride for injection or 5% (w/v) dextrose
Route of administration	IV	IV	IV
Dosing instructions	1500 mg IV q4w[a]	75 mg IV q4w for 4 doses[a]	Dosing to match durvalumab or tremelimumab
Packaging and labeling	Study treatment will be provided in 500-mg vials. Each vial will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.[b]	Study treatment will be provided in 400-mg or 25-mg vials. Each vial will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Sourced locally by site
Provider	AstraZeneca	AstraZeneca	Sourced locally by site

[a] If a patient's weight falls to ≤30 kg, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo q4w and 1 mg/kg of tremelimumab or placebo q4w, as applicable based on treatment assignment, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of 1500 mg durvalumab or placebo and 75 mg tremelimumab or placebo q4w, as applicable based on treatment assignment.

[b] 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.

IV Intravenous; qXw Every X weeks; w/v Weight/volume.

6.1.1.1 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The label-claim volume is 10 mL.

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

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product must be kept in the original packaging until use to prevent excessive light exposure.

Preparation of durvalumab (MEDI4736) doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration must 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 room temperatures, the total time must not exceed 24 hours.

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 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 durvalumab (MEDI4736) 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. **The IV bag should be covered with a translucent colored or opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel to maintain double-blind conditions.**

If patient 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 1 hour (±10 minutes), however, if there are interruptions, the total allowed time must 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 (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

6.1.1.2 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg or 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The label-claim volume is 20 mL for the 400-mg vial and 1.25 mL for the 25-mg vial.

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

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product must be kept in the original container until use to prevent excessive light exposure.

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab 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 tremelimumab vial to the start of administration must 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 room temperatures, the total time must not exceed 24 hours.

A dose of 75 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 tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 3.8 mL (ie, 75 mg; dose volume rounded to the nearest tenth mL) of tremelimumab to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. **The IV bag should be covered with a translucent colored or opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel to maintain double-blind conditions.**

If patient weight falls to ≤30 kg, weight-based dosing at 1 mg/kg will be administered using an IV bag size selected such that the final concentration is within 0.1 to 10 mg/mL.

Standard infusion time is 1 hour (±10 minutes), however, if there are interruptions, the total allowed infusion time must 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. The 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. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

6.1.1.3 Placebo

An IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose (approximately) matching the IV bag volume containing durvalumab or tremelimumab will be used for placebo. **The IV bag should be covered with a translucent colored or opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel to maintain double-blind conditions.**

If patient weight falls to ≤30 kg, weight-based dosing will be administered at 20 mg/kg for durvalumab placebo, using an IV bag size selected such that the final concentration is within 1 to 15 mg/mL, and at 1 mg/kg for tremelimumab placebo, using an IV bag size selected such that the final concentration is within 0.1 to 10 mg/mL.

Standard infusion time is 1 hour (±10 minutes), however, if there are interruptions, the total allowed infusion time must 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. The infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits, a new placebo dose must be prepared.

6.1.2 Dose and treatment regimens

In this double-blind study, patients will receive 1 of the following treatments, based on treatment group assignment:

- Durvalumab monotherapy: Durvalumab (1500 mg intravenous [IV]) q4w in combination with placebo (IV) q4w for 4 doses/cycles each, followed by durvalumab 1500 mg q4w. The first durvalumab monotherapy 1500 mg dose q4w will be 4 weeks after the final dose of durvalumab in combination with placebo.

- Placebo: Placebo (IV) q4w in combination with a second placebo (IV) q4w for 4 doses/cycles each, followed by a single placebo q4w. The first placebo monotherapy dose q4w will be 4 weeks after the final dose of the 2 placebo in combination.

- Durvalumab in combination with tremelimumab: Durvalumab (1500 mg IV) q4w in combination with tremelimumab (75 mg IV) q4w for 4 doses/cycles each, followed by

durvalumab 1500 mg q4w. The first durvalumab monotherapy 1500 mg dose q4w will be 4 weeks after the final dose of durvalumab in combination with tremelimumab.

Initially, all patients will be randomized in a 1:1:1 ratio to the 3 treatment groups. However, once 600 patients have been randomized, subsequent patients will be randomized 1:1 to either durvalumab monotherapy or placebo. Patients randomized to durvalumab monotherapy or placebo after completion of randomization to the durvalumab and tremelimumab combination group, will receive only 1 infusion of durvalumab or placebo.

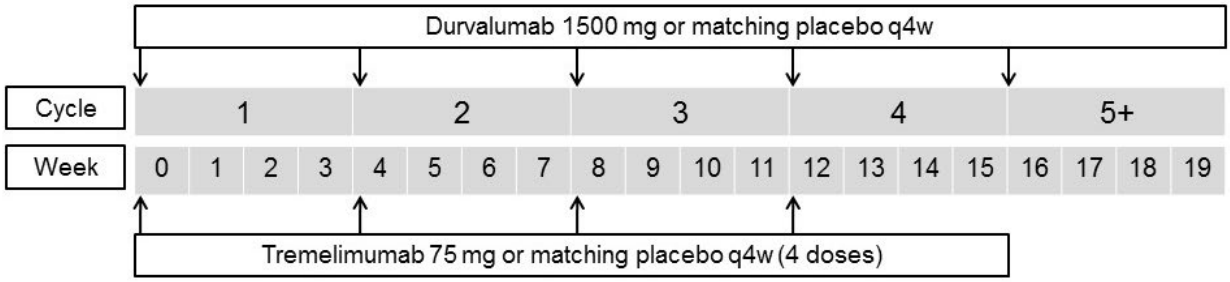
During combination treatment, tremelimumab or placebo will be administered first; the durvalumab or placebo infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab or placebo infusion. If there are no clinically significant infusion reactions with the first cycle, and at the discretion of the Investigator, then for all other cycles, the durvalumab or placebo can be given immediately after the tremelimumab or placebo infusion has finished.

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

Treatment in all treatment groups will continue until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurs first.

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 q4w and 1 mg/kg tremelimumab or placebo q4w after consultation between the 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 plus tremelimumab 75 mg or placebo q4w.

Figure 2 Dosing schedule



6.1.3 Duration of treatment

All treatment will be administered beginning on Day 1 until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurs first.

Post final data cut-off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurs first. For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

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

6.1.4 Storage

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

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

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

IPs will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The unblinded pharmacist is responsible for managing the IPs from receipt by the study site until the return of all unused IP to AstraZeneca. AstraZeneca will provide the study documents "Procedures for drug accountability" and 'Procedures for drug storage," which describe the specific requirements.

6.2 Measures to minimize bias: randomization and blinding

6.2.1 Patient enrollment and randomization

Patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups: durvalumab monotherapy, placebo, or durvalumab and tremelimumab combination therapy. Initially, all patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups: durvalumab monotherapy, placebo, or durvalumab and tremelimumab combination therapy. However, once 600 patients have been

randomized, subsequent patients will be randomized 1:1 to either durvalumab monotherapy or placebo. Randomization will be stratified by TNM stage (I/II versus III) and receipt of PCI (yes versus no).

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

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.

At screening/baseline (Days -42 to -1), the Investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained after completion of chemoradiotherapy and within 42 days of randomization and the first dose of IP. For patients with a single target lesion (TL), if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.
- Obtain a unique 7-digit enrollment number (E-code), through the IVRS/IWRS in the following format [redacted] This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
- Determine patient eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional, not applicable for China).

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

- Obtain a unique randomization number via the IVRS/IWRS. Numbers will start at [redacted] and will be assigned [redacted] by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 3 treatment groups.

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

Patients will begin treatment on Day 1. Every effort should be made to minimize the time between randomization and starting treatment. Treatment can start up to 3 working days after randomization, as long as first dose of IP is still within 1 to 42 days after the completion of CRT. 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 randomized 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 from the study.

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

6.2.3 Methods for assigning treatment groups

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

Patients will be identified to the IVRS/IWRS per country regulations. Randomization codes will be assigned [redacted], within each stratum, as patients become eligible for randomization. The IVRS/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 IVRS/IWRS will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS. Investigators will remain blinded to each patient's assigned study treatment throughout the course of the study. To maintain this blind, an otherwise uninvolved 3rd party (ie, the unblinded pharmacist) will be unblinded and responsible for the reconstitution and dispensation of all study treatment and will endeavor to ensure that there are no differences in time taken to dispense following randomization. The IV bag should be covered with a translucent colored or opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel to maintain double-blind conditions.

The IVRS/IWRS will be programmed with blind-breaking instructions. 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 case report form (CRF) (electronic or paper), as applicable. Study unblinding should not occur until database lock 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 all IPs should be recorded in the appropriate sections of the eCRF.

Any change from the dosing schedule, dose delays/interruptions, and dose discontinuations should be recorded in 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. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.4 Concomitant therapy

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

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

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

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

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

In addition, PCI will not be permitted during the study. If PCI is indicated, it must be conducted after completion of cCRT and protocol mandated brain imaging to confirm the absence of cerebral metastases, and completed within 1 to 42 days prior to randomization and the first dose of IP.

Table 6 Prohibited concomitant medications

Prohibited medication/class of drug:	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.
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-α blockers	Should not be given concomitantly or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab or placebo during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab or placebo (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab or placebo (saline or dextrose solution). Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

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

AE Adverse event; EGFR Epidermal growth factor receptor; IP Investigational product; mAb Monoclonal antibody; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1; TKI Tyrosine kinase inhibitor.

Table 7 Supportive medications

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

6.4.1 Other concomitant treatment

Medication other than that described above that 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 CRF.

6.4.2 Durvalumab drug-drug interactions

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

6.4.3 Rescue medication

As a result of imAEs that could potentially be experienced by patients on durvalumab ± tremelimumab, steroids and other immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into the category of other

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 administered to all applicable patients, regardless of blinded treatment, by the unblinded pharmacist and stored according to the labeled storage conditions, with temperature excursions reported accordingly by the unblinded pharmacist. If required for use as a result of an imAE, then the IVRS/IWRS will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the time. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS.

6.5 Dose modification

Dose delays are permitted for immuno-oncology therapy (see Dosing Modification and Toxicity Management Guidelines). However, **dose reduction is not permitted**.

6.6 Continued Access to Study Intervention After the End of the Study

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

After the final DCO for this study, AstraZeneca will continue to supply durvalumab to participants who were randomised to receive durvalumab monotherapy or durvalumab and tremelimumab combination therapy until PD occurs as judged by the investigator, or until completion of a participant's current 24-month treatment period, or until meeting any other discontinuation criteria, as defined in Section 7.1. Participants should be followed according to the institution's standard of care assessments. No further data collection is required, except for reporting of SAEs.

Participants who were randomised to receive other study interventions (ie, placebo), or who discontinue from the study, should continue appropriate treatment at the discretion of the investigator.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

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

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study

(eg, for safety and survival follow up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).

- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5)
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Clinical progression or RECIST 1.1-defined radiological progression (refer to Appendix F)

7.1.1 Procedures for discontinuation of study treatment

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

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

Patients who permanently discontinue IP for reasons other than RECIST 1.1-defined radiological progression should continue to have RECIST scans performed q8w ±1w for the first 72 weeks (relative to the date of randomization), followed by q12w ±1w until up to 96 weeks relative to the date of randomization, and then q24w ±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological PD plus one follow-up scan or death (whichever comes first) as defined in the SoAs.

If a patient is discontinued for RECIST 1.1-defined radiological progression, then the patient should have 1 follow-up scan performed no earlier than 4 weeks later and no later than the next scheduled imaging visit. The follow-up scan is evaluated using RECIST 1.1 criteria described in Appendix F.

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

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

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

7.2 Lost to follow-up

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

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

- Lost to follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

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

7.3 Withdrawal from the study

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. If previous received chemotherapy and/or radiotherapy differs from those specified in the eligibility criteria, please discuss with the study team.

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

Procedures conducted as part of the patient's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed post completion of chemoradiotherapy and up to 42 days before randomization and first dose of study drug.

8.1 Efficacy assessments

This study will evaluate dual primary endpoints of PFS and OS for durvalumab monotherapy versus placebo. Efficacy assessments of PFS, objective response rate (ORR), PFS at 18 months and at 24 months from randomization (PFS18 and PFS24), and time to death or distant metastasis (TTDM) will be derived (by AstraZeneca) using BICR RECIST 1.1 assessments. In addition, OS, OS at 24 months and at 36 months from randomization (OS24 and OS36), and time from randomization to second progression (PFS2) will be evaluated.

Tumor assessments utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands), collected during screening/baseline and at regular (follow-up) intervals during the study. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Any other

areas of disease involvement (eg, pelvis, brain) should be additionally imaged based on the signs and symptoms of individual patients. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoAs). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Scanning/tumor assessments continue throughout the study until RECIST 1.1-defined radiological progression plus one follow-up scan (if clinically feasible). Scanning/tumor assessments up to progression may continue after the PFS analysis and up to the end of the study.

The RECIST 1.1 guidelines (Appendix F) provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed post-CRT within 42 days before randomization and start of study treatment. The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and Non-Target Lesions (NTLs). On study images are evaluated for TLs and NTLs chosen at baseline and for New Lesions (NLs) when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall time point responses (CR, PR, SD, PD, or Not Evaluable [NE]).

A follow-up scan is to be collected after the initial RECIST 1.1-defined PD, no earlier than 4 weeks later and no later than the next scheduled imaging visit. The follow-up scan is evaluated using RECIST 1.1 criteria described in Appendix F.

8.1.1 Central reading of scans

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization (CRO) for 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. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based, in part, upon the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter (also referred to as “Imaging Charter”).

8.1.2 Survival assessments

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

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

8.1.3 Clinical outcome assessments

A clinical outcome assessment is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. PRO is one type of clinical outcome assessment. PRO is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating the effectiveness of treatments in clinical studies and will aid in understanding of the benefit/risk evaluation. The following PRO instruments will be administered in this study: EORTC QLQ-C30 v3 (core questionnaire), EORTC QLQ-LC13 (lung cancer module), PRO-CTCAE, Patient's Global Impression of Severity (PGIS), and 5-level health state utility index (EQ-5D-5L) (see Appendix H).

8.1.3.1 EORTC QLQ-C30 and QLQ-LC13

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures symptoms, functioning, and global health status/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/vomiting); a 2-item global QoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

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

8.1.3.2 PRO-CTCAE

The PRO-CTCAE will only be administered in countries where a linguistically validated version exists.

PRO-CTCAE was developed by the National Cancer Institute (NCI) in recognition that collecting treatment-related symptom data directly from patients can improve accuracy and efficiency. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Basch et al 2009, Litwin et al 1998, Sprangers and Aaronson 1992). To date, 81 symptoms of the CTCAE (version 4) have been identified to be amenable to patient reporting, but not all items are administered in any clinical study. Response options vary in frequency, severity, and interference with usual activities. For this study, 9 symptoms are considered relevant for this cancer treatment (see Appendix H).

8.1.3.3 PGIS

The PGIS item is included to assess how a patient perceives his/her overall current severity of cancer symptoms. Patients will choose from response options from "no symptoms" to "very severe."

8.1.3.4 EQ-5D-5L

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

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

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

8.1.3.5 Administration of electronic patient-reported outcome questionnaires

Other than at the baseline visit where assessments are completed at site, patients will complete the PRO assessments outside the site by using a handheld electronic device (electronic patient-reported outcome [ePRO]). The following best-practice guidelines should be followed when collecting PRO data via an electronic device:

- Site staff should explain the value and relevance of hearing directly from the patients how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patient has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- Remind patients that there are no right or wrong answers; avoid bias by not clarifying items.
- Train the patients on how to use the ePRO device using the materials and training provided by the ePRO vendor. Also, provide guidance on whom to call if there are problems with the device by providing the patient information pamphlet provided by the ePRO vendor.
- It is vital that the ePRO reporting is initiated prior to dosing and prior to any other assessments while the patients are still in the clinic on Cycle 1 Day 1, as specified in the study plan, to capture the effect of study treatment.

- If the patient is unable to read (eg, is blind or illiterate), that patient is exempted from completing the ePROs and may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff.

- All PRO questionnaires are to be completed using the ePRO device. If the device is not yet at the site or there is a technical problem, the study team may grant use of a paper backup using electronic screenshots for baseline only. Study team approval must be obtained prior to the use of a paper backup using electronic screenshots at baseline. If not, the use of a paper backup will be considered a protocol deviation.

In order to minimize missing data, compliance must be checked frequently to identify problems early. If compliance drops below 90%, a check-in call from the site to ask the patient if he/she has any difficulties is highly recommended.

8.2 Safety assessments

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

8.2.1 Clinical safety laboratory assessments

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

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 8 (clinical chemistry), Table 9 (hematology), and Table 10 (urinalysis).

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

The following laboratory variables will be measured:

Table 8 Clinical chemistry

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

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

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; TSH Thyroid-stimulating hormone.

Table 9 Hematology

Absolute neutrophil count[a]	Absolute lymphocyte count[a]
Hemoglobin	Platelet count
Total white cell count	Activated partial thromboplastin time[b]
International normalized ratio[b]	

[a] Can be recorded as absolute counts or as percentages.
[b] For coagulation parameters, activated partial thromboplastin time 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 10 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis should be done at screening and then as clinically indicated.
Note: Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red and white blood cells.

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

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

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

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

8.2.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

8.2.3 Vital signs

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

First infusion day

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

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

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

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

Subsequent infusions

BP, pulse, respiration rate and other vital signs should be measured and collected/recorded in eCRF prior to the start of each infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion]). Patients should be carefully monitored, and BP and other vital signs should be measured during and after infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

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

8.2.4 Electrocardiograms

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

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

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

8.2.5 WHO/ECOG performance status

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

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

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

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

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

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

5. Dead

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

8.2.6 Other safety assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

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

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan

(ii) Tumor markers: Particular tumor markers which are related to disease progression.

(iii) Additional Clinical chemistry: C-reactive protein, lactate dehydrogenase (LDH)

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.

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

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

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 8.4.1. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

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

8.3.3 Follow-up of AEs and SAEs

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

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

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

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

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)

- Causality assessment in relation to other medication, as explained in Section 8.3.5
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.5 Causality collection

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

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

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

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory 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 term, 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 that is unequivocally due to disease progression should not be reported as an AE/SAE.

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

8.3.8 Hy's law

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

8.3.9 Disease progression

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

8.3.10 New cancers

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

8.3.11 Deaths

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

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

Deaths occurring after the protocol defined safety follow-up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death

occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to study drug, then it should also be reported as an SAE.

8.3.12 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

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

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

AESI/imAEs observed with anti PD-L/PD-1 agents such as durvalumab and durvalumab in combination with tremelimumab include:

- Pneumonitis,
- Hepatitis,
- Diarrhea/colitis,
- Intestinal perforation,
- Endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus),
- Nephritis,
- Rash/dermatitis,
- Myocarditis,
- Myositis/polymyositis,
- Pancreatitis

- Rare/less frequent imAEs (including, but not limited to hematological events, neuromuscular toxicities [such as myasthenia gravis and Guillain-Barre syndrome], non-infectious encephalitis, non-infectious meningitis, pericarditis, rheumatological events, sarcoidosis, skin events, uveitis [and other events involving the eye], and vasculitis).

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 and tremelimumab IBs. 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). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

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

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). All data after the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

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

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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 electronic data capture system, an automated email alert is sent to the designated AstraZeneca representative.

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

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

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug

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

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

8.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product 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 1day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

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

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy, should if possible, be followed up and documented.

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

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

8.4.3 Overdose

8.4.3.1 Durvalumab or tremelimumab

Use of durvalumab or tremelimumab 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 or tremelimumab, 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 study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately or **not later than 24 hours** of when he or she becomes aware of it.

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

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

8.4.4 Medication error, Drug abuse, Drug misuse

8.4.4.1 Timelines

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.1) and **within 30 days** for all other events.

8.4.4.2 Medication error

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

The full definition and examples of Medication Error can be found in Appendix B 8.

8.4.4.3 Drug abuse

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

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

8.4.4.4 Drug misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs/study intervention(s) or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of Drug Misuse can be found in Appendix B 8.

8.4.5 Management of IP-related toxicities

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).

- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted

- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE, Version 4.03.

8.4.5.1 Specific toxicity management and dose modification information

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 inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these two compounds, these guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (i.e. 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 other cancer treatment. The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" 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 and tremelimumab should be permanently discontinued (see Section 7.1of this protocol and the Dosing Modification and Toxicity Management Guidelines). Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting Investigator.

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

8.5 Pharmacokinetics

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5.1 Collection of PK samples

Blood samples for determination of durvalumab and tremelimumab concentration in serum will be obtained according to the SoAs.

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

8.5.2 Collection of ADA samples

The presence of ADA will be assessed in serum samples taken according to the SoAs.

Samples will be measured for the presence of ADA and neutralizing antibody (nAb) for both durvalumab and tremelimumab using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naive validation samples will be employed. In addition, the presence of nAb will be tested for all ADA-positive samples using a validated assay.

8.5.3 Storage and destruction of pharmacokinetic/ADA samples

PK and ADA samples will be destroyed within 5 years of CSR finalization . In China, samples will be destroyed after the finalization of the Bioanalytical reports.

PK and ADA samples may be disposed of, destroyed, or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the CSR.

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

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to the AstraZeneca-designated Biobank) – not applicable for China.

8.6 Pharmacodynamics

Pharmacodynamic samples will not be taken during the study.

8.7 Genetics (Not applicable for China)

8.7.1 Optional exploratory genetic sample (Not applicable for China)

If the patient agrees to participate in the optional genetic research study, a blood sample will be collected. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

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

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

8.7.2 Storage and destruction of genetic samples (Not applicable for China)

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR 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.

8.8 Biomarkers

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

At Screening, a pre-study-treatment tumor sample must be available. The following tumor samples will be accepted in the following order of preference;

1. An unstained, archived tumor tissue block (formalin-fixed paraffin-embedded). Not applicable for patients recruited in China, where only tumor tissue slides will be collected (see point 2 below).
2. Newly cut, unstained slides with tissue sections 4-5 µm thick (as described in the Laboratory Manual). A minimum of 15 unstained slides are required for analysis of PD-L1 and TMB biomarkers. Investigators are strongly encouraged to provide 15 unstained slides, but smaller numbers of slides will be accepted if 15 slides are unobtainable. For patients recruited in China, newly cut, unstained slides with tissue sections up to 5 µm thick will be collected from an archived tumor sample. The number of slides should be sufficient for PD-L1 analysis (as described in the Laboratory Manual).
3. An optional tumor biopsy following completion of chemoradiotherapy, should be considered for patients without archival tumor blocks/slides, provided it is technically

feasible and not associated with unacceptable clinical risk (by investigator judgement). Patients recruited in China will only have a newly acquired tumor biopsy, if archival tumor slides are not available (tumor tissue slides only will be collected for patients recruited in China)

4. If an archival tumor blocks/slides are not available and a newly acquired tumor biopsy is not technically or clinically feasible, then cell blocks from FNA (Fine Needle Aspirate) samples will be accepted. Samples must first be spun down to capture all the cells in a single pellet (as described in the Laboratory Manual). The pellets should then be placed in formalin, processed and embedded in paraffin blocks in a manner identical to that of biopsy tissue. For patients recruited in China, tumor cell slides from FNA will be allowed, if no archival tumor slides available and a newly acquired tumor biopsy is not technically or clinically feasible.

An optional core needle tumor biopsy following completion of the most recent therapy, or upon evidence of PD after randomization, should be performed according to institutional practice, provided it is not associated with unacceptable clinical risk. If provided, the sample should be of a sufficient quantity to allow for analysis (see the Laboratory Manual). Tumor lesions planned for biopsy must not be used as index lesions for assessment of disease. This optional sample will not be collected from Chinese patients.

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

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

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy as described in Section 8.8.1.

The results may be pooled with biomarker data from other durvalumab/tremelimumab studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

8.8.1 Secondary and exploratory biomarkers

Baseline biomarker measures will be correlated with outcomes. Note that samples will be obtained from patients randomized to each treatment group. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with durvalumab monotherapy or durvalumab and tremelimumab combination therapy versus placebo.

Additional sample collections and analyses may be completed at select study sites by site specific- amendment. All samples collected for such exploratory analyses will be stored at the

study site, a reference laboratory, or at AstraZeneca's facilities and may be used for subsequent research relevant to evaluating response to immunotherapy.

The secondary and exploratory biomarker plan is described by sample type below.

Whole blood for DNA/single-nucleotide polymorphism genotyping (Not applicable for China)

Genomic DNA will be extracted from whole blood obtained pre-treatment from all patients. Genotyping of DNA may be performed to determine association between genotype and clinical benefit and/or with likelihood of drug-related AEs. Genotyping data may be also be used to subtract naturally occurring mutations and help to unambiguously identify true somatic mutations in tumor tissue. Genes associated with SCLC development, progression, or likelihood of response to CRT may likewise be investigated. Genotyping will occur retrospectively, data will not be shared with patients, and results will not impact treatment decisions.

Genotypes may also be correlated with biomarker measures (eg, gene and/or protein expression) obtained from other sample types described in this secondary and exploratory biomarker section. A primary hypothesis is that different genotypes will be associated with different expression levels of factors within the PD-1 signaling and other immune-related pathways. Such variations in expression may affect the ability of an individual to mount an appropriate immune reaction to tumor and/or affect the likelihood of response to therapeutics targeting these pathways. Therefore, genotyping may provide easy-to-measure, baseline information regarding a patient's immune system, and a goal of this research is to understand how such genetic information may be used to predict pharmacodynamic responses to therapy.

Whole blood gene expression (PaxGene-RNA) (Not applicable for China)

Whole blood samples will be obtained from all patients as described in the SoAs. Total RNA will 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.

Focus is likely to be given to, but not limited to, the expression of immunomodulatory genes. Correlations with outcome data will be performed on predictive markers with the aim of identifying useful expression thresholds for identifying patients likely to receive benefit.

Soluble factors – plasma (Not applicable for China)

Plasma will be obtained from all patients as described in the SoAs. Plasma may be used to evaluate mutant circulating tumor DNA (ctDNA). Overall mutational burden and/or somatic mutations/genomic alterations in plasma may be assessed using state-of-the-art methodologies. The concentrations of a panel of relevant cytokines, chemokines, and other immune-related markers may also be measured. Such measurements may be correlated with response.

Tumor markers

This study will mandate the availability of archival/diagnostic tumor tissue that may be analyzed for various biomarkers.

SCLC is characterized by its high mutational burden, as described in Section 2.1. Recent data from CheckMate-032 (NCT01928394) have shown that patients with a high tumor burden (ie, high TMB) derive greater clinical benefit from PD-1 blockade alone or in combination with CTLA-4 blockade. Also, data presented from an ES-SCLC cohort in the Phase 2 KEYNOTE-158 study (NCT02628067), showed that PD-1 blockade had greater clinical benefit in PD-L1-positive patients than in PD-L1 negative patients (Hyun Cheol Chung et al 2018). To better understand the significance of these findings and any impact this may have on patients in the present study (ADRIATIC), TMB may be assessed in both tumor and blood samples and PD-L1 status will be assessed in tumor samples. TMB related testing or analysis will not be conducted for China patients.

Other tissue-based biomarkers may be assessed, including but not limited to, the study of expression of tumor- and/or immune-related genes, SCLC molecular subtypes, and other pathways related to the disease or response to therapy using state-of-the-art technologies. TMB and somatic mutations/genomic alterations may also be assessed (not applicable for China).

Stool sample for microbiome analysis

Recent studies have shown that the gut microbiome may play an important role in a patient's response to immunotherapy (Sivan et al 2015, Vetizou et al 2015). Stool samples collected from patients will be used to study microbial diversity as well as the different species of microbes present in the patient to be correlated with response to therapy, as well as the effect of treatment on the microbiome over time. These samples are optional and will only be collected in North American and European countries.

Stool samples may be collected within 3 days prior to the visit at the site or by the patient in a home setting.

Management of biomarker data

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

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

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

For all countries except China:

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 secondary and 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 tremelimumab to generate hypotheses to be tested in future research.

For China:

Samples will be stored and disposed according to China laws and regulations.
The stained tissue slides (PD-L1 and H&E slides) will be retained at the testing laboratory as raw data for a minimum of 10 years after study closure and repatriated or discarded at the end of the retention period. Collected tissue slides for PD-L1 testing, if unstained, will be repatriated to the sites or discarded 5 years after study drug approved for marketing in China.

Summaries and analyses for secondary and 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 tremelimumab to generate hypotheses to be tested in future research. Samples collected from Chinese patients will be stored until study analysis is complete and used only for study purpose.

8.8.3 Labeling and shipment of biological samples

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

8.9 Health Economics

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

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

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

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

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

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The dual primary objectives are to assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS and OS.

The statistical hypotheses for primary PFS are:

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

The statistical hypotheses for primary OS are:

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

The study will be considered positive (ie, a success) if either of the above null hypotheses is rejected based on the primary analysis of PFS or OS in the FAS.

The following statistical hypotheses for the key secondary endpoints of PFS and OS comparing durvalumab in combination with tremelimumab versus placebo will be tested if the null hypothesis for both dual primary endpoints (PFS and OS, durvalumab monotherapy versus placebo) is rejected (see Section 9.5.7):

- H0: No difference between durvalumab in combination with tremelimumab and placebo
- H1: Difference between durvalumab in combination with tremelimumab and placebo

Analyses will be stratified by disease stage (I/II versus III) based on the TNM classification and receipt of PCI (yes versus no).

Statistical analyses of the durvalumab in combination with tremelimumab group will be performed in the combination analysis set to prevent bias being introduced from an imbalance in the follow-up, recruitment period and number of patients across treatment arms.

9.2 Sample size determination

Approximately 965 patients will be recruited globally in order to randomize approximately 724 patients to durvalumab monotherapy (approximately 262 patients), placebo (approximately 262 patients), or durvalumab + tremelimumab combination therapy (approximately 200 patients) over a period of 38 months. Initially, patients will be randomized 1:1:1 to the 3 treatment groups. Following implementation of CSP Version 4, once 600 patients have been randomized, a further 124 patients will subsequently be randomized 1:1 to durvalumab monotherapy or placebo until a total of 724 patients have been randomized.

The primary PFS analysis will occur at the earliest of:

1. When approximately 370 PFS BICR events have occurred (70.6% maturity) in the durvalumab monotherapy and placebo treatment groups
2. At OS-IA2, if OS-IA2 is statistically significant (durvalumab monotherapy vs placebo)
3. 36 months after the last patient randomized

With 370 PFS BICR events, if the true PFS HR is 0.65 for durvalumab monotherapy versus placebo, the study will have approximately 90% power to demonstrate a statistically significant difference in PFS between durvalumab monotherapy and placebo, with an overall 2-sided significance level of 0.5%. The true HR of 0.65 translates to a 5.4 month benefit in median PFS over 10 months on placebo if PFS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of 0.743 (Critical value (CV)). A recruitment period of approximately 38 months are expected for the primary PFS analysis. At this time, approximately 309 PFS BICR events are also expected to have occurred in the durvalumab in combination with tremelimumab and placebo treatment groups.

One interim analysis of PFS will be performed when approximately 308 PFS BICR events have occurred across the durvalumab monotherapy and placebo treatment groups (information fraction 83.2%, maturity 58.8%). At this time, approximately 274 PFS BICR events are also expected to have occurred in the durvalumab in combination with tremelimumab and placebo treatment groups. With 308 PFS BICR events across the durvalumab monotherapy and placebo treatment groups, the study will have 75% power to detect a PFS HR of 0.65 (CV=0.700) at a 0.184% significance level. The alpha level (0.5%, 2 sided) will be split between the interim and primary analyses using the Lan and DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach. The actual boundary will be calculated at the time of the interim analysis, based on assuming 370 PFS BICR events at the primary PFS analysis.

The primary OS analysis will occur when approximately 348 death events have occurred (66.4% maturity) in the durvalumab monotherapy and placebo treatment groups. If the true OS HR is 0.73 for durvalumab monotherapy versus placebo, the study will have 80% power to demonstrate a statistically significant difference in OS between durvalumab monotherapy and placebo. The true HR of 0.73 translates to an approximate 8.9 month benefit in median OS over 24 months on placebo if OS is exponentially distributed. The smallest treatment difference that would be statistically significant is an HR of 0.797.

Two interim analyses of OS will be performed. The first at the time of the PFS interim analysis with approximately 242 death events anticipated across the durvalumab monotherapy and placebo treatment groups (information fraction 69.5%, maturity 46.2%) which would provide 48% power to detect a PFS HR of 0.73 (CV=0.725). The second with approximately 299 death events anticipated across the durvalumab monotherapy and placebo treatment groups (information fraction 85.9%, maturity 57.1%) which would provide 68% power to detect a PFS HR of 0.73 (CV=0.770). The alpha level (4.5%, 2-sided) will be split between the interim and primary analyses using the Lan and DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach. The actual boundaries will be calculated at the time of each interim, based on 348 death events being observed at the primary OS analysis.

For a description of the analyses for PFS and OS, refer to Sections 9.5.1.1 and 9.5.1.2. For further details of the MTP, interim analyses, alpha allocation and alpha spend, refer to Sections 9.5.7 and 9.6.

9.3 Populations for analyses

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

Table 11 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
PFS, OS, PFS18, PFS24, TTDM, OS24, OS36, PFS2, and PRO endpoints	Full analysis set, Combination analysis set
ORR	Full analysis set, Combination analysis set
Demography	Full analysis set, Combination analysis set
PK data	PK analysis set
Safety data	
Exposure	Safety analysis set, Combination safety analysis set,
Adverse events	Safety analysis set, Combination safety analysis set
Laboratory measurements	Safety analysis set
Vital signs	Safety analysis set
Electrocardiograms	Safety analysis set
ADA	ADA analysis set

ADA Anti-drug antibody; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomization; OS36 Proportion of patients alive at 36 months from randomization; PFS Progression-free survival; PFS2 Time from randomization to second progression; PFS18 Progression-free survival at 18 months following randomization; PFS24 Progression-free survival at 24 months following randomization; PK Pharmacokinetic(s); PRO Patient-reported outcome; TTDM Time to death or distant metastasis.

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 Combination analysis set

For analyses involving the durvalumab and tremelimumab combination treatment group, only the first 600 patients randomized (across all 3 arms) will be included in the analyses, and all will be included in the treatment group to which they were randomized.

9.3.3 Safety analysis set

The safety analysis set (SAS) will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized using the SAS according to the treatment received, that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

9.3.4 Combination safety analysis set

The combination safety analysis set will consist of all patients from the combination analysis set who received at least 1 dose of study treatment. Data will be summarized according to the treatment they actually received.

9.3.5 PK analysis set

All patients who receive at least 1 dose of IP per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

9.3.6 ADA analysis set

The ADA analysis set includes all patients in the safety analysis set who have non-missing baseline ADA and at least 1 non-missing post-baseline ADA result of the same IP (durvalumab or tremelimumab).

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 of PFS and the analyses of the secondary endpoints of ORR, PFS18, PFS24, and TTDM will be based on BICR tumor assessments using RECIST 1.1. In addition, the primary endpoint of OS and the secondary endpoints of OS24, OS36, and PFS2 will be evaluated.

Blinded Independent Central Review

Images will be collected centrally, verified, and stored. For BICR, each patient's scans will be reviewed by 2 independent primary radiologist reviewers using RECIST 1.1 criteria. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). If any of the overall visit responses (CR, PR, SD, PD, or NE) differ between the 2 primary radiologists, the case will be adjudicated by a third independent radiologist who will choose all assessments of the primary reviewer with which they agree more. If no differences in overall visit responses are identified, then the assessments from the primary radiologist who completed their review of baseline scans first will be used for the analysis. Endpoints (e.g., PFS) will be derived from the scan dates that contributed to the overall visit responses.

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

Investigator RECIST 1.1-based assessments

All RECIST 1.1-based assessments, whether scheduled or unscheduled, will be included in the calculations, regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed post-CRT within the 42 days prior to randomization and first dose of IP. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE; unless there is evidence of progression, in which case the response will be assigned as PD).

Please refer to Appendix F for the definitions of CR, PR, SD, and PD.

9.4.1.2 Progression-free survival

PFS (per RECIST 1.1, as assessed by BICR, will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 1). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits (NE is not considered a missed visit). If the patient has no evaluable visits 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 date of death as the event date.

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

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

- For BICR assessments, the date of progression will be determined based on the earliest scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of the reviewer who read baseline first if there is no adjudication.
- For Investigator assessments, the date of progression will be determined by the earliest of the RECIST assessment/scan dates of the component that indicates progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

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

9.4.1.3 Overall survival

OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made 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 Objective response rate

ORR (per RECIST 1.1 using Investigator assessments) is defined as the number (%) of patients with at least 1 visit response of CR or PR (i.e., unconfirmed response). Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

9.4.1.5 Progression-free survival at 18 months and 24 months

The PFS18 and PFS24 will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed by BICR) at 18 months and 24 months, respectively.

9.4.1.6 Time to death or distant metastasis

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

has no evaluable visits or does not have baseline data, he/she will be censored at Day 1 unless they die within 2 visits of baseline.

9.4.1.7 Proportion of patients alive at 24 months and 36 months after randomization

The OS24 and OS36 will be defined as the Kaplan-Meier estimate of OS at 24 months and 36 months after randomization, respectively.

9.4.1.8 Time from randomization to second progression

PFS2 will be defined as the time from the date of randomization to the earliest of the progression event subsequent to first subsequent therapy or death. The date of second progression will be recorded by the Investigator in the eCRF at each assessment and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, that is, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

9.4.2 Calculation or derivation of safety variables

9.4.2.1 Adverse events

Data from all cycles of treatment will be combined in the presentation of safety data. “On treatment” will be defined as assessments between date of first dose of IP and 90 days following discontinuation of IP. For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after first dose of IP or prior to dosing and which worsens following exposure to the treatment.

AEs observed up until 90 days following discontinuation of IP 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 IP 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 IP (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 IP) will be flagged in the data listings.

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

Other significant adverse events (OAEs)

During the evaluation of the AE data, an AstraZeneca/MedImmune medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert’s judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs. Examples of these are marked hematological and other laboratory

abnormalities and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

9.4.2.2 Safety assessments

For the change-from-baseline summaries for laboratory data, physical examinations, and vital signs, the baseline value will be the latest result obtained prior to the start of study treatment. A listing of ECGs will be provided, as it will be collected as clinically indicated after screening.

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

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

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

For example:

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

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

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

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

The EORTC QLQ-C30 consists of 30 questions that are grouped into 5 multi-item functional scales (physical, role, cognitive, emotional, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), 5 single items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), and a 2-item global measure of health status/quality of life (GHS/QoL), and a single item on the financial impact of the disease. The QLQ-LC13 is a lung cancer-specific module from the EORTC for lung cancer comprising 13 questions to assess lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication. With the exception of a multi-item scale for dyspnea, all are single items. The dyspnea scale will only be used if all 3 items have been scored; otherwise, the items are treated as single-item measures.

All items are scored between 1 (“not at all”) to 4 (“very much”) with the exception of the 2 GHS/QoL items which are scored 1 (“very poor”) to 7 (“excellent”). 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 (EORTC QLQ-C30 Scoring Manual, Third Edition) and the 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 (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Definition of clinically meaningful changes

Changes in score compared to baseline will be evaluated. A minimum clinically 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 in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline 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 improvment, no change, or deterioration as shown in Table 12.

Table 12 Visit responses for symptoms and HRQoL

Score	Change from baseline	Visit response
QLQ-C30/QLQ-LC13 symptom scales/items	≥+10	Deterioration
	≤-10	Improvement
	Otherwise	No change
QLQ-C30 functional scales and GHS/QoL	≥+10	Improvement
	≤-10	Deterioration
	Otherwise	No change

GHS Global health status; HRQoL Health-related quality of life; QLQ-C30 30-Item core quality of life questionnaire; QLQ-LC13 Lung cancer module; QoL Quality of life.

Time to symptom deterioration and improvement rates will be evaluated for all symptoms and HRQoL outcomes. Further details will be provided in the SAP.

9.4.4 Calculation or derivation of PGIS

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

9.4.5 Calculation or derivation of PRO-CTCAE

PRO-CTCAE data will be presented using summaries and descriptive statistics based on the Full Analysis Set and further details will be provided in the SAP.

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

The health state utility will be assessed using the EQ-5D-5L (exploratory). The index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; see Section 8.1.3.4). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems). A unique EQ-5D health state is referred to by a 5-digit code, allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where value sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied (Oemar and Janssen 2013). In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analog scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

9.4.7 Calculation or derivation of pharmacokinetic variables

9.4.7.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modelling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints will be evaluated. The results of such an analysis will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

9.4.7.2 Pharmacokinetic analysis

The actual sampling times will be used in the PK calculations. PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. Samples below the lower limit of quantification will be treated as missing in the analyses.

9.4.7.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADA to durvalumab and to tremelimumab. ADA titer and the presence of nAb will be reported for samples confirmed positive for the presence of

ADA. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

9.4.8 Calculation or derivation of biomarker variables

Biomarker status, as defined in the secondary and exploratory objectives, will be assessed for evaluable patients in each treatment group according to prespecified criteria that will be detailed in the SAP.

9.4.9 Calculation or derivation of pharmacogenetic variables (Not Applicable for China)

In the case of 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 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 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

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 clinical study report.

If this study achieves statistical significance for either of the dual primary endpoints of PFS and/or OS at one of the planned interim analyses, then that will be considered the primary analysis for that endpoint. Further analyses for that particular endpoint may still occur depending on the need to have long-term follow up or more mature data. The final analysis of the study will then be the last assessment of long-term benefit.

9.5.1 Efficacy analyses

The primary aim of the study is to assess the efficacy of durvalumab monotherapy versus placebo in terms of PFS (per RECIST 1.1 as assessed by BICR) and OS.

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.

In general, baseline will be the last observed assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables (including PRO), baseline is defined as the last observed measurement prior to randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS. PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized on the SAS.

All outputs will be summarized by treatment group for all randomized patients (FAS). However, for analyses involving the durvalumab and tremelimumab combination treatment group, only those patients randomized up to and including the date of the 600th patient will be included in the analyses (combination analysis set, approximately 200 patients per arm).

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

Table 13 details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint. Note, all endpoints compare durvalumab monotherapy and durvalumab and tremelimumab combination therapy versus placebo in all randomized patients (FAS), unless otherwise indicated.

Table 13 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank tests for: • Primary analysis using BICR RECIST 1.1 assessments (durvalumab monotherapy versus placebo) • Sensitivity analyses using BICR RECIST 1.1 assessments 1) Interval censored analysis – evaluation time bias 2) Analysis using alternative censoring rules – attrition bias • Sensitivity analysis using site Investigator RECIST 1.1 assessments – ascertainment bias • Secondary analysis using BICR RECIST 1.1 assessments (durvalumab + tremelimumab versus placebo and durvalumab + tremelimumab versus durvalumab monotherapy) Subgroup analysis using Cox proportional hazards models Additional analysis using Cox proportional hazards models to determine the effect of covariates on the HR estimate Additional analysis using Cox proportional hazards models to determine the consistency of treatment effect between subgroups

Endpoints analyzed	Notes
Overall survival	Stratified log-rank tests for: • Primary analysis (durvalumab monotherapy versus placebo) • Secondary analysis (durvalumab + tremelimumab versus placebo and durvalumab + tremelimumab versus durvalumab monotherapy) Sensitivity analysis using a Kaplan-Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias Subgroup analysis using Cox proportional hazards models Additional analysis using Cox proportional hazards models to determine the effect of covariates on the HR estimate Additional analysis using Cox proportional hazards models to determine the consistency of treatment effect between subgroups
Objective response rate	Cochran-Mantel-Haenszel test for difference in proportions (using Investigator RECIST 1.1 assessments) adjusting for the same factors as the primary endpoint for: • Secondary analysis (durvalumab monotherapy and durvalumab + tremelimumab combination therapy versus placebo and durvalumab + tremelimumab versus durvalumab monotherapy)
PFS at 18 months and 24 months	Kaplan-Meier estimates
Time to death or distant metastasis	Stratified log-rank test using BICR tumor data (RECIST 1.1)
Time from randomization to second progression	Stratified log-rank test using site Investigator RECIST 1.1 assessments
OS at 24 and 36 months	Kaplan-Meier estimates of survival at 24 months and 36 months and analyses following the method described by Klein et al (Klein et al 2007)
Change from baseline in key symptoms (EORTC QLQ-C30 and QLQ-LC13)	Mixed-model repeated measures analysis
GHSQoL/Function improvement rate (EORTC QLQ-C30 endpoints)	Presented using summaries and descriptive statistics
Symptom improvement rate (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Logistic regression
Time to GHSQoL/Function deterioration (EORTC QLQ-C30 endpoints)	Stratified log-rank test

Endpoints analyzed	Notes
Time to symptom deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Stratified log-rank test
Treatment-related symptoms (PRO-CTCAE and PGIS)	Presented using summaries and descriptive statistic

BICR Blinded Independent Central Review; CMH Cochran–Mantel–Haenszel; CTCAE Common Terminology Criteria for Adverse Event; EORTC European Organisation for Research and Treatment of Cancer; GHS/QoL Global health score/Health-related quality of life; ORR Objective response rate; OS Overall survival; PCI Prophylactic cranial irradiation; PFS Progression-free survival; PGIS Patient's Global Impression of Severity; PRO Patient-reported outcome; QLQ-C30 30-Item core quality of life questionnaire; QLQ-LC13 Lung cancer module; SAP Statistical analysis plan.

9.5.1.1 Progression-free survival

The primary PFS analysis will be based on the programmatically derived RECIST 1.1 using BICR tumor assessments. The analysis will be performed in the FAS using a stratified log-rank test adjusting for TNM stage (I/II versus III) and receipt of PCI (yes versus no). The effect of durvalumab monotherapy and durvalumab and tremelimumab combination therapy versus placebo treatment will be estimated by the hazard ratio (HR) together with its corresponding confidence interval (CI) (95% and [1-adjusted alpha] × 100%) from a stratified Cox proportional hazards model.

In order to ensure there are at least 5 events within each strata; if there are too few events in the Stage I/II stratification level, TNM stage may be excluded from the models leaving receipt of PCI as the sole stratification factor.

Secondary PFS analyses will be performed using the same methodology as for the primary analysis.

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

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

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

supported by a Kaplan-Meier plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

Ascertainment bias will be assessed by analyzing the site Investigator data. The stratified log-rank test will be repeated on PFS using the site Investigator data based on RECIST. Disagreements between Investigator and central reviews of RECIST progression will be presented for each treatment group.

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 time-periods. 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 PFS rate) will also help in understanding the treatment benefit.

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using BICR assessments) between durvalumab monotherapy and durvalumab and tremelimumab combination therapy versus placebo in the following subgroups of the FAS (but not limited to):

- TNM stage (Stage I/II versus III)
- Receipt of PCI (yes versus no)
- Time from end date of cCRT to randomization in this study (<14 days, ≥14 to <28 days, ≥28 days)
- Time from last dose of radiotherapy to randomization in this study (<28 days, ≥28 to <56 days, ≥56 to <84 days, ≥84 days)
- Prior platinum chemotherapy (carboplatin versus cisplatin)
- Prior radiotherapy regimen (daily versus twice daily)
- Best response to CRT (CR versus PR versus SD)
- Sex (male versus female)
- Age (<65 versus ≥65 years of age)
- PD-L1 status (< 1% versus ≥ 1%)
- Smoking status (smoker versus non-smoker [never smoker])
- Race/ethnicity

- Geographic region
- WHO/ECOG PS (0 versus 1)

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. Forest plot(s) will be generated.

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

Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. A model will be constructed, containing the treatment and the stratification factors, to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test.

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

Additionally, for each subgroup, the HR (durvalumab monotherapy or durvalumab and tremelimumab combination therapy: placebo) and 95% CI will be calculated from a Cox proportional hazards model with treatment as the only covariate. These will be presented on a Forest plot including the HR and 95% CI from the overall population.

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 PFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

9.5.1.2 Overall survival

The primary analysis of OS in the FAS will be analyzed using a stratified log-rank test, using the same methodology as described for the PFS endpoint. The treatment effect will be estimated by the HR together with its corresponding CIs (95% and [1-adjusted alpha] × 100%) from a stratified Cox proportional hazards model. 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 OS for each treatment.

9.5.1.3 Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using BICR tumor data, for unconfirmed and confirmed responses. The analysis will be performed using a Cochran-Mantel-Haenszel (CMH) test, stratified using the same stratification factors as for the primary endpoint. The effect of treatment will be estimated by the difference in proportions between treatment groups, together with its corresponding 95% CI and p-value (2-sided). The CI for the difference in proportions between the treatment groups will be computed using Miettinen and

Nurminen's (MN) stratified confidence limits. This analysis will be performed in the FAS, including all patients with measurable disease at baseline.

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

Analyses will be repeated using the site Investigator data as per RECIST 1.1, for unconfirmed and confirmed responses.

9.5.1.4 Progression-free survival at 18 months and 24 months

The proportion of patients alive and progression free at 18 months and 24 months (ie, PFS18 and PFS24) and corresponding 95% CIs will be summarized (using the Kaplan-Meier curve) and presented by treatment group.

9.5.1.5 Time to death or distant metastasis

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

9.5.1.6 Proportion of patients alive at 24 and 36 months

The proportion of patients alive at 24 and 36 months (ie, OS24 and OS36) and corresponding 95% CIs will be summarized (using the Kaplan-Meier curve) and presented by treatment group.

9.5.1.7 Time from randomization to second progression

Second progression (PFS2) in the FAS will be analyzed using a stratified log-rank test, using the same methodology as described for the primary PFS endpoint. The treatment effect will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

For supportive purposes, the time to the start of subsequent therapy will be analyzed using the same methodology and model. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan-Meier plot of the time to the start of subsequent therapy will be presented by treatment group. No multiplicity adjustment will be applied, as these are viewed as supportive endpoints.

A summary table of first subsequent therapies by treatment group will be provided, as well as the response to first subsequent therapy by treatment group.

9.5.1.8 Duration of response

Descriptive data will be provided for the duration of response in responding patients, including the associated Kaplan-Meier curves and the estimated medians (without any formal comparison of treatment groups or p-value attached). This analysis will be performed in the FAS.

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

Five symptoms have been identified as primary:

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

The physical functioning, role functioning and overall health status domains (GHS/QoL) of the EORTC QLQ-C30 are furthermore pre-specified endpoints of interest.

Mixed-model repeated measures analysis

Change from baseline in dyspnea, cough, and chest pain scores as assessed by the EORTC QLQ-LC13 GHS/QoL, physical functioning, role functioning, and fatigue and appetite loss as assessed by the EORTC QLQ-C30 will be the primary analysis and assessment of PRO outcome measures. The analysis will be performed using a linear mixed model for repeated measures analysis of change from baseline in the scores for each assessment time point. No multiplicity adjustment will be applied, as these are viewed as supportive secondary endpoints.

Time to deterioration

Time to symptom and function/HRQoL deterioration will be analyzed for each of the symptom scales/items, function scales, and global health status/QoL in EORTC QLQ-C30 and QLQLC13. This will be achieved by comparing between treatment groups using a stratified log-rank test as described for the primary analysis of OS. The HR and 95% CI for each scale/item will be presented graphically on a forest plot.

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

Improvement rate

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

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

Change from baseline

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score, and each functional domain will be reported by assessment time point 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 time point for each ordinal item (in terms of the proportion of patients in the categories of improvement, stable, and deterioration as defined in Table 12) will also be produced for each treatment group.

9.5.1.10 Health care resource use

An exploratory health economic analysis of hospital episodes including type of contact (hospitalization, outpatient, and day case), reason, length of stay by ward type (including intensive care unit), and procedures and tests may be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of durvalumab monotherapy and the durvalumab and tremelimumab combination therapy. This would include providing descriptive statistics as appropriate, including means, median, and ranges.

9.5.2 Safety analyses

Safety and tolerability data will be presented by treatment group using the safety population.

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 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 clinical laboratory findings (including chemistry, hematology, and urinalysis), physical examinations, vital signs, and ECGs. Exposure to durvalumab monotherapy, durvalumab and tremelimumab combination therapy, and placebo will be summarized. Time on study; durvalumab monotherapy, durvalumab and tremelimumab combination therapy, and placebo dose delays will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

A listing of all subjects affected by the COVID-19 pandemic, and subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic will be generated. In addition, all COVID-19 related non-important PDs and issues will be summarized and listed. Additional analyses might be conducted to investigate the impact of COVID-19 on study endpoints.

9.5.3 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day, and a summary will be provided for all evaluable patients.

9.5.4 Immunogenicity data

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable ADA to durvalumab and to tremelimumab. ADA titer and nAb data will be listed for samples confirmed positive for the presence of ADA.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

9.5.5 Pharmacokinetic/pharmacodynamic relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modeling approach.

9.5.6 Biomarker data

The relationship of PD-L1 expression (secondary endpoint) and, if applicable, of exploratory biomarkers to clinical outcomes (including but not restricted to) of PFS, OS, and ORR will be presented. TMB related testing or analysis is not applicable in China.

PD-L1 expression determined by validated SP263 IHC assay will be reported in the CSR. The relationship between tissue- and blood-based secondary and exploratory biomarkers to clinical outcomes (PFS, OS, and ORR) will be assessed. Summaries and analyses for secondary and exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.5.7 Methods for multiplicity control

The MTP shown in Figure 3 will be used to strongly control the family-wise type I error rate (alpha) at 5% (2-sided) for testing the following primary and key secondary endpoints:

- Primary endpoints: PFS and OS for durvalumab monotherapy versus placebo
- Key secondary endpoints: PFS and OS for durvalumab in combination with tremelimumab versus placebo

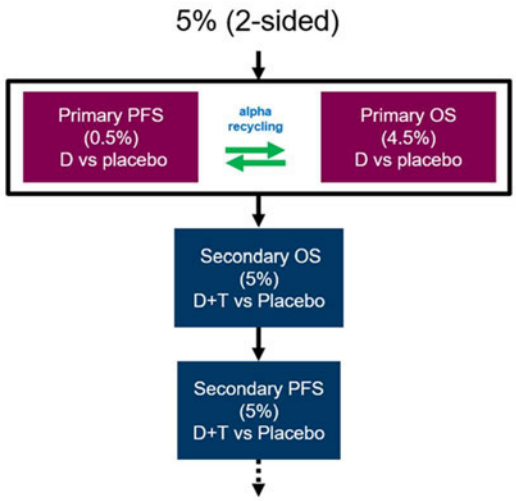
The testing procedure is hierarchical starting with testing the 2 dual primary endpoints of PFS (per BICR) and OS as outlined in Figure 3. The overall 5% type I error (2-sided) is split among the 2 dual primary endpoints. An alpha level of 0.5% is allocated to PFS and an alpha level of 4.5% is allocated to OS. For PFS, 1 interim analysis plus 1 primary analysis is planned (2 total). For OS, 2 interim analyses plus 1 primary analysis (3 total) are planned. The 0.5% alpha level for PFS will be split between 2 potential analysis timepoints, and the 4.5% alpha level for OS will be split between 3 potential analysis timepoints, even if all planned tests are not performed (if the prior MTP levels do not pass at an interim). The 0.5% alpha level for PFS, and the 4.5% alpha level for OS, are controlled at the time of the interim and primary analyses using the

Lan-DeMets spending function that approximates an O'Brien Fleming approach, as described in Section 9.6.

If any of the PFS analyses are significant, then the allocated test mass (0.5%) can be recycled to OS giving a total test mass of 5% for OS. If neither of the PFS analyses are significant, but OS is significant at the 4.5% level, at either an interim or primary analysis (where the alpha was controlled by the Lan-DeMets spending function), then the 4.5% can be recycled to test PFS at 5%. If OS is significant at either an interim or primary analysis, and the alpha recycled to re-test PFS, then PFS can only be tested using the information available at the time of that original PFS analysis.

If both PFS and OS are statistically significant for the primary analyses comparing durvalumab monotherapy versus placebo, then the 5% alpha can be carried down to test durvalumab in combination with tremelimumab versus placebo. OS will be tested at 5% and then, if significant PFS will be tested at a 5% alpha level. Further details will be provided in the SAP.

Figure 3 Multiple testing procedure



D durvalumab; OS overall survival; PFS progression-free survival; T tremelimumab.

9.6 Interim analyses

Three interim analyses are planned: 1 for PFS and 2 for OS.

PFS has the potential to be analyzed on 2 occasions, once at the interim analysis (PFS-IA) and then at the primary PFS analysis. OS has the potential to be analyzed on 3 occasions: once at the PFS interim analysis (OS-IA1), then at an interim analysis (OS-IA2), and for the primary OS analysis.

The planned PFS-IA will occur when approximately 308 PFS BICR events have occurred in the durvalumab monotherapy and placebo treatment groups (58.8% maturity). OS-IA1 will occur at the same time when it is anticipated that approximately 242 death events in the durvalumab monotherapy and placebo treatment groups (46.2% maturity) will have occurred.

The planned OS-IA2 will occur when approximately 299 death events have occurred in the durvalumab monotherapy and placebo treatment groups (57.1% maturity).

The interim analyses will be assessed by an IDMC (further details are given in the IDMC charter). The recommendations from the IDMC will not reveal the results of the analysis but will take the form of "Continue/Modify/Recommend Early Submission/Stop".

PFS interim analysis

For the comparison of durvalumab monotherapy versus placebo, approximately 308 PFS BICR events (58.8% maturity) will be available for the interim analysis. The Lan-DeMets spending function that approximates an O'Brien Fleming approach will be used to account for multiplicity introduced by including an interim analysis for superiority (Lan and DeMets 1983).

At the time of the PFS-IA, the significance level will be calculated by the IDMC based on the actual number of events observed as a proportion of the planned primary number of events (n = 370). If for example 83.2% of the number of PFS BICR events required at the time of the primary PFS analysis are available at the time of PFS-IA (ie, 308/370), the 2-sided significance level to be applied for the PFS-IA would be 0.184%, and the 2-sided significance level to be applied for the primary PFS analysis would be 0.444% (controlled at an overall alpha level of 0.5%).

OS interim analyses

For the comparison of durvalumab monotherapy versus placebo, approximately 242 and 299 death events (46.2% and 57.1% maturity) will be available for the first and the second interim OS analyses, respectively. The Lan-DeMets spending function that approximates an O'Brien Fleming approach will be used to account for multiplicity introduced by including an interim analysis for superiority (Lan and DeMets 1983).

At the time of each interim analysis, the significance level will be calculated by the IDMC based on the actual number of events observed as a proportion of the planned primary number of events (n = 348). If for example 69.5% and 85.9% of the number of death events required at the time of the primary OS analysis are available at the time of each interim analysis respectively (ie, 242/348 and 299/348), the 2-sided significance level to be applied for the first and second OS interim analyses would be 1.243% and 2.398%, respectively, and the 2-sided significance level to be applied for the primary OS analysis would be 3.616% (controlled at an overall alpha level of 4.5%).

If both the PFS interim and OS interim analysis results do not meet the efficacy boundary for superiority, the study will remain blinded and continue to be followed for PFS and survival. The

recommendations from the IDMC will not reveal the results of the analysis but will take the form of "Continue/Modify/Recommend Early Submission/Stop."

The key secondary comparison of durvalumab in combination with tremelimumab versus placebo will similarly use a Lan-DeMets spending function to define significance boundaries for PFS and OS. These will be based on the number of events for the comparison and are therefore distinct from those defined for the boundaries for the primary comparison of durvalumab monotherapy versus placebo. Further details will be provided in the SAP.

9.6.1 Data monitoring committee

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

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

An IDMC comprised of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule and for the planned interim analyses. The safety review will take place after the first 20 patients have been randomized into each of the 3 treatment groups (ie, after a total of 60 patients have been randomized to the study). In addition, the IDMC will review planned interim analyses and inform the Sponsor whether the interim boundaries specified in Section 9.6 are met. The recommendations from the IDMC will not reveal the results of the analyses but will take the form of "Continue/Modify/Recommend early submission/Stop."

The study may also be stopped based on the findings of the interim safety analysis conducted by the IDMC.

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

10. REFERENCES

Aaronson et al 1993
Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

AJCC Cancer Staging Manual, 8th Edition
Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al, editors. AJCC Cancer Staging Manual, Eighth Edition. American Joint Committee on Cancer (AJCC); 2017. Available on request.

Alexandrov et al 2013
Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Blankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.

Antonia 2016
Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Elder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicenter, open-label, Phase 1/2 trial. Lancet Oncol 2016;17(7):883-95.

Antonia et al 2017
Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in Stage III nonsmall-cell lung cancer. N Engl J Med 2017;377:1919-29.

Antonia et al 2018
Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018. In print (DOI: 10.1056/NEJMoa1809697)

Aupérin et al 1999
Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small cell lung cancer in complete remission. N Engl J Med 1999;341(7):476-84.

Basch et al 2009
Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationship with clinical outcomes. J Natl Cancer Inst 2009;101:1624-32.

Bergman et al 1994
Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;30A(5):635-42.

Brahmer et al 2012
Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-65.

Brody et al 2017
Brody R, Zhang Y, Ballas M, Siddiqui MK, Gupta P, Barker C, et al. PD-L1 expression in advanced NSCLC: Insights into risk stratification and treatment selection from a systematic literature review. Lung Cancer 2017;112:200-15.

Burman et al 2009
Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni-based multiple tests. Stat Med 2009;28:739-61.

CheckMate-032 WCLC Presentation 2016
CheckMate-032: Nivolumab ± ipilimumab in recurrent SCLC 2-year Overall Survival. Presented at the World Conference on Lung Cancer (WCLC) 2016; December 3-7; Vienna, Austria.

Cho et al 2018
Cho DC, Mahipal A, Dowlati A, Chow WA, Segal NH, Chung KY et al. Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). J Clin Oncol, 2018 ASCO Annual Meeting Abstracts;36: (suppl; abstr 8517).

Dunn et al 2004
Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

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;45:228-47.

EORTC QLQ-C30 Scoring Manual, Third Edition
EORTC QLQ-C30 Scoring Manual, Third Edition. 2001, EORTC, Brussels.

EuroQoL Group 1990
EuroQol Group. EuroQol - A new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208.

EuroQoL Group 2013
EuroQol Group. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument, Version 2.0, October 2013. Available from: URL: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L_v2.0_October_2013.pdf. Accessed 21 November 2013.

Fairman et al 2014
Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, et al. Pharmacokinetics of durvalumab, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumours. J Clin Oncol, 2014 ASCO Annual Meeting Abstracts;32(5s): (suppl; abstr 2602).

Faivre-Finn et al 2017
Faivre-Finn C, Snee M, Ashcroft L, Appel W, Barlesi F, Bhatnagar A, et al. Concurrent once daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3 randomised- superiority trial. Lancet Oncol 2017;18(8):1116-25.

Fayers et al 2001
Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A; EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.

FDA Guidance 2011
Food and Drug Administration. Guidance for industry: Clinical trial endpoints for the approval of non-small cell lung cancer drugs and biologics. June 2011. Available from: URL: http://www.fda.gov/downloads/Drugs/Guidances/UCM259421.pdf. Accessed 21 May 2014.

Fife and Bluestone 2008
Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev 2008;224:166-82.

Foster et al 2015
Foster NR, Renfro LA, Schild SE, Redman MW, Wang XF, Dahlberg SE, et al. Multitrial evaluation of progression-free survival as a surrogate end point for overall survival in first-line extensive-stage small-cell lung cancer. J Thorac Oncol 2015;10(7):1099-106.

Früh et al 2013
Früh M, De Ruysscher D, Popat S, Crinò L, Peters S, Felip E. Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2013;24(Suppl 6):vi99-105.

Gail and Simon 1985
Gail M, Simon R. Tests for qualitative interactions between treatment effects and patient subsets. Biometrics 1985;41(2):361-72.

GLOBOCAN 2018
GLOBOCAN. Lung cancer, new cases and deaths worldwide in 2018. International Agency for Research on Cancer, World Health Organization; Lyon, 2018. Available from: http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. Accessed on 06 December 2018.

Goldman et al 2018
Goldman JW, Dowlati A, Antonia SJ, Nemunaitis JJ, Butler MO, Howard N et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). J Clin Oncol, 2018 ASCO Annual Meeting Abstracts;36: (suppl; abstr 8518).

Goldman et al 2020
Goldman JW, Garassino MC, Chen Y, Reinmuth N, Hotta K, Poltoratkiy A, et al. LBA86 Durvalumab (D) ± tremelimumab (T) + platinum-etoposide (EP) in 1L ES-SCLC: Characterization of long-term clinical benefit and tumour mutational burden (TMB) in CASPIAN. Annals Oncol. 2020;31_suppl 4:S1212-3.

Grønberg et al 2016
Grønberg BH, Halvorsen TO, Flotten O, Brustugun OT, Brunsvig PF, Aasebo U, et al. Randomised phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer. Acta Oncol 2016;55(5):591-7.

Hellmann et al 2018
Hellmann MD, Callahan MK, Awad MM, Calvo E, Ascierto PA, Atmaca A, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. Cancer Cell 2018;33(5):853-61.

Herdman et al 2011
Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-36.

Hirano et al 2005
Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089-96.

Horita et al 2015
Horita N, Yamamoto M, Sato T, T, Nagakura H, Tashiro K, et al. Topotecan for relapsed small-cell lung cancer: systematic review and meta-analysis of 1347 patients. Sci Rep 2015;5:15437.

Howlander et al 2016
Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975 – 2013, based on November 2015 SEER data submission, posted to the SEER website, April 2016. Bethesda, MD: National Cancer Institute; 2016. Available at: http://seer.cancer.gov/csr/1975_2013/.

Hyun Cheol Chung et al 2018
Hyun Cheol Chung, Jose A. Lopez-Martin, Stephen Chuan-Hao Kao, Wilson H. Miller, Willeke Ros, Bo Gao, Aurelien Marabelle, Maya Gottfried, Alona Zer, Jean-Pierre Delord, Nicolas Penel, Shadia Ibrahim Jalal, Lei Xu, Susan Zeigenfuss, Scott K. Pruitt, and Sarina Anne Piha-Paul. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. Journal of Clinical Oncology 2018 36:15_suppl, 8506-8506

IASLC Staging Manual in Thoracic Oncology 2016
Rami-Pora R, editor. Staging manual in thoracic oncology (2nd edition; includes 8th edition tumor, node, and metastatic classification [TNM] information for lung cancer, plural mesothelioma, thymic malignancies, and carcinoma of the oesophagus and of oesophagogastric junction). IASLC; 2016. Available on request.

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293-7.

Janssen et al 2008a
Janssen MF, Birnie E, Haagsma JA, Bonsel GJ. Comparing the standard EQ-5D three-level system with a five-level version. Value Health 2008;11(2):275-84.

Janssen et al 2008b
Janssen MF, Birnie E, Bonsel GJ. Quantification of the level descriptors for the standard EQ-5D three-level system and a five-level version according to two methods. Qual Life Res 2008;17(3):463-73.

Keir et al 2008
Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.

Klein et al 2007
Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med 2007;26(24):4505-19.

Lan and DeMets 1983
Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.

Litwin et al 1998
Litwin MS, Lubeck DP, Henning JM, et al. Differences in urologist and patient assessments of health-related quality of life in men with prostate cancer: results of the CaPSURE database. J Urol 1998;159:1988-92.

Mauguen et al 2013
Mauguen A, Pignon JP, Burdett S, Domerg C, Fisher D, Paulus R, et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung

cancer: a re-analysis of meta-analyses of individual patients' data. Lancet Oncol 2013;14(7):619-26.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferonalpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet 2013;52:1017-27.

NCCN 2017
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Small Cell Lung Cancer. Version 2.2018.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Oemar and Janssen 2013
Oemar M, Janssen B. EQ-5D-3L User Guide: Basic information on how to use the EQ-5D-3L instrument V5.0 (October 2013). Available from: URL: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-3L_UserGuide_2013_v5.0_October_2013.pdf. Accessed 07 January 2014.

Okazaki and Honjo 2007
Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19(7):813-24.

Okudaira et al 2009
Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an antitumor effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

Osoba et al 1998
Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16(1):139-44.

Owonikoko et al 2019
Owonikoko TK, Kim HR, Govindan R, Ready N, Reck M, Peters S, et al. LBA1_PR Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): Results from the double-blind, randomized phase III CheckMate 451 study. Annals Oncol. 2019;30(suppl_2):ii77-80.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

Paz-Ares et al 2019
Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al; CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394(10212):1929-39.

Paz-Ares et al 2020
Paz-Ares LG, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated results from the phase III CASPIAN study. J Clin Oncol. 2020;38, no. 15_suppl:9002.

Pazdur 2008
Pazdur R. Endpoints for assessing drug activity in clinical trials. Oncologist 2008;13(Suppl 2):19-21.

Peifer et al 2012
Peifer M, Ferneandes-Cuesta L, Sos ML, Seidel D, Kasper LH, Plenker D, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet 2012;44(10):1104-10.

Peters et al 2020
Peters S, Pujol J-L, Dafni U, Dómine M, Becker A, Andrade J, et al. LBA84 Consolidation ipilimumab and nivolumab vs observation in limited stage SCLC after chemo-radiotherapy: Results from the ETOP/IFCT 4-12 STIMULI trial. Annals Oncol. 2020;31_suppl 4:S1211.

Pickard et al 2007
Pickard AS, De Leon MC, Kohlmann T, Cella D, Rosenbloom S. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. Med Care 2007;45(3):259-63.

Powles et al 2014
Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515(7528):558-62.

Qin et al 2016
Qin A, Coffey DG, Warren EH, Ramnath N. Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. Cancer Med 2016; 9:2169-70.

Ready et al 2020
Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: Results from the CheckMate 032 randomized cohort. J Thorac Oncol. 2020;15(3):426-35.

Reck et al 2016
Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016;375:1823-33.

Riaz et al 2012
Riaz SP, Luchtenborg M, Coupland VH, Spicer J, Peake MD, Moller H. Trends in incidence of of small cell lung cancer and all lung cancer. Lung Cancer 2012;75(3):280-4.

Rizvi 2015
Rizvi NA. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015:348(6230):124-8.

Rizvi et al 2015
Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with nonsmall cell lung cancer (NSCLC). J Clin Oncol 2015;33:Abstract 8032.

Schadendorf et al 2013
Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma [abstract 24]. Presented at European Cancer Congress 2013 (ECCO-ESMO-ESTRO); 27 September to 01 October 2013; Amsterdam, The Netherlands.

Seckl et al 2017
Seckl MJ, Ottensmeier CH, Cullen M, Schmid P, Ngai Y, Muthukumar D, et al. Multicenter phase III randomized double-blind placebo-controlled trial of Pravestin added to first-line standard chemotherapy in small cell lung cancer (LUNGSTAR). J Clin Oncol 2017;35(14):1506-14.

Segal et al 2015
Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015;33:Abstract 3011.

Sivan et al 2015
Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015;350:1084-1089.

Snyder et al 2014
Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371(23):2189-99.

Spigel et al 2017
Spigel D, McLeod M, Hussein M, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). Presented at ESMO 2017 Congress; September 8-12, 2017; Madrid, Spain. Abstract 1297O.

Sprangers and Aaronson 1992
Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. J Clin Epidemiol 1992;45:743-60.

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015;3(9):1052-62.

Sun and Chen 2010
Sun X, Chen C. Comparison of Finkelstein's method with the conventional approach for interval-censored data analysis. Stat Biopharm Res 2010;2(1):97-108.

Tarhini and Kirkwood 2008
Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. Expert Opin Biol Ther 2008;8:1583-93.

Topalian et al 2012
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.

Vetizou et al 2015
Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 2015;350:1079-1084

Van Allen et al 2015
Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 2015;350(6257):207-11.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012-24.

Wang et al 2014
Wang E, Kang D, Bae KS, Marshall MA, Pavlov D, Parivar K. Population pharmacokinetic and pharmacodynamics analysis of tremelimumab in patients with metastatic melanoma. J Clin Pharmacol 2014;54(10):1108-16.

Wang et al 2017
Wang S, Tang J, Sun T, Zheng X, Hongliu JL, Zhou X, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. Nature Scientific Reports 2017;7, Article number 1339.

Wolchok et al 2009
Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

Zelen 1973
Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 3. 1973 Mar;4(2):31-42.

Zhang et al 2008
Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Antitumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. Cytotherapy 2008;10(7):711-9.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18-28.

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.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca 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. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

- For all studies except those utilising medical devices, investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
    - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.

- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
    - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
    - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

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 (Not Applicable for China).

If a patient's partner becomes pregnant during or within 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy, 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 (Not Applicable for China). 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

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

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

A 7 Data quality assurance

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

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

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

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

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

AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Oversite Plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 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, including interactive voice response system printouts, are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Publication policy

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

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

Appendix B Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

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

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

Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant 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 tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

B 3 Life threatening

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

B 4 Hospitalization

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

B 5 Important medical event or medical treatment

Medical and scientific 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, hospitalization, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

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

B 6 CTCAE grade

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the criteria recommended in the CTCAE manual that converts severity levels into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

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

B 7 A guide to interpreting the causality question

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

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

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

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

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

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

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

B 8 Medication error, Drug abuse, Drug misuse

Medication error

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

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

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

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

- Drug name confusion
- Dispensing error (eg, medication prepared incorrectly, even if it was not actually given to the participant)
- Drug not administered as indicated, for example, wrong route, dose (error greater than +/- 10%), 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.

Drug abuse

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

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

Examples of drug abuse include but are not limited to:

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

Drug misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs/study interventions or AstraZeneca NIMPs, outside the

intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

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

Examples of drug misuse include but are not limited to:

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

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 center 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 sample shipment.

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.
- 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, the action documented and the site informed.

Appendix D Genetics (Not applicable for China)

D 1 Use/analysis of DNA

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

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

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

Genetic research may consist of the analysis of the structure of the patient´s DNA (ie, the entire genome).

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

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

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

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

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

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

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:
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 Appendix C 2.

Not applicable for China.

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.

Not applicable for China.

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.

Not applicable for China.

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

Not applicable for China.

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

Not applicable for China.

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

E 1 Introduction

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

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

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 product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's law (PHL)

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

Hy's law (HL)

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

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

E 3 Identification of potential Hy's law cases

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

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

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

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

E 4 Follow-up

E 4.1 Potential Hy's law criteria not met

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's law criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 8.4 Safety Reporting and Appendix E, Section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the subject's condition

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data.

- Subsequent to this contact the Investigator will:

    - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.

    - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

    - Complete the three Liver CRF Modules as information becomes available

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

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

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP 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 patient matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, 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 IP:

- 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 met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

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

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

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

- If there is no significant change, no action is required

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix E, Section 4.2.

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

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

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

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

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

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

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

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

If there is no significant change, no action is required.

If there is a significant change, follow the process described in Appendix E, Section 4.2 for reporting PHL as an SAE.

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

E 8 Laboratory tests

Recommended Hy's Law lab kit for 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[#] IgM and 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 antibody (Anti-LKM) Anti-Smooth Muscle antibody (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

HBV DNA is only recommended when IgG anti-HBc is positive.
* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China.

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

Introduction

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

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

Measurable:

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

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[2]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination (manual palpation) that is not measurable by CT or MRI.
- Brain metastasis

Special cases:

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as Target Lesions (TLs).

Target Lesions (TLs):

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at

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

baseline. Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

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

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

Non-Target Lesions (NTLs):

All additional measurable lesions not recorded as TLs and non-measurable lesions (or sites of disease) should be identified as NTLs at baseline.

Imaging Modalities

A summary of the imaging modalities to be used for RECIST 1.1 assessment of Target Lesions, Non-Target Lesions, and New Lesions is provided in Table 14.

Table 14 Summary of imaging modalities for tumor assessment

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

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

CT and MRI

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

It is recommended that IV contrast-enhanced CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement (eg, pelvis, brain) should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to intravenous CT contrast, a non-contrast CT examination of the chest and an MRI with intravenous MRI contrast of the abdomen is appropriate. In patients with severely compromised renal function a non-contrast CT examination of the chest and abdomen is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over IV

contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility and scanner across all imaging time points per patient.

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

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

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

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

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

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

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

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

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

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions may be recorded in case positive hot-spots appear on a

bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan which cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

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

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

Tumor response evaluation

Schedule of evaluation

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

Baseline assessments should be performed post-CRT and no more than 42 days before the date of randomization and the first dose of IP, and ideally should be performed as close as possible to the date of randomization. Efficacy by RECIST 1.1 for all patients will be assessed according to the schedules of assessment. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled imaging visits.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be

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

identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

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

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, definitive radiotherapy, embolization, surgery, etc. during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST case report form. If a TL has been completely removed (surgery), the longest diameter should be recorded as 0 mm.

Evaluation of target lesions

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

Table 15 Evaluation of target lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable disease (SD)	Neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) – this includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg missing anatomy) or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response
Not applicable (NA)	Only relevant if there were no Target Lesions at baseline

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NA Not applicable; SD Stable disease; TL Target lesion.

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 16).

Table 16 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if there were no Non-Target Lesions at baseline

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NA Not applicable; NTL Non-target lesion; TL Target lesion.

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

New lesions

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

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

Symptomatic deterioration

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

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

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

Table 17 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/non-PD*)
NE	Non PD or NE or NA	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no target and/or non-target lesions at baseline), NED No Evidence of Disease (only relevant if there were neither target nor non-target lesions at baseline).
* Non-CR/Non-PD for Overall Response if only non-target lesions (no TLs) are present at baseline.

Central Review
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. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based, in part, upon the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter (also referred to as "Imaging Charter").

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

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

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

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

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

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

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

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

MRI Scan

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

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

References

Eisenhauer et al 2009

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

Appendix G 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 (DGR) 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 (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- 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 patient 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 H Patient-reported outcomes

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

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

ENGLISH

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

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 8 May 2018

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 DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have HEARTBURN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

5.	In the last 7 days, what was the SEVERITY of your WHEEZING (WHISTLING NOISE IN THE CHEST WITH BREATHING) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

6.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

7.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 8 May 2018

8.	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe	○ Not applicable

9.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Patient Global Impression of Severity for Cancer Symptoms

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

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

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

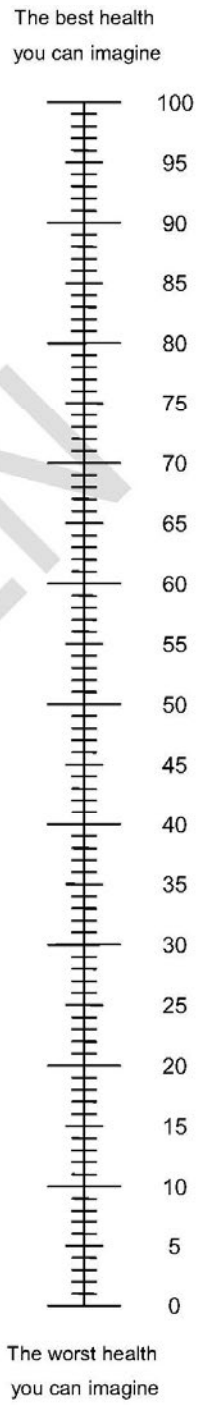
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



Appendix I Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody(s)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{ss}	area under the concentration versus time curve at steady state
B7-H1	B7 homolog 1
BICR	Blinded Independent Central Review
BID	twice daily
BoR	best objective response
BP	blood pressure
CD	cluster of differentiation
CI	confidence interval
CL	creatinine clearance
$C_{max,ss}$	maximum drug concentration at steady state
CR	complete response
CRF	case report form
CRO	Contract Research Organization
CRT	chemoradiation therapy
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
$C_{trough,ss}$	median trough concentration at steady state
DCO	data cut-off
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor

Abbreviation or special term	Explanation
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient reported outcome
ES-SCLC	extensive stage small-cell lung cancer
EQ-5D-5L	EuroQoL 5 dimension, 5-level health state utility index
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	HBV surface antigen
HBV	hepatitis B
HCV	hepatitis C
HIV	human immunodeficiency virus
HR	hazard ratio
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
IA	interim analysis
IB	Investigator Brochure
IC	immune cell
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
ILD	interstitial lung disease
imAE	immune-mediated adverse event
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	investigational product
irAE	immune-related adverse event

Abbreviation or special term	Explanation
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LDH	lactate dehydrogenase
LFT	liver function test
LIMS	laboratory information management system
LS-SCLC	limited stage small-cell lung cancer
mAb	monoclonal antibody
MOA	mechanism of action
MRI	magnetic resonance imaging
MTP	multiple testing procedure
nAb	neutralizing antibody
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of disease
NIMP	Non-Investigational Medicinal Product
NL	New Lesion
NSCLC	non-small cell lung cancer
NTL(s)	non-target lesion(s)
OAE	other significant adverse event
ORR	objective response rate
OS	overall survival
OS24	proportion of patients alive at 24 months from randomization
OS36	proportion of patients alive at 36 months from randomization
OS-IA1	first interim analysis of OS
OS-IA2	second interim analysis of OS
PCI	prophylactic cranial irradiation
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1

Abbreviation or special term	Explanation
PFS	progression-free survival
PFS18	Progression-free survival at 18 months following randomization
PFS2	time from randomization to second progression
PFS24	Progression-free survival at 24 months following randomization
PGIS	Patient's Global Impression of Severity
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PS	performance status
QD	once daily
QLQ-C30	30-item core quality of life questionnaire
QLQ-LC13	lung cancer module
QoL	quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
qXw	every X weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SCLC	small-cell lung cancer
SD	stable disease
SNP	single-nucleotide polymorphism
SoA	schedule of activities
sPD-L1	soluble programmed cell death ligand 1
SpO2	saturation of peripheral oxygen
T_3	triiodothyronine
T_4	thyroxine
T-cell	T lymphocyte
TCs	tumor cells
TKI	tyrosine kinase inhibitor

Abbreviation or special term	Explanation
TL(s)	target lesion(s)
TMB	tumor mutational burden
TMG	Toxicity Management Guidelines
TNF-α	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
TTDM	time to death or distant metastasis
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WT	body weight

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d933qc00001-csp-v5		
Document Title:	D933QC00001 Clinical Study Protocol version 5	
Document ID:	Doc ID-003781249	
Version Label:	6.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
14-Jan-2023 01:26 UTC	[redacted]	Content Approval
13-Jan-2023 20:08 UTC	[redacted]	Content Approval
13-Jan-2023 17:43 UTC	[redacted]	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.