Document Type:	Final Protocols
Document Dates:	Protocol Version 4.0 (14 July 2020)
Study Title:	Phase II Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab plus Olaparib Combination Therapy Compared with Durvalumab Monotherapy as Maintenance Therapy in Patients whose Disease has not Progressed Following Standard of Care Platinum-Based Chemotherapy with Durvalumab in First-Line Stage IV Non-Small Cell Lung Cancer (ORION)
Protocol Reference Number:	D9102C00001
NCT Number:	NCT03775486

Clinical Study Protocol	
Drug Substance	Olaparib (AZD2281) and Durvalumab (MEDI4736)
Study Code	D9102C00001
Version	4.0
Date	14 July 2020

A Phase II Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab plus Olaparib Combination Therapy Compared with Durvalumab Monotherapy as Maintenance Therapy in Patients whose Disease has not Progressed Following Standard of Care Platinum-Based Chemotherapy with Durvalumab in First-Line Stage IV Non-Small Cell Lung Cancer (ORION)

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): IND 140261

VERSION HISTORY

Version 1.0, 12 July 2018
Initial creation
Version 2.0: 17 September 2018, Revision based on comments received from US FDA.
- The term 'induction phase' is replaced by 'Initial therapy' through-out the document.
- Figure 1 updated to be consistent with the usage of term 'Initial therapy'.
- Section 6.1.3: Addition of 'No decline in WHO/ECOG PS and addition of following statement: In addition to the criteria above, written informed consent will be required to continue treatment in the setting of PD. This consent document will specify that treatment beyond initial evidence of PD is not the standard-of-care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available.
- Section 6.1.3: Deletion of following statement: accompanied by a decline in WHO/ECOG PS to >1.
- Figure 7: updated to be consistent with the usage of term: Initial therapy
Version 3.0: 02 December 2019, Revision based on providing a formal alpha-spending plan for the key secondary endpoint of OS, update of Hy's law text and minor corrections and clarifications throughout the protocol to improve readability and correct errors.
- Section 1.1: For standard of care treatment, provided clarification/guidance on delayed or missed dose(s).
- Sections 2.3.2.1 and 8.3.12.1: Based on current Investigator's Brochure, updated information on potential risks and adverse events of interest for durvalumab.
- Table 1: Clarified that tumor assessments must be performed within 28 days prior to first-dose administration. Removed footnote with required infusion times for cisplatin and carboplatin.
- Table 2, Synopsis, and Section 4.1: Clarified the window for eligibility into maintenance phase and that laboratory assessments for eligibility should be taken after the last dose of chemotherapy in the initial therapy.
- Table 2: Clarified footnote e, regarding subsequent labortory assessments. Clarified footnote k, regarding use of CrCl measurements to determine olaparib/placebo dose.
- Table 3: Modified visit window from 3 to 5 days for end of therapy visit.
- Table 3 and Section 7.1.1: Added text for tumor assessments for patients not randomized into maintenance.

- Table 5, Synopsis: Clarified study objective for disease-related symptoms and HRQoL to assess time to deterioration.
- Section 2.2: Updated Background section to match current protocol template.
- Section 5.1, Inclusion criterion 13: Clarified that archival and new tumor samples, if collected, must be submitted as separate samples.
- Section 5.1, Table 14, Synopsis: Clarified that the CrCl is calculated by the investigator or designee as this is what will be used for decision making, eg, starting olaparib/placebo treatment and dose changes.
- Section 6.1.1.2: Clarified if a patient meets criteria for randomization before being dosed in maintenance but is later found to not meet criteria to start olaparib/placebo before C1D1 dosing, durvalumab as monotherapy may be started, with olaparib/placebo dosing to commence once the patient again meets the hematology/clinical chemistry requirements and conditions specified in Section 1.1.
- Section 6.1.1.3: Removed text regarding duration of standard of care infusions; guidance in the prescribing information should be used.
- Section 6.1.2.2: Added clarification on dosing for patients who meet criteria for randomization before maintenance phase treatment who were later found to not meet critera to start olaparib/placebo before C1D1 dosing.
- Sections 6.2.1, 8.8, and 9.4.5: Clarified testing of PD-L1; samples will be collected from all enrolled patients, with testing to be carried out for all enrolled patients.
- Section 6.2.4: Clarified blinded CRO staff will not have access to the randomization.
- Section 6.4.3: Clarified the administration of rescue medication by a pharmacist.
- Section 7.1: Added clarification for end of therapy visit for patients who discontinue therapy.
- Section 8.2.1, Table 14: Updated footnote d to include option for 24-hour urine test to assess creatinine and CrCl.
- Section 8.2.1, Table 15: Updated footnote a to remove reference to calculation of counts by Data Management if percentage provided.
- Section 8.3.4: Updated adverse event data collection text to state all changes in CTCAE grade for a calendar day will be recorded, rather than recording only the maximum grade
- Section 8.4.5.1: Updated language to align with current protocol template.

- Section 8.8.1: Clarified that where necessary, EGFR/ALK testing is to be carried out locally at sites and in only cases where sites do not have capability to carry out local testing, samples should be sent to central laboratory. Removed recommendations for number of slides to refer instead to the laboratory manual.
- Sections 9.2, 9.5.8, 9.6, Synopsis: Updated these sections to provide a formal alpha-spending plan for the key secondary endpoint of OS, following the pre-specified hierarchical approach in the event the primary analysis of PFS is statistically significant. OS will be analyzed at the time of each PFS analysis, in the event that PFS is positive at the same timepoint. Timing of interim and final analyses have been updated to reflect most recent randomization information.
- Section 9.3, Table 17: Removed the separate reference to ADA data in this table.
- Section 9.3.1: Added new subsection for FAS for the initial therapy phase, separate from FAS for the maintenance phase.
- Section 9.3.2.2: Clarified safety analysis set for maintenance phase consists of patients who received at least 1 dose of any study treatment.
- Table 19: Clarified analysis for HRQoL/function.
- Section 9.5.1.1, Synopsis: Updated description of modeling and analysis of primary endpoint PFS.
-Section 9.5.1.2: Updated analysis plan for secondary endpoints to clarify Kaplan-Meier plots will be presented by treatment arm.
- Section 9.5.1.4: Clarified subgroup analyses, including adding objective response to intial therapy subgroup analysis and clarifying minimum number of events per subgroup for analysis.
- Section 9.5.1.5: Removed subsection for analysis of OS due to redundancy with the analysis of secondary variables subsection. Added pre-specified primary PRO measures and updated description of analysis methods for PRO endpoints.
- Section 9.6.1: Updated to indicate interim analysis and final analysis results are not specific to PFS, since OS will be analyzed at those timepoints in the event that PFS is positive at the same timepoint.
- Appendix E: Updated text regarding evaluation of Hy's law.
- Updated abbreviation for safety analysis set from SAS to SAF for clarity.
Version 4.0: 14 July 2020, Revised to remove the first interim analysis for PFS and OS.
- Section 1.2, Section 4.1: Clarified that follow-up tumor assessments will not be required for patients who are not randomized into the maintenance phase.

- Table 3: Removed the Day 30 tumor assessments from the schedule of activities for patients who have discontinued all study treatment.
- Section 6.1.3: Updated estimated data cut-off timing and maturity rate. Maturity rate updated in other sections as appropriate.
- Section 9.2, Section 9.5.1.1, Section 9.5.8, Section 9.6, Section 1.2: Removed first interim analysis at 104 PFS events, as well as the first interim analysis for OS which was to occur at the time of the interim analysis for PFS.
- Section 9.6.1, Section 1.2: Clarified that the IDMC will review the OS interim analysis results. Updated the IDMC meeting frequency to refer to the IDMC Charter for further details.
- Table 23 in Appendix F: Updated overall response to NED for patients with no new lesions and with target/non-target lesions not available. Clarified for the target lesion responses of SD or NE, the non-target lesions response may be Non PD or NE or NA.

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

The procedures for the initial therapy and maintenance phases in this study are presented in Table 1 and Table 2, respectively. The procedures for patients who have discontinued all study treatment are shown in Table 3.

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

For durvalumab treatment:

- Patients may delay dosing under the following 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 version 1.1 [RECIST 1.1]) and patient-reported outcome (PRO) assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see current Investigator Brochure [IB] for durvalumab). If there is a dosing delay while on the every 3 weeks (q3w) schedule (initial therapy phase), all future dosing days for durvalumab should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days.
  - In the event that standard of care (SoC) is delayed during the initial therapy phase, durvalumab administration must also be delayed.

For standard of care treatment:

- Patients may delay standard of care treatment or miss Day 8 or Day 15 (for gemcitabine or nab-paclitaxel dosing) per Investigator judgment and subsequently resume dosing per local standard clinical practice.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.

For olaparib/placebo treatment:

- Prior to the start of maintenance treatment with olaparib/placebo and after the last dose of chemotherapy in the initial therapy, the patient should have his or her hematological/clinical chemistry parameters re-checked. The patient must meet the following requirements without blood transfusions in the past 28 days in order to receive treatment with olaparib/placebo:
  - Hemoglobin (Hb) ≥ 10 g/dL
  - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
  - Platelet count ≥ 100×10^9/L
  - Serum bilirubin ≤1.5 × the upper limit of normal (ULN); unless due to Gilbert's syndrome, in which case patients will be allowed in consultation with their physician and AstraZeneca
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN
  - Creatinine clearance (CrCl) ≥51 mL/min calculated by the investigator or designee using the Cockcroft-Gault equation (using actual body weight [WT]) or measured by 24-hour urine collection

    If the patient does not meet these requirements initially, then the hematology and clinical chemistry parameters should be checked at the next cycle. However, the Investigator may check these laboratory results/parameters earlier (eg, mid cycle) at an unscheduled visit. Once olaparib/placebo is administered, these laboratory thresholds are not required for continued olaparib administration. However, patients must continue to be monitored and assessed (eg, lab parameters and toxicities) per Table 2, and dose delays and modifications for olaparib/placebo should be followed per Sections 6.5 and 8.4.5.2 and Appendix G.
- Patients may interrupt and subsequently resume dosing per Appendix G. Dose reductions may also occur if the study treatment dose is not tolerable.
  - If dosing must be interrupted for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.
  - If a patient meets criteria for randomization before being dosed in maintenance but is later found to not meet criteria to start olaparib/placebo before C1D1 dosing, durvalumab as monotherapy may be started, with olaparib/placebo dosing to commence once the patient again meets the hematology/clinical chemistry requirements and conditions specified above.

One cycle is equal to 28 days (56 doses of olaparib/placebo administered twice daily [BID])

Table 1 Schedule of activities for screening and initial therapy phase (durvalumab plus SoC chemotherapy)

	Screening	C1		C2		C3		C4		For details, see Section
		During initial therapy phase, 1 cycle = 21 days, unless SoC dosing is delayed (eg, for toxicity reasons)								
Week	-4 to -1	0	1	3	4	6	7	9	10	
Day	-28 to -1	1	8	22	29	43	50	64	71	
Window	NA	+3	±2	+3	±2	+3	±2	+3	±2	
Informed consent										
Informed consent: study procedures[a]	X									5.1
CCI	CCI									CCI
Study procedures										
Physical examination (full)	X									8.2.2
Targeted physical examination		X	X	X	X	X	X	X	X	8.2.2
Vital signs[b]	X	X	X	X	X	X	X	X	X	8.2.3
12-lead ECG[c,d]	X	As clinically indicated								8.2.4
Concomitant medications	X	X	X	X	X	X	X	X	X	6.4
Demography	X									6.2.1
Eligibility criteria	X									5.1, 5.2
Medical/surgical history	X									6.2.1
Laboratory assessments[e]										
Clinical chemistry[f]	X	X[g]		X		X		X		Table 14
Hematology[f]	X	X[g]		X		X		X		Table 15
APTT and INR[d]	X	As clinically indicated								Table 15

	Screening	C1		C2		C3		C4		For details, see Section
		During initial therapy phase, 1 cycle = 21 days, unless SoC dosing is delayed (eg, for toxicity reasons)								
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	
Window	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	
TSH[h] (reflex free T3 or free T4[i])	X	X		X		X		X		Table 14
Urinalysis[d]	X	As clinically indicated								Table 16
Hepatitis B and C and HIV	X									8.2.1
Pregnancy test[j]	X	X[g]		X		X		X		8.2.1
Pharmacokinetics										
Durvalumab PK sample (serum)		X[k]		X[l]				X[l]		8.5
Safety monitoring										
WHO/ECOG PS	X	X		X		X		X		8.2.6
AE/SAE assessment[m]	X	X	X	X	X	X	X	X	X	8.3
Early patient review for safety			X		X		X		X	8.2.5
Drug accountability		X		X		X		X		6.3
Pre-randomization medication										
Folic acid/vitamin B12[n]	X	Continue in line with local practice								6.2.1
IP administration (Interval between 2 consecutive doses of durvalumab must be at least 21 days)										
All patients										
Durvalumab[o,p]		X		X		X		X		6.1.1.1, 6.1.2.1
Investigator's choice of platinum-based doublet therapy (SoC), depending on NSCLC histology:										
Nab-paclitaxel[q]		X	X	X	X	X	X	X	X	6.1.2.1

	Screening	C1		C2		C3		C4		For details, see Section
		During initial therapy phase, 1 cycle = 21 days, unless SoC dosing is delayed (eg, for toxicity reasons)								
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	
Window	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	
Carboplatin or cisplatin		X		X		X		X		6.1.2.1
Gemcitabine		X	X	X	X	X	X	X	X	6.1.2.1
Pemetrexed (pemetrexed maintenance therapy will not be allowed following the initial therapy phase)		X		X		X		X		6.1.2.1
Other assessments and assays										
Durvalumab immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)		X[l]		X[l]				X[l]		8.5
CCI [redacted]	[redacted]					[redacted]				[redacted]
CCI [redacted]		[redacted]								[redacted]
CCI [redacted]		[redacted]								[redacted]
CCI [redacted]		[redacted]								[redacted]
Tumor biopsy (newly acquired or archival <3 years old or both)	X									8.8
EGFR and *ALK* test[t]	X									6.2.1
Efficacy evaluations										
Tumor assessments (CT or MRI) (RECIST 1.1)[u,v]	X[v]	Initial therapy phase on-study tumor assessments occur 14 to 28 days after C2D1 and C4D1[w] of the initial therapy phase.								8.1

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated. Every effort should be made to minimize the time between screening and starting treatment (ie, within 1 day after enrollment).

Note: Each cycle during the initial therapy phase is 21 days (unless SoC dosing is delayed). For durvalumab, if there is a dosing delay while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days. For SoC, dosing delays should be managed as per local prescribing guidelines. In the event that SoC is delayed, durvalumab administration must also be delayed.

[a] 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 sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent is included in the main patient ICF. Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary. Tumor biopsies at progression are optional, and the treating physician will judge the feasibility of such a procedure. 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 28 days of enrollment.

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

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

[d] Individual sites are required to indicate in the unscheduled visit eCRF if an ECG, APTT/INR assessment, or urinalysis was performed during study treatment.

[e] Laboratory assessments should be performed according to local standard clinical practice for SoC; if these items are performed on Day 8 or 15 of each cycle per local standard clinical practice, results do not need to be recorded in the clinical database unless abnormal results are associated with AEs and SAEs. Criteria for reporting AEs based on laboratory tests are provided in Section 8.3.7.

[f] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[g] If these screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

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

[i] 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.

[j] Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of the IP (ie, durvalumab or SoC) and then q3w during the initial therapy phase. A urine or serum pregnancy test is acceptable. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing treatment administration.

[k] Within 1 hour of the end of infusion.

[l] Pre-dose (may not exceed 6 hours prior to the start of infusion) same day as infusion.

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

[n] To be administered in line with local practice for patients with non-squamous tumors who will receive pemetrexed. Folic acid and vitamin B12 should commence prior to treatment initiation for up to 7 days, in line with local practice.

[o] Durvalumab will be infused first, followed by the SoC chemotherapy regimen.

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

[q] Nab-paclitaxel will be dosed at Days 1 (±2), 8 (±2), and 15 (±2) of each 3-week cycle. For patients receiving nab-paclitaxel, Day 15 assessments are identical to the Day 8 assessments. Only patients receiving nab-paclitaxel need to attend the visits on Day 15 of each cycle. All patients will attend the Day 8 assessments of each 3-week cycle, regardless of the treatment they are receiving.

[r] CCI

[s] CCI

[t] For patients with unknown status of *ALK* and/or *EGFR* NSCLC. If *EGFR* and *ALK* status is unknown, then the tumor sample (archive or fresh, primary or metastatic) should be used first for local *EGFR* mutation and *ALK* fusion testing. (If patients have squamous histology or are known to have a tumor with a *KRAS* mutation, then *EGFR* and *ALK* testing are not required.)

[u] See Section 6.1.3 and Section 8.1 for additional details relevant to this sampling.

[v] A CT (preferred) or MRI must be performed within 28 days prior to and as close as possible to first-dose administration, and this scan is designated as the "Initial Therapy Baseline" scan; ie, lesions are classified as initial therapy baseline TLs or NTLs. A patient's diagnostic scan may be used as a baseline scan for the initial therapy phase only if taken within 28 days of first-dose administration and in accordance with the scan acquisition requirements (ie, chest and abdomen [including the entire liver and both adrenal glands] IV contrast-enhanced CT/MRI) outlined in Appendix F. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to resume subsequent assessments according to the original imaging visit schedule (relative to the date of randomization). 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 during the study.

[w] The scan at 14 to 28 days after C4D1 of the initial therapy phase will be compared with the initial therapy baseline scan to determine eligibility for the maintenance phase and will also be the "Maintenance Baseline" scan for the assessment of response during the maintenance phase (for those patients eligible for randomization into the maintenance phase) with new RECIST 1.1 baseline assignment of TLs/NTLs.

ADA Anti-drug antibody; AE Adverse event; ALK Anaplastic lymphoma kinase; APTT Activated partial thromboplastin time; C Cycle; CT Computed tomography; CCI ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EGFR epidermal growth factor receptor; HIV Human immunodeficiency virus; CCI ; ICF Informed consent form; IP Investigational product; INR International normalized ratio; IV Intravenous; LFT Liver function test; MRI Magnetic resonance imaging; NA Not applicable; Nab Nanoparticle albumin-bound; NSCLC Non-small cell lung cancer; NTL Non-target lesion; CCI PK Pharmacokinetics; PS Performance status; q3w Every 3 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; CCI SAE Serious adverse event; SoC Standard of care; T3 Triiodothyronine; T4 Thyroxine; TL Target lesion, TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 2 Schedule of activities for maintenance phase (durvalumab plus olaparib/placebo)

	C1[a]	C2 until PD[a]	For details, see Section
Week	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**	
Day	**1**	**Every 28 days ±3 days unless dosing needs to be held for toxicity reasons**	
Study procedures			
Targeted physical examination (based on symptoms)	X	X	8.2.2
Vital signs[b]	X	X	8.2.3
12-lead ECG[c,d]	As clinically indicated		8.2.4
Concomitant medications	X	X	6.4
Randomization eligibility criteria	X[a]		5.1, 5.2
Laboratory assessments			
Clinical chemistry[e]	X	X	Table 14
Hematology[e]	X	X	Table 15
APTT and INR[d]	As clinically indicated		Table 15
TSH (reflex free T3 or free T4[f])	X	X	Table 14
Urinalysis[d]	X	As clinically indicated	Table 16
Pregnancy test[g]	X	X	8.2.1
Pharmacokinetics			
Durvalumab PK sample (serum)	X[h]	At C2D1 and q12w thereafter[i]	8.5
Safety monitoring			
WHO/ECOG PS	X	X	8.2.6
AE/SAE assessment[j]	X	X	8.3
Early patient review for safety	2 weeks ±2 days after receiving the first dose of each of the first 2 cycles of olaparib/placebo maintenance therapy; the form of contact and procedures conducted will be at the Investigator's discretion.		8.2.5

	C1[a]	C2 until PD[a]	For details, see Section
Week	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**	
Day	**1**	**Every 28 days ±3 days unless dosing needs to be held for toxicity reasons**	
Drug accountability	X	X	6.3
IP administration			
Durvalumab[k]	X	X	6.1.1.1, 6.1.2.2
Olaparib/placebo[k,l]	X	X	6.1.1.2, 6.1.2.2
PRO assessments			
EORTC QLQ-LC13, EORTC QLQ-C30, CCI [redacted], CCI [redacted][m]	X	X (±7 days)	8.1.3
Other assessments and assays			
Durvalumab immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)	X[i]	At C2D1 and q12w thereafter[i]	8.5
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]		[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
Optional tumor biopsy (at progression)		X[o]	8.8
Efficacy evaluations			
Tumor assessments (CT or MRI) (RECIST 1.1)[p,q]	Maintenance phase on-study tumor assessments occur q8w ±1 week relative to the date of randomization beginning 8 weeks after randomization for the first 48 weeks and then q12w ±1 week thereafter until RECIST 1.1-defined radiological PD plus one or more additional follow-up scans if clinically feasible. The schedule of q8w ±1 week for the first 48 weeks and then q12w ±1 week thereafter MUST be followed regardless of any delays in dosing.		8.1

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

Note: If there is a dosing delay during the treatment schedule, subsequent time between 2 consecutive doses of durvalumab cannot be less than 21 days (olaparib/placebo administration may continue as scheduled if durvalumab is delayed).

[a] Confirmation of eligibility criteria for randomization (eligibility scan and other specific criteria; see Sections 5.1 and 5.2 for criteria that must be met at randomization) will take place 14 to 28 days after C4D1 of the initial therapy phase. Laboratory assessments for eligibility should be taken after the last dose of chemotherapy in the initial therapy phase and re-checked prior to receiving maintenance treatment (see footnote e below). If determined eligible, patients will be randomized within 5 weeks after C4D1 of the initial therapy phase; every effort should be made to minimize the time between confirmation of eligibility, randomization, and starting maintenance treatment. Patients will continue to receive maintenance treatment until clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Tumor biopsies at progression are optional, and the treating physician will judge the feasibility of such a procedure.

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

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

[d] Individual sites are required to indicate in the unscheduled visit eCRF if an ECG, APTT/INR assessment, or urinalysis was performed during study treatment.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated. Note that CrCl is measured at Day 1 of each cycle during the maintenance phase. Please note that if a patient's creatinine clearance measurement after initial therapy meets eligibility criteria for randomization, and the subsequent creatinine clearance measurement prior to C1D1 (of maintenance therapy) do not (eg, CrCl <51 mL/min), then although the patient can be randomized and receive durvalumab maintenance, the patient cannot start olaparib/placebo therapy until CrCl and other applicable laboratory parameters meet threshold and conditions specified in Section 1.1.

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

[g] Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of the IP (ie, durvalumab, olaparib, or placebo) and then q4w. A urine or serum pregnancy test is acceptable. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing treatment administration.

[h] Within 1 hour of the end of infusion.

[i] Pre-dose (may not exceed 6 hours prior to the start of infusion) same day as infusion.

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

[k] Results for LFTs, electrolytes, full blood count, and creatinine must be available before commencing IP administration (within 3 days) and reviewed by the treating physician or Investigator prior to dosing. The CrCl measured on D1 of each cycle will be used to determine the olaparib/placebo dose. Patients can dose reduce olaparib/placebo due to CrCl changes specified in Table 12. However, once olaparib/placebo dose is reduced due to CrCl changes, escalation is not permitted.

[l] Olaparib/placebo is to be administered continually BID; see Section 6.5 for dose modifications for olaparib/placebo. Olaparib/placebo will be administered once the patient is able to meet all the hematology/clinical chemistry requirements specified in Section 1.1 without blood transfusions within the past 28 days. Once olaparib/placebo administration is allowed, olaparib/placebo will be dispensed to patients at each visit until clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met. All patients must return their bottle(s) of olaparib/placebo at Day 1 of each subsequent cycle.

[m] Will be administered using a site-based, electronic patient-reported outcome (ePRO) device. The PRO questionnaires are to be completed prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions. CCI

CCI

[n] CCI

[o] An optional tumor biopsy (FFPE sample) may be taken at disease progression if the patient provides separate consent; this should be performed as soon as possible after disease progression is confirmed.

[p] See Section 6.1.3 and Section 8.1 for additional details relevant to this sampling.

[q] The scan at 14 to 28 days after C4D1 of the initial therapy phase will be compared with the initial therapy baseline scan to determine eligibility for the maintenance phase and will also be the "Maintenance Baseline" scan for the assessment of response during the maintenance phase (for those patients eligible for randomization into the maintenance phase) with new RECIST 1.1 baseline assignment of TLs/NTLs. Patients who are treated through progression will have scans collected and RECIST assessments performed according to the imaging schedule until discontinuing treatment (ie, entering follow-up; see Section 6.1.3 for more details). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to resume subsequent assessments according to the original imaging visit schedule (relative to the date of randomization). 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 during the study.

ADA Anti-drug antibody; AE Adverse event; APTT Activated partial thromboplastin time; BID twice daily; C Cycle; CrCl Creatinine clearance; CT Computed tomography; CCI CCI D Day; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC European Organisation for Research and Treatment of Cancer; ePRO electronic patient-reported outcome; CCI FFPE Formalin-fixed, paraffin embedded; CCI IP Investigational product; INR International normalized ratio; LFT Liver function test; MRI Magnetic resonance imaging; NTL Non-target lesion; CCI PD Progressive disease; CCI PK Pharmacokinetics; CCI ; PS Performance status; q12w Every 12 weeks; q4w Every 4 weeks; q8w Every 8 weeks; QLQ-C30 30-item Core Quality of Life Questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; CCI SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TL Target lesion; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 3 Schedule of activities for patients who have discontinued all study treatment

Evaluation	Time since last dose of IP								For details, see Section
	Day (±5)	Months (±1 week)						12 months and every 2 months thereafter (±2 weeks)	
	30	2	3	4	6	8	10		
Physical examination (full)	X								8.2.2
Vital signs (temperature, respiratory rate, BP, and pulse)	X	X	X						8.2.3
Weight	X	X	X		X				8.2.3
Pregnancy test[a,b]	X	As clinically indicated							8.2.1
AE/SAE assessment[c]	X	X	X						8.3
Concomitant medications	X	X	X						6.4
WHO/ECOG PS	At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy[d]								8.2.6
Subsequent anticancer therapy[e]	X	X	X	X	X	X	X	X	8.1.2
Survival status[f]		X		X	X	X	X	X	8.1.2
Hematology	X	X	X						Table 15
Clinical chemistry	X	X	X						Table 14
Urinalysis[b]	As clinically indicated								Table 16
TSH (reflex free T3 or free T4)[g]	X	X	X						Table 14
Durvalumab PK sample (serum)[h]			X						8.5
Durvalumab immunogenicity assessments (ADA sampling to identify ADA responses in patient circulation)[h]			X		X				8.5

Evaluation	Time since last dose of IP								For details, see Section
	Day (±5)	Months (±1 week)						12 months and every 2 months thereafter (±2 weeks)	
	30	2	3	4	6	8	10		
EORTC QLQ-LC13, EORTC QLQ-C30, CCI [redacted][i]	q4w (±7 days; relative to date of last dose of IP) up to 3 months post-treatment discontinuation. For patients who discontinue study treatment due to toxicity (or symptomatic deterioration), PRO assessments should be performed as follows: q4w (±7 days relative to date of last dose of IP for the first 3 months and q8w ±7 days thereafter) until 3 months post-RECIST 1.1-defined radiological PD. For patients who are not randomized into the maintenance phase for any reason, durvalumab will be discontinued and PRO assessments will not be required.								8.1.3
CCI [redacted]	[redacted]								
Tumor assessments (CT or MRI) (RECIST 1.1)[k]		On-study tumor assessments occur q8w ±1 week relative to the date of randomization beginning 8 weeks after randomization for the first 48 weeks and then q12w ±1 week thereafter until RECIST 1.1-defined radiological PD plus one or more additional follow-up scans if clinically feasible. The schedule of q8w ±1 week for the first 48 weeks and then q12w ±1 week thereafter MUST be followed regardless of any delays in dosing in the maintenance phase. For patients who are not randomized into the maintenance phase for any reason, durvalumab will be discontinued and follow-up tumor assessments will not be required.							8.1

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

[b] Individual sites are required to indicate in the unscheduled visit eCRF if a pregnancy test or urinalysis was performed during the follow-up (post-treatment discontinuation) period.

[c] AEs and SAEs will be collected through 90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later (see Section 8.3.2.1 for reporting of AEs after the follow-up period).

[d] WHO/ECOG PS 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 PS should be provided when information on subsequent anticancer therapy is provided, where possible.

[e] Details of any treatment for NSCLC after the last dose of the IP must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.

[f] Patients may be contacted in the week following data cut-offs to confirm survival status. Details of any treatment for NSCLC after the last dose of the IP must be recorded in the eCRF.

[g] 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.

[h] PK and immunogenicity samples for durvalumab are collected 90 days (3 months; ±7 days) after treatment with durvalumab ends. In addition, a final sample for ADA is taken 6 months (±7 days) after treatment with durvalumab ends.

[i] CCI

[j] CCI

[k] Patients will have on-study scans done q8w ±1 week relative to the date of randomization for the first 48 weeks and then q12w ±1 week thereafter until RECIST 1.1-defined radiological PD plus one or more additional follow-up scans if clinically feasible. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to resume subsequent assessments according to the original imaging visit schedule (relative to the date of randomization). 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 during the study.

ADA Anti-drug antibody; AE Adverse event; BP Blood pressure; CT Computerized tomography; CCI ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC European Organisation for Research and Treatment of Cancer; ePRO electronic patient-reported outcome; CCI IP Investigational product; CCI CCI IV Intravenous; MRI Magnetic resonance imaging; NSCLC Non-small cell lung cancer; PD Progressive disease; CCI PK Pharmacokinetics; CCI ; PS Performance status; q12w Every 12 weeks; q4w Every 4 weeks; q8w Every 8 weeks; QLQ-C30 30-item Core Quality of Life Questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone; w Week; WHO World Health Organization.

1.2 Synopsis

International Co-ordinating Investigator

Protocol Title: A Phase II Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab plus Olaparib Combination Therapy Compared with Durvalumab Monotherapy as Maintenance Therapy in Patients whose Disease has not Progressed Following Standard of Care Platinum-Based Chemotherapy with Durvalumab in First-Line Stage IV Non-Small Cell Lung Cancer (ORION)

Short Title: ORION Study

Rationale:

Current SoC therapies for metastatic non-small cell lung cancer (NSCLC) have mixed outcomes with responses to systemic chemotherapy in the first-line setting of approximately 20% to 40% and a median overall survival (OS) of approximately 11 to 14 months (Breslow 1974, Carbone et al 2017, Paz-Ares et al 2013, Socinski et al 2018, Gandhi et al 2018). Treatments are associated with a variety of significant side effects, including neutropenia, nausea, vomiting and dehydration, and alopecia (Sandler et al 2006, Scagliotti et al 2008). The KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, and KEYNOTE-407 studies, along with the IMpower131 and IMpower150 studies, have shown that immunotherapy alone or in combination with chemotherapy can be effective first-line treatment for patients with metastatic NSCLC (Gandhi et al 2018, Jotte et al 2018, Lopes et al 2018, Paz-Ares et al 2018, Reck et al 2016, Socinski et al 2018).

Results from these studies have been encouraging and represent a substantive advance, but further improvement is needed. All of the aforementioned studies yielded a median progression-free survival (PFS) of <1 year. Furthermore, there are no approved maintenance immunotherapy-based combination regimens for patients with squamous histology. Increased DNA damage triggered through polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase (PARP) inhibition has the potential to not only provide antitumor activity but also modify tumor immunogenicity and sensitize tumors to immune checkpoint inhibition, promoting a more durable antitumor response. Therefore, in this Phase II study, the combination of durvalumab plus olaparib will be investigated to determine if this combination

can prolong PFS in the maintenance setting in patients whose Stage IV NSCLC has not progressed following SoC platinum-based chemotherapy with durvalumab.

Table 4 Study objectives

Primary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed)	PFS: Time from date of randomization until the date of objective radiological disease progression according to Investigator assessment using RECIST 1.1 or death (by any cause in the absence of progression)
Secondary objectives:	**Endpoints/variables:**
To further assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of OS, ORR, and DoR	OS: Time from date of randomization until the date of death by any cause ORR: Percentage of patients with an Investigator-assessed response of CR or PR after randomization DoR: Time from the date of first documented response following randomization until the first date of documented progression or death in the absence of disease progression
To further assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed) in the HRRm population	PFS: Time from date of randomization until the date of objective radiological disease progression according to Investigator assessment in HRRm population using RECIST 1.1 or death (by any cause in the absence of progression)
To assess the PK of durvalumab in combination with olaparib	Concentration of durvalumab
To assess disease-related symptoms and HRQoL in patients treated with durvalumab plus olaparib combination therapy compared with durvalumab monotherapy	Change from baseline and time to deterioration (for maintenance phase) in EORTC QLQ-C30 and EORTC QLQ-LC13
To investigate the immunogenicity of durvalumab	Presence of ADAs for durvalumab
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability profile of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy	AEs, physical examinations, laboratory findings, and vital signs
CCI [redacted]	[redacted]
CCI [redacted]	CCI [redacted]

Table 4 Study objectives

CCI	CCI

ADA Anti-drug antibody; AE Adverse event; CR Complete response; CCI DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; CCI HRQoL Health-related quality of life; CCI HRRm Homologous recombination repair related gene mutation; IHC Immunohistochemistry; CCI ORR Objective response rate; OS Overall survival; CCI PFS Progression-free survival; CCI PK Pharmacokinetics; PR Partial response; CCI QLQ-C30 30-item Core Quality of Life Questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; CCI .

Overall design:

This is a Phase II randomized, multi-center, double-blind, global study to determine the efficacy and safety of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy as maintenance therapy in patients whose disease has not progressed following SoC platinum-based chemotherapy with durvalumab in first-line Stage IV NSCLC. There will be approximately 80 sites in the study. During the initial therapy phase, approximately 350 to 400 patients will receive treatment with durvalumab, along with the Investigator's choice of platinum-based doublet therapy for squamous NSCLC (nanoparticle albumin-bound [nab]-paclitaxel plus carboplatin or gemcitabine plus carboplatin/cisplatin) and nonsquamous NSCLC (nab-paclitaxel plus carboplatin or pemetrexed plus carboplatin/cisplatin) for 4 cycles.

It is estimated that approximately 350 to 400 patients will be enrolled in the initial therapy phase in order for approximately 250 patients who have not progressed (ie, maintained complete response [CR], partial response [PR], or stable disease [SD] throughout the initial therapy phase according to Investigator-assessed RECIST 1.1) to be randomized into the maintenance phase of the study (patients completing the initial therapy phase who are not randomized cannot continue durvalumab). Patients will be randomized 1:1 to receive either durvalumab plus placebo or durvalumab plus olaparib maintenance therapy. Randomization will be stratified by histologic subtype (squamous or nonsquamous) and objective response (CR/PR or SD; obtained at the last visit prior to randomization [Cycle 4 scan]) during the initial therapy phase.

Confirmation of eligibility criteria for randomization (eligibility scan and other specific criteria; see Sections 5.1 and 5.2 for criteria that must be met at randomization) will take place 14 to 28 days after Cycle 4 Day 1 of the initial therapy phase. Laboratory assessments for eligibility should be taken after the last dose of chemotherapy in the initial therapy phase. If determined eligible, patients will be randomized within 5 weeks after Cycle 4 Day 1 of the initial therapy phase; every effort should be made to minimize the time between confirmation of eligibility, randomization, and starting maintenance treatment. Patients will receive maintenance treatment until specific discontinuation criteria are met, including clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unacceptable toxicity, and withdrawal of consent. Note that crossover within the study will not be permitted.

Study Period:

Estimated date of first patient enrolled: Q4 2018

Estimated date of last patient completed: Q1 2022

Number of patients:

Approximately 350 to 400 patients will be enrolled in the initial therapy phase of the study. Approximately 250 patients globally who have not progressed will be randomized in a 1:1 ratio to either the durvalumab plus olaparib treatment arm or the durvalumab plus placebo treatment arm, approximately 125 patients per arm. The randomization will be stratified based on objective response to durvalumab plus chemotherapy (CR/PR or SD; obtained at the last visit prior to randomization [Cycle 4 scan]) and histology (squamous or nonsquamous).

Treatments and treatment duration:

Durvalumab (MEDI4736) and platinum-based chemotherapy (initial therapy phase)

During the initial therapy phase, all patients will receive durvalumab 1500 mg via intravenous (IV) infusion q3w for 4 cycles, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met. If a patient's WT falls to 30 kg or below, the patient should receive WT-based dosing equivalent to 20 mg/kg of durvalumab q3w after consultation between Investigator and Study Physician until the WT improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q3w. If there is a dosing delay during the treatment schedule for durvalumab, all future dosing days for durvalumab should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days. The standard infusion time is 60 minutes. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

In addition to durvalumab, patients in the initial therapy phase will also receive 1 of the following SoC regimens as part of their treatment regimen (durvalumab will be infused first, followed by the SoC chemotherapy regimen):

- Nab-paclitaxel plus carboplatin (squamous and nonsquamous patients): Nab-paclitaxel 100 mg/m^2 via IV infusion on Days 1, 8, and 15 of each 3-week cycle and carboplatin area under the concentration-time curve (AUC) 5 or 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 2).
- Gemcitabine plus carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 3-week cycle and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 3).
- Gemcitabine plus cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 3-week cycle and cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 3).
- Pemetrexed plus carboplatin (nonsquamous patients only): Pemetrexed 500 mg/m^2 and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 4). Pemetrexed maintenance therapy will not be allowed following the initial therapy phase.
- Pemetrexed plus cisplatin (nonsquamous patients only): Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 4). Pemetrexed maintenance therapy will not be allowed following the initial therapy phase.

In the event that SoC is delayed during the initial therapy phase, durvalumab administration must also be delayed.

In the event of unfavorable tolerability, patients can switch between cisplatin and carboplatin therapy at any point during the study.

Durvalumab monotherapy and durvalumab plus olaparib combination therapy (maintenance phase)

During the maintenance phase, all patients will receive durvalumab 1500 mg via IV infusion every 4 weeks (q4w). Patients will also receive 300 mg oral olaparib (durvalumab plus olaparib treatment arm) or its matching placebo (durvalumab plus placebo treatment arm) BID continually until clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD (Figure 5 and Figure 6), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met.

Before commencing olaparib/placebo treatment, patients must first meet the hematology/clinical chemistry requirements specified in Section 1.1 without blood transfusions in the past 28 days.

If a patient's WT falls to 30 kg or below, the patient should receive WT-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between Investigator and Study

Physician until the WT improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w. If there is a dosing delay during the treatment schedule for durvalumab, subsequent time between 2 consecutive doses of durvalumab cannot be less than 21 days; olaparib/placebo administration may continue as scheduled if durvalumab is delayed. The standard infusion time for durvalumab is 60 minutes. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

See Section 7.1 for details about discontinuation of either durvalumab or olaparib/placebo in the maintenance phase.

Duration of treatment

Unless specific treatment discontinuation criteria are met, treatment during the initial therapy phase will continue for only 4 cycles of durvalumab plus chemotherapy. There is no maximum treatment duration for the maintenance phase; patients will receive maintenance treatment until specific discontinuation criteria are met, including clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unacceptable toxicity, and withdrawal of consent.

Progression during treatment

Patients with clinical disease progression (as assessed by the Investigator), in the initial therapy or maintenance phase of the study, are not eligible for treatment through progression. Patients who are clinically stable with RECIST 1.1-defined radiological PD at Cycle 2 of the initial therapy phase may continue to receive study treatment at the discretion of the Investigator and patient; however, if the patient continues to show a RECIST 1.1-defined radiological PD at Cycle 4, the patient will not be eligible for the maintenance phase of the study. Patients completing the initial therapy phase who are not randomized cannot continue durvalumab.

During the maintenance phase, patients who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is to be collected after the initial RECIST 1.1-defined radiological PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix F.

Patients with PD in the maintenance phase who continue to receive investigational product (IP) at the discretion of the Investigator and patient (following consultation with AstraZeneca) will have tumor assessments on their regular imaging schedule for the duration of treatment. However, patients will not be permitted to continue immunotherapy or olaparib/placebo if

progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) in the target lesions (TLs) to either the initial therapy (durvalumab plus chemotherapy) or maintenance treatment (durvalumab or olaparib/placebo) of the study regardless of the appearance of new lesions. Patients who have discontinued durvalumab will not be permitted to be treated with olaparib/placebo monotherapy after progression.

Follow-up of patients post discontinuation of study drug

Patients who have discontinued treatment in the maintenance phase for any reason other than RECIST 1.1-defined radiological PD will be followed up with tumor assessments until RECIST 1.1-defined radiological PD, plus one or more additional follow-up scans if clinically feasible. Patients who discontinue treatment due to RECIST 1.1-defined radiological PD will have one or more additional follow-up scans, if clinically feasible. All patients will be followed for survival. For patients who are not randomized into the maintenance phase for any reason, follow-up tumor assessments will not be required.

Survival

All patients enrolled in the study should be followed up for survival. Assessments for survival must be made every 2 months following treatment discontinuation. See Section 7.3 for further details on survival follow-up for patients who choose to withdraw from the study.

Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) will be established to perform an assessment of the safety of durvalumab plus olaparib therapy combinations in this population on an ongoing basis. The IDMC will be comprised of independent experts. The committee will meet at a frequency outlined in the IDMC Charter.

IDMC members will be consulted to ensure appropriate frequency. Following each meeting, the IDMC will report to AstraZeneca and may recommend changes in the conduct of the study.

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

Statistical methods

The primary objective of this study is to assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy during the maintenance phase in terms of PFS as determined by Investigator assessment according to RECIST 1.1 in all randomized patients. A key secondary objective is to assess the efficacy of durvalumab plus olaparib compared with durvalumab monotherapy in terms of OS. In order to provide strong control of the type I error rate α=5% (2-sided), the testing procedure for the primary endpoint and key secondary endpoint is hierarchical.

Additional, secondary efficacy variables include objective response rate (ORR) and duration of response (DoR) in the full analysis set (FAS), and PFS as determined by Investigator assessment according to RECIST 1.1 in the homologous recombination repair related gene mutation (HRRm) subgroup. Sensitivity analyses for the primary endpoint will be performed, including analyzing PFS according to blinded independent central review (BICR) in the FAS.

Approximately 350 to 400 patients will be enrolled in the initial therapy phase of the study. Approximately 250 patients globally who have not progressed will be randomized in a 1:1 ratio to either the durvalumab plus olaparib treatment arm or the durvalumab plus placebo treatment arm, approximately 125 patients per arm. The randomization will be stratified based on objective response to durvalumab plus chemotherapy (CR/PR or SD; obtained at the last visit prior to randomization [Cycle 4 scan]) and histology (squamous or nonsquamous).

The primary analyses will be based on Investigator-recorded assessment of disease progression using RECIST 1.1 criteria. CCI

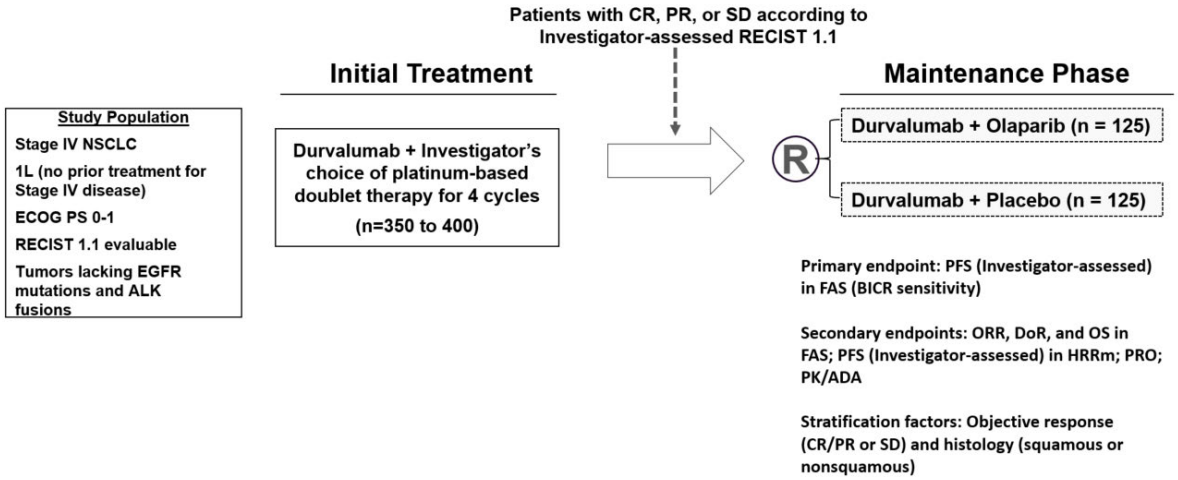
The effect of durvalumab + olaparib versus durvalumab + placebo will be estimated by the HR together with its 95% CI from a stratified Cox model (an HR less than 1 will favor durvalumab in combination with olaparib). The CI will be calculated using a profile likelihood approach.

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

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



Note: Crossover within the study will not be permitted.

1L First-line; ADA Anti-drug antibodies; *ALK* Anaplastic lymphoma kinase; BICR Blinded independent central review; CR Complete response; ECOG Eastern Cooperative Oncology Group; *EGFR* Epidermal growth factor receptor; DoR duration of response; FAS Full analysis set; HRRm Homologous recombination repair related gene mutation; NSCLC Non-small cell lung cancer; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetic; PR Partial response; PRO Patient-reported outcome; PS Performance status; R Randomization; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SD Stable disease.

2. INTRODUCTION

2.1 Study rationale

Current SoC therapies for metastatic NSCLC have mixed outcomes with responses to systemic chemotherapy in the first-line setting of approximately 20% to 40% and a median OS of approximately 11 to 14 months (Breslow 1974, Carbone et al 2017, Paz-Ares et al 2013, Socinski et al 2018, Gandhi et al 2018). Treatments are associated with a variety of significant side effects, including neutropenia, nausea, vomiting and dehydration, and alopecia (Sandler et al 2006, Scagliotti et al 2008). The KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, and KEYNOTE-407 studies, along with the IMpower131 and IMpower150 studies, have shown that immunotherapy alone or in combination with chemotherapy can be effective first-line treatment for patients with metastatic NSCLC (Gandhi et al 2018, Jotte et al 2018, Lopes et al 2018, Paz-Ares et al 2018, Reck et al 2016, Socinski et al 2018).

Results from these studies have been encouraging and represent a substantive advance, but further improvement is needed. All of the aforementioned studies yielded a median PFS of <1 year. Furthermore, there are no approved maintenance immunotherapy-based combination regimens for patients with squamous histology. Increased DNA damage triggered through PARP inhibition has the potential to not only provide antitumor activity but also modify tumor immunogenicity and sensitize tumors to immune checkpoint inhibition, promoting a more durable antitumor response. Therefore, in this Phase II study, the combination of durvalumab plus olaparib will be investigated to determine if this combination can prolong PFS in the maintenance setting in patients whose Stage IV NSCLC has not progressed following SoC platinum-based chemotherapy with durvalumab.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab and olaparib is provided in the respective IB for each compound.

2.2.1 Non-small cell lung cancer

Lung cancer has been the most common cancer in the world for several decades, with an estimated 1.8 million new cases in 2012 (12.9% of all new cancers), and was also the most common cause of death from cancer in 2012, with 1.6 million deaths (19.4% of cancer deaths; GLOBOCAN 2012). NSCLC represents 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of patients with NSCLC have advanced or metastatic disease not amenable to potentially curative surgical resection. Furthermore, approximately 50% of patients with early-stage NSCLC who have undergone surgery subsequently develop distant recurrence and die as a result of NSCLC (Pisters and LeChevalier 2005).

Despite advances in the diagnosis, imaging, staging, and treatment of NSCLC, the estimated 5-year OS for patients in Europe and the United States (US) continues to be exceedingly low

(11% and 17%, respectively; D'Addario et al 2010, Howlander et al 2017). The 5-year OS for patients in the US from the time of diagnosis of metastatic NSCLC is only 4.5% (Howlander et al 2017). Patients presenting with metastatic NSCLC without a targetable mutation (ie, epidermal growth factor receptor [*EGFR*] or anaplastic lymphoma kinase [*ALK*] mutation) demonstrate responses to chemotherapy-based systemic treatment of approximately 20% to 40%, have a median PFS of between approximately 6 to 9 months and a median OS of 11 to 14 months (Breslow 1974, Carbone et al 2017, Gandhi et al 2018, Paz-Ares et al 2013, Socinski et al 2018). The DoRs are also limited, and toxicities can be a major limiting factor.

Common first-line treatment regimens for metastatic NSCLC without a targetable mutation are platinum-based doublets and include carboplatin and paclitaxel (eg, nab-paclitaxel, carboplatin and gemcitabine, carboplatin and pemetrexed (nonsquamous only), cisplatin and gemcitabine, and cisplatin and pemetrexed (nonsquamous only). Although platinum-based doublets are interchangeable in terms of efficacy when used alone, these doublets vary to some extent with regard to convenience, associated toxicities, and cost, with the selection of a specific regimen often dictated by local practice and individualized on a case-by-case basis.

Maintenance therapy with either continuation or switch of a component of the patient's initial treatment regimen is an option for patients following initial treatment. Choice of therapy is influenced by histologic subtype (squamous or nonsquamous), with choices including single agent chemotherapy, bevacizumab, or pemetrexed. There have been multiple studies that have illustrated the efficacy of continued maintenance therapy of various agents with improved median PFS and median OS compared to observation/best supportive care (Sandler et al 2006, Fidias et al 2009, Pérol et al 2012, Ciuleanu et al 2009, Paz-Ares et al 2013). However, upon review of the overall data from these studies, the anticipated PFS and OS remain poor and, as such, there remains significant room for improvement with many studies currently investigating different combinations of these approved agents, immunotherapy, and other novel agents in the maintenance setting.

2.2.2 Immunotherapies

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

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

signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells (TCs) exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

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

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. 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 preclinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015a, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (Fife and Bluestone 2008). Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and initial therapy 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.

Preclinical data has 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, along with durvalumab and atezolizumab, 2 anti-PD-L1 agents, have been granted approvals by agencies for the treatment of a number of malignancies including metastatic melanoma, squamous and nonsquamous cell NSCLC, squamous cell carcinoma of the head and neck (SCCHN), 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.

2.2.3 Immunotherapy in non-small cell lung cancer

A plateau has apparently been reached with platinum-based doublet chemotherapy with regards to efficacy, in addition to concerns regarding DoR, and tolerability. Therefore, other mechanisms and modalities have been explored to improve upon traditional therapies. The opportunity to explore immune therapies greatly expanded with the identification of the checkpoint inhibitor agents. These agents demonstrated clinically meaningful responses in metastatic NSCLC, with some patients exhibiting durable responses even after discontinuing therapy (Malhotra et al 2017). As a result, the treatment landscape of NSCLC across different lines of therapies has continuously evolved since the introduction of checkpoint inhibitor agents.

For the treatment of NSCLC in the first-line setting, pembrolizumab (a PD-1 inhibitor) recently gained FDA approval for the first-line treatment of metastatic NSCLC in patients with high PD-L1 expression and without *EGFR* or *ALK* genomic tumor aberrations. Regulatory approval was based on safety and efficacy data from the KEYNOTE-024 study. Results from this study, which included patients with metastatic NSCLC and PD-L1 expression on at least 50% of TCs and with no activating *EGFR* mutations or *ALK* fusions, demonstrated that patients treated with pembrolizumab had a longer median PFS (10.3 versus 6.0 months, HR for disease progression or death, 0.5) and OS (median OS not reached in either group, HR for death, 0.60) and higher ORR (44.8% versus 27.8%) compared with patients treated with platinum-based therapy (Reck et al 2016).

Similar results were seen in patients with TCs with ≥50% PD-L1 expression in the KEYNOTE-042 study, which included patients of a similar population comparing pembrolizumab with platinum-based chemotherapy (Lopes et al 2018). Analysis in this study showed that patients with a ≥50% PD-L1 expression derived the greatest benefit from pembrolizumab monotherapy in terms of median PFS (7.1 versus 6.4 months, HR for disease progression or death 0.81), median OS (20 versus 12.2 months, HR for death 0.69), and ORR (39.5% versus 32.0%). An exploratory analysis of patients with a PD-L1 expression of

between 1% and 49% showed a modest benefit in this patient population in terms of median OS (13.4 versus 12.1 months, HR for death 0.92).

In addition to the efficacy of monotherapy checkpoint inhibition demonstrated in NSCLC in patients with high expression of PD-L1, the KEYNOTE-189 and IMpower150 studies demonstrated the efficacy of checkpoint inhibition in combination with chemotherapy. The KEYNOTE-189 study is a randomized Phase III study that compared the efficacy and safety of pembrolizumab plus a platinum-based agent and pemetrexed to pemetrexed and a platinum-based agent alone as first-line therapy for patients with Stage IV nonsquamous NSCLC. The IMpower150 study is a Phase III study that compared the efficacy and safety of atezolizumab plus bevacizumab, carboplatin, and paclitaxel to bevacizumab, carboplatin, and paclitaxel alone in a similar patient population as KEYNOTE-189.

The KEYNOTE-189 patients who were treated with first-line pembrolizumab in combination with pemetrexed and platinum chemotherapy had a longer median PFS (8.8 versus 4.9 months, HR for disease progression or death 0.52), median OS (OS not reached versus 11.3 months, HR for death 0.49), and higher ORR (47.6% versus 18.9%) compared with pemetrexed plus platinum chemotherapy (Gandhi et al 2018). The IMpower150 patients who were treated with first-line atezolizumab in combination with bevacizumab and chemotherapy had a longer median PFS (8.3 versus 6.8 months, HR for progression or death 0.62), median OS (19.2 versus 14.7 months, HR for death 0.78), and higher ORR (63.5% versus 48%) compared with bevacizumab and chemotherapy (Socinski et al 2018).

Encouraging efficacy results were also demonstrated utilizing checkpoint inhibition in combination with chemotherapy for the KEYNOTE-407 and IMpower131 studies in Stage IV squamous NSCLC patients. Both KEYNOTE-407 and IMpower131 are Phase III studies, comparing pembrolizumab or atezolizumab plus paclitaxel/nab-paclitaxel and carboplatin to paclitaxel/nab-paclitaxel and carboplatin as first-line therapy for patients with Stage IV squamous NSCLC, respectively. The KEYNOTE-407 patients who were treated with first-line pembrolizumab in combination with paclitaxel or nab-paclitaxel had a longer median PFS (6.4 versus 4.8 months, HR for disease progression or death 0.56) and median OS (15.9 versus 11.3 months, HR for death 0.64) compared with paclitaxel/nab-paclitaxel and carboplatin (Paz-Ares et al 2018). The IMpower131 patients who were treated with first-line atezolizumab in combination with nab-paclitaxel and carboplatin had a longer median PFS (6.3 versus 5.6 months, HR for disease progression or death 0.71) and greater ORR (49% versus 41%) compared with nab-paclitaxel and carboplatin (Jotte et al 2018). However, the OS benefit demonstrated by the atezolizumab plus chemotherapy combination was modest (median OS: 14 versus 13.9 months, HR for death 0.96).

All of these aforementioned studies have shown that immunotherapy alone or in combination with chemotherapy can be an effective first-line treatment option for patients with metastatic NSCLC.

2.2.4 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G 1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed 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 (IFN)-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 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 Section 4.3.1 and Section 8.3.12.1. Refer to the current durvalumab IB for a complete summary of preclinical and clinical information including safety, efficacy, and PK.

2.2.5 Olaparib

Olaparib (LYNPARZA™) is a potent inhibitor of PARP that received marketing approval (tablet formulation) in the US on 17 August 2017 for the following indication: "Lynparza is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a CR or PR to platinum-based chemotherapy; and for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (*BRCA*)-mutated (g*BRCA*m) advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy". In January 2018, olaparib (tablet formulation) also received marketing approval in the US for the following indication: "Lynparza is indicated in patients with deleterious or suspected deleterious g*BRCA*m, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine

treatment." In the European Union (EU), the tablet formulation of olaparib received marketing authorization in February 2018 as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Furthermore, as of 1 March 2017, the capsule formulation of olaparib has received marketing approval in more than 50 countries including those in the EU and the US and Switzerland, Australia, and Canada. The capsule formulation is indicated for ovarian cancer only.

Details on the safety profile of olaparib monotherapy are summarized in Section 4.3.4 and Section 8.3.12.2. Refer to the current olaparib IB for a complete summary of preclinical and clinical information including safety, efficacy, and PK. The tablet formulation will be used for this study.

2.2.6 Durvalumab in combination with olaparib in the full analysis set

In this study, the PARP inhibitor olaparib will be combined with the PD-L1 inhibitor durvalumab in patients who do not progress following treatment combination of platinum-based chemotherapy with durvalumab. Combining durvalumab with olaparib therapy may yield additive mechanisms to promote a more robust and durable antitumor response. There have been preclinical data to suggest that olaparib may potentiate the efficacy of DNA-damaging chemotherapies including platinum-containing agents (Evers et al 2008, Rottenberg et al 2008) along with clinical evidence that olaparib can be an effective option in platinum-sensitive tumors including ovarian cancer (Oza et al 2015, Ledermann et al 2012). There is also preclinical evidence to support olaparib as an effective option for other platinum-sensitive tumors such as NSCLC through an analysis that demonstrated the correlation of olaparib response with several SoC chemotherapies in a panel of NSCLC cancer cell lines. CCI [redacted]

This correlation between olaparib and platinum sensitivity is theorized to be due to the underlying mechanisms surrounding platinum agents and PARP inhibition, as TCs exhibiting DNA repair gene loss of function mutations lack effective, accurate mechanisms for DNA repair.

Inhibition of PARP in sensitive TCs results in accumulating levels of DNA damage and genomic instability, ultimately resulting in cell death (Farmer et al 2005). Furthermore, accumulating DNA damage has the potential to modify the immunogenicity of tumors through a number of key mechanisms:

- Triggering of intracellular signaling events that result in the activation of nuclear factor kappa B and interferon regulatory factor 7. These transcriptional regulators result in the increased production of cytokines and chemokines that have the potential to promote antitumor immunity, such as type I IFNs (Chatzinikolaou et al 2014).
- Upregulation of surface receptors such as major histocompatibility complex, ligands for natural-killer group 2, member D and inducible T-cell costimulatory ligand, which render TCs more visible to detection by cytotoxic T cells (Tang et al 2014).
- Increasing the number of CD8(+) T and natural killer cells, boosting production of IFN-γ and tumor necrosis factor (TNF)-α, and prolonging survival of mice bearing *BRCA*1-deficient murine ovarian cancer cell line (Huang et al 2015).
- Death of TCs and release of antigen, which may help to promote antigen presentation and immune priming (Kroemer et al 2013).

These effects would be expected to help promote a more robust antitumor immune response than that obtained with monotherapy PD-1 or PD-L1 inhibition through improved lung tumor immunogenicity. In keeping with this hypothesis, several tumor types with genetic defects expected to lead to increased DNA damage show evidence of enhanced immune recognition (Mulligan et al 2014) and published data link DNA repair gene mutation frequency, tumor mutational burden (TMB), and clinical benefit from checkpoint inhibition in NSCLC (Rizvi et al 2015b).

Details on the safety profile of durvalumab plus olaparib combination therapy are summarized in Section 2.3.2.3. Details on the efficacy of durvalumab plus olaparib combination therapy are summarized in Section 2.3.1.3.

2.2.6.1 Rationale for the combination of durvalumab plus olaparib for HRRm tumors

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HRR). Tumors with homologous recombination deficiencies cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. The MOA for olaparib results from the trapping of inactive PARP onto the SSBs preventing their repair (Helleday 2011, Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HRR. Therefore, in such tumor types, the addition of olaparib to durvalumab may offer a

potentially more robust antitumor response compared with non HRRm tumors with a higher amount of accumulating DNA damage to potentially increase lung tumor immunogenicity.

2.2.7 Durvalumab in combination with chemotherapy

The use of combination chemotherapy is a mainstay of oncology therapy. The goal of combination chemotherapy is to utilize agents that affect cancer cells by different mechanisms, thus reducing the risk of developing resistance. Current studies are now adding immunotherapeutics to chemotherapeutics with encouraging activity in Stage IV NSCLC (see Section 2.2.3).

In addition to the PD-1/PD-L1 chemotherapy combination studies mentioned in Section 2.2.3, data for durvalumab with or without tremelimumab with standard platinum-based chemotherapy in advanced cancers are being generated from 2 ongoing Phase I studies: the internal Study D419SC00001 (n=10) and a Phase Ib study (NCT02537418) run by the Canadian Cancer Trials Group (CCTG; n=118; Daaboul et al 2017). The combinations tested are tolerable and toxicities manageable. Preliminary results from the CCTG study were presented for the NSCLC cohorts at the International Association for the Study of Lung Cancer (IASLC) 2016 meeting; the overall ORR in NSCLC cohort (n=24) was 52.9% (Juergens et al 2017).

In summary, the efficacy, safety, and tolerability data of immunotherapies in combination with chemotherapy support the continued development of these treatments for NSCLC.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of durvalumab and olaparib may be found in the respective IB for each compound.

2.3.1 Potential benefits

2.3.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first-in-human, single-agent study (Study CD-ON-MEDI4736-1108; hereafter referred to as Study 1108) in patients with advanced solid tumors and the study of durvalumab monotherapy in NSCLC (Study D4191C00003 [ATLANTIC]). In Study 1108, as of 7 May 2015, 456 of 694 patients treated with durvalumab 10 mg/kg every 2 weeks (q2w) were evaluable for response (defined as having ≥24-week follow-up, measurable disease at baseline, and ≥1 follow-up scan or discontinued because of disease progression or death without any follow-up scan). Data from treatment-naïve patients with NSCLC in this study (n=59) showed a favorable disease control rate (DCR) at ≥12 weeks of 56% when durvalumab was given 10 mg/kg q2w (Antonia et al 2016).

In PD-L1 unselected patients, the ORR, based on Investigator assessment per RECIST 1.1, ranged from 0% in uveal melanoma to 20.0% in bladder cancer, and DCR at 24 weeks ranged from 4.2% in triple-negative breast cancer to 39.1% in advanced cutaneous melanoma. PD-L1 status was known for 383 of the 456 response-evaluable patients. Across the PD-L1-positive tumors (defined as PD-L1 TC ≥25%), ORR was highest (>10%) for bladder cancer, advanced cutaneous melanoma, and hepatocellular carcinoma (33.3% each); NSCLC (26.7%); and SCCHN (18.2%). Moreover, in the PD-L1-positive subset, DCR at 24 weeks was highest (>10%) in advanced cutaneous melanoma (66.7%), NSCLC (36.0%), hepatocellular carcinoma and bladder cancer (33.3% each), and SCCHN (18.2%).

A total of 444 patients with locally advanced or metastatic NSCLC were treated in the ATLANTIC study. As of the data cut-off (DCO) of 3 June 2016, in Cohort 2 (*EGFR*/*ALK* wild type/unknown, PD-L1 expression on ≥25% of TCs), durvalumab monotherapy showed clinically meaningful activity based on ORR in patients with locally advanced or metastatic NSCLC who had received at least 2 prior systemic treatment regimens. The responses were numerically greater in the PD-L1 TC ≥25% group (16.4%) compared with the PD-L1 expression on less than 25% of TCs (PD-L1 TC <25%) group (7.5%). The DCR at 6 months was 28.8% in the PD-L1 TC ≥25% group and 20.4% in the PD-L1 TC <25% group. The median OS was 10.9 months in the PD-L1 TC ≥25% patients and 9.3 months in the PD-L1 TC <25% patients. For the PD-L1 TC ≥25% patients, the OS rate at 6 and 12 months were 67.4% and 47.7%, respectively. For the PD-L1 TC <25% patients, the OS rate at 6 and 12 months were 60.3% and 34.5%, respectively. Observed PFS was numerically longer in the PD-L1 TC ≥25% group compared with the PD-L1 TC <25% group. In Cohort 3 (*EGFR*/*ALK* wild type/unknown, PD-L1 expression on ≥90% of TCs [PD-L1 TC ≥90%]), the ORR was 30.9%. The DCR at 6 months was 38.2%. Observed PFS and OS were similar to PD-L1 TC ≥25% patients in Cohort 2. For patients with PD-L1 ≥90% in the combined Cohorts 2 and 3, the ORR was 23.2%. The DCR at 6 months was 34.1%. Observed PFS and OS were similar to PD-L1 TC ≥25% patients in Cohort 2. For patients who responded, the response was durable across various subgroups (median DoR of 12.3 months in the PD-L1 TC ≥25% group in Cohort 2). In Cohort 2, 66.7% of responders in the PD-L1 TC ≥25% group had their first response at the time of the first on-treatment tumor assessment (Week 8). The median time to response was 1.9 months. In Cohort 1 (*EGFR*/*ALK* positive), the ORR was numerically lower than in the *EGFR*/*ALK* wild type/unknown cohorts. The responses were numerically greater in the PD-L1 TC ≥25% group (12.2%) compared with the PD-L1 TC <25% group (3.6%). The DCR at ≥6 months was 28.8% in the PD-L1 TC ≥25% group, 20.4% in the PD-L1 TC <25% group, and 38.2% in the PD-L1 TC ≥90% group. Observed PFS and OS were numerically longer in the PD-L1 TC ≥25% group compared with the PD-L1 TC <25% group (Garassino et al 2016; CCI).

2.3.1.2 Olaparib

As of 15 December 2017, approximately 8319 patients were estimated to have received olaparib in the clinical program. An estimated 5835 patients with ovarian, breast, pancreatic, gastric, and a variety of other solid tumors were estimated to have received treatment with olaparib. Since 2012/2013, most new clinical studies have utilized the tablet formulation, which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. In the AstraZeneca-sponsored, interventional studies, olaparib was given either as monotherapy (3133 patients) or in combination with chemotherapy or other anticancer agents, including studies where patients received monotherapy and combination therapy sequentially (1442 patients).

Data from the available nonclinical studies and subsequent clinical development program demonstrate that olaparib appears to be active and generally well tolerated in patients with solid tumors including those with *BRCA*m cancers. In ovarian cancer, responses have been seen in all patient groups, including platinum-resistant and refractory cancer (refer to the current olaparib IB for further details). Furthermore, as described in Section 2.2.6, there is nonclinical evidence demonstrating a strong correlation between platinum and olaparib responsiveness in multiple tumor types (including NSCLC), as well as evidence showing PARP inhibition having the potential to modify the immunogenicity of tumors, leading to enhanced susceptibility to immune checkpoint inhibition. These findings suggest that olaparib may be a potential maintenance option in combination with durvalumab for patients with Stage IV NSCLC.

2.3.1.3 Durvalumab plus olaparib combination therapy

As noted in Section 2.2.6, the hypothesis to be tested in this study is that increased DNA damage triggered through PARP inhibition will result in enhanced antitumor immunity that can be further enhanced through combination with an immune checkpoint inhibitor in NSCLC. Encouraging clinical activity has been seen to date with durvalumab in combination with olaparib outside of NSCLC (Lee et al 2017, Karzai et al 2018, Domchek et al 2018).

2.3.1.4 Durvalumab plus chemotherapy

Studies evaluating agents targeting PD-L1/PD-1 in combination with chemotherapy have yielded encouraging results (see results of these studies in Section 2.2.3).

In addition, data on durvalumab ± tremelimumab with standard platinum-based chemotherapy in advanced cancers are being generated from an ongoing Phase IB study (NCT02537418) run by the CCTG. A total of 118 patients with different tumor types have been dosed with various chemotherapy regimens. The overall ORR in the NSCLC cohort (n=24) was 52.9% (95% CI: 28% to 77%) (Daaboul et al 2017, Juergens et al 2017).

2.3.2 Overall risks

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

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and that may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal (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 hypothyroidism and hyperthyroidism.

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, hyperthyroidism and hypothyroidism, and type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (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, cough, decreased appetite, dyspnea and nausea. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Toxicity Criteria 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 **Olaparib**

From the available data to date in patients with advanced cancer, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure. Adverse laboratory findings and/or clinical diagnoses considered to be causally associated with administration of olaparib monotherapy include hematological effects (anemia, neutropenia, lymphopenia, thrombocytopenia, mean corpuscular volume elevation, and increase in blood creatinine), nausea and vomiting, decreased appetite, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), headache, dizziness, and cough. Most of these events were generally mild or moderate in intensity.

An analysis of data from 13 AstraZeneca-sponsored monotherapy studies in 1006 patients with ovarian cancer (634/1006 [63%]) and other non-ovarian solid tumors (372/1006 [37%]) who received olaparib capsule at a range of doses estimated that 16.0% (161/1006) of patients had been exposed to olaparib (capsule) for >12 months, 8.3% for >18 months, and 4.1% for >24 months at the time of database closure for the respective studies. Twenty-one patients (2.1%) had received ≥48 months of olaparib exposure.

In a relatively small number of patients, pneumonitis, myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), and new primary malignancies have been observed. Evidence from across the development program for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events.

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

2.3.2.3 **Durvalumab plus olaparib combination therapy**

Encouraging clinical activity, combined with acceptable and manageable safety, has been seen to date with durvalumab in combination with olaparib. In general, the toxicity profiles of durvalumab and olaparib are non-overlapping. Pneumonitis is considered to be the most important potential exception. See Section 8.2.7 for the management guidelines for pneumonitis that integrate the guidance provided for these 2 agents.

mAbs are not metabolized through classical hepatic enzymes pathways. Olaparib has previously been combined with another mAb (bevacizumab) without significant drug-drug interaction. Therefore, no PK interaction is anticipated within this study.

Clinical data on the tolerability and safety of durvalumab plus olaparib combination therapy are emerging. A Phase I, dose escalation study reported that there were no dose-limiting toxicities (DLTs) for durvalumab (10 mg/kg q2w or 1500 mg q4w) plus olaparib (200 or 300 mg BID) combination therapy in 12 female patients with recurrent women's cancers. The most frequent treatment-emergent AEs were hematologic toxicities, including lymphopenia and anemia (Lee et al 2017). The combination of durvalumab (1500 mg q4w) plus olaparib

(300 mg BID) is also being evaluated in several tumor types in Study NCT02734004 with reported safety data in small cell lung cancer. The most frequent Grade 3 and worse AEs in this study were anemia (39.5%) and lymphopenia (13.2%). The majority of other AEs could be attributed to underlying disease (Krebs et al 2017). Thus far, treatment-related AEs for durvalumab plus olaparib combination therapy have been consistent across studies and indications, with no evidence of an increase in frequency or severity of immune-mediated adverse events (imAEs).

2.3.2.4 Durvalumab plus chemotherapy

Two ongoing studies are evaluating the safety and tolerability of combining durvalumab and tremelimumab with different chemotherapy regimens in patients with solid tumors. One study is an AstraZeneca internal study (D419SC00001), and the other is CCTG Study NCT02537418.

As of 12 July 2017, a total of 10 patients with advanced solid tumors have been treated with durvalumab and tremelimumab in combination with chemotherapy in Study D419SC00001. All 10 patients had at least 1 AE (regardless of causality). The AEs (all grades) reported in >20% of patients were nausea (80.0%); decreased appetite (70.0%); neutrophil count decreased (60%); anemia, cough, insomnia, and pyrexia (50.0% each); constipation, dizziness, dyspnea, neutropenia, pruritus, and rash (40.0% each); and abdominal pain, back pain, diarrhea, febrile neutropenia, headache, hypokalemia, myalgia, and vomiting (30.0% each). SAEs were reported in a total of 5 patients (50.0%). With the exception of diarrhea and pyrexia (2 patients each), all the other SAEs were reported in 1 patient each. One patient had a fatal AE of lung infection that was considered treatment related. A total of 20.0% of patients had AEs that led to permanent discontinuation of treatment.

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

nephritis. The few significant findings are likely due to the nature of combining numerous agents.

External clinical data also support these findings. In KEYNOTE-189, in patients with NSCLC treated with pembrolizumab and chemotherapy or chemotherapy alone, the incidence of Grade 3 or worse AEs was 67.2% and 65%, respectively. In the pembrolizumab plus chemotherapy group, the most common Grade 3 or worse AEs (AE frequency ≥5%) were anemia (16.3%), neutropenia (15.8%), thrombocytopenia (7.9%), asthenia (6.2%), fatigue (5.7%), and diarrhea (5.2%). In the chemotherapy-alone group, the most common Grade 3 or worse AEs (AE frequency ≥5%) were anemia (15.3%); neutropenia (11.9%); thrombocytopenia (6.9%); dyspnea (5.4%); and decreased neutrophil count, pancytopenia, and thrombocytopenia (3% each). AEs that led to death occurred in 6.7% of patients in the pembrolizumab-combination group and 5.9% of patients in the placebo-combination group. Of note, acute kidney injury occurred more frequently in the pembrolizumab-combination group than in the placebo-combination group (5.2% vs. 0.5%). In the pembrolizumab-combination group, acute kidney injury was ≥Grade 3 in 8 patients (2.0%) and led to the discontinuation of all trial therapy in 8 patients (2.0%) (Gandhi et al 2018).

For the IMpower150 study, AEs related to any treatment (as determined by the investigator) occurred in 94.4% of patients in the atezolizumab + bevacizumab + chemotherapy group (ABCP) and in 95.4% of patients in the bevacizumab + chemotherapy group (BCP). The most common Grade 3 or 4 treatment-related AEs were neutropenia, decreased neutrophil count, febrile neutropenia, and hypertension. The incidences of rash, stomatitis, febrile neutropenia, and hemoptysis were higher by less than 10% among patients in the ABCP group than among those in the BCP group. Treatment-related deaths occurred in 11 patients (2.8%) in the ABCP group and in 9 patients (2.3%) in the BCP group. The 5 deaths in the ABCP group were due to pulmonary hemorrhage or hemoptysis, 4 of which occurred in patients with potential high-risk features (eg, tumor infiltration of great vessels or cavitation). Treatment-related SAEs were noted in 25.4% of patients in the ABCP group and in 19.3% of those in the BCP group (Socinski et al 2018).

For the KEYNOTE-407 and IMpower131 Stage IV squamous NSCLC studies, the observed AEs were consistent with the known safety profiles of pembrolizumab and chemotherapy and atezolizumab and chemotherapy, respectively with no new safety signals identified (Jotte et al 2018, Paz-Ares et al 2018).

2.3.3 Overall benefit/risk

Recent progress in immunotherapy for first-line NSCLC has been a substantive advance, although further improvement is needed. Although data from the PD-1/PD-L1 monotherapy and chemotherapy combination studies are encouraging, these studies yielded a median PFS of <1 year. Furthermore, there are currently no PD-1/PD-L1 combination maintenance

regimens in patients with squamous NSCLC. Therefore, additional treatment options with a tolerable safety profile are urgently needed to prolong PFS in these patients.

Treatment with durvalumab and olaparib has shown activity in several tumor types (Section 2.3.1.3) with a subset of patients deriving meaningful and durable responses with a well-tolerated safety profile. Furthermore, the molecular targeting of olaparib to specific subsets of tumors that lack sufficient DNA damage repair mechanisms may provide a further opportunity for more effective and tolerable treatment for some patients.

The study design also aims to minimize potential risks. For example, monitoring is in place via an IDMC to assess the safety and tolerability of the durvalumab plus olaparib/placebo combination following durvalumab plus SoC-platinum-based chemotherapy.

Therefore, based upon the available nonclinical and clinical safety data, the strength of scientific hypothesis of the complementary effect of the 2 treatment agents, and the mitigations designed for this study, the investigation of the potential therapeutic efficacy of the combination of durvalumab plus olaparib in the maintenance setting in patients whose disease has not progressed following durvalumab plus platinum-based chemotherapy in patients with first-line Stage IV NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design.

3. OBJECTIVES AND ENDPOINTS

Table 5 Study objectives

Primary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed)	PFS: Time from date of randomization until the date of objective radiological disease progression according to Investigator assessment using RECIST 1.1 or death (by any cause in the absence of progression)
Secondary objectives:	**Endpoints/variables:**
To further assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of OS, ORR, and DoR	OS: Time from date of randomization until the date of death by any cause ORR: Percentage of patients with an Investigator-assessed response of CR or PR after randomization DoR: Time from the date of first documented response following randomization until the first date of documented progression or death in the absence of disease progression
To further assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed) in the HRRm population	PFS: Time from date of randomization until the date of objective radiological disease progression according to Investigator assessment in HRRm population using RECIST 1.1 or death (by any cause in the absence of progression)

Table 5 Study objectives

To assess the PK of durvalumab in combination with olaparib	Concentration of durvalumab
To assess disease-related symptoms and HRQoL in patients treated with durvalumab plus olaparib combination therapy compared with durvalumab monotherapy	Change from baseline and time to deterioration (for maintenance phase) in EORTC QLQ-C30 and EORTC QLQ-LC13
To investigate the immunogenicity of durvalumab	Presence of ADAs for durvalumab
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability profile of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy	AEs, physical examinations, laboratory findings, and vital signs
CCI	
CCI	CCI
CCI	CCI

ADA Anti-drug antibody; AE Adverse event; CR Complete response; CCI ; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; CCI ; HRQoL Health-related quality of life; HRR Homologous recombination repair; HRRm Homologous recombination repair related gene mutation; IHC Immunohistochemistry; CCI ORR Objective response rate; OS Overall survival; PD-L1 Programmed cell death ligand 1; PFS Progression free survival; CCI PK Pharmacokinetics; PR Partial response; PRO Patient-reported outcome; QLQ-C30 30-item Core Quality of Life Questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; TMB Tumor mutational burden.

4. STUDY DESIGN

4.1 Overall design

This is a Phase II randomized, multi-center, double-blind, global study to determine the efficacy and safety of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy as maintenance therapy in patients whose disease has not progressed following SoC platinum-based chemotherapy with durvalumab in first-line

Stage IV NSCLC. There will be approximately 80 sites in the study. During the initial therapy phase, approximately 350 to 400 patients will receive treatment with durvalumab, along with the Investigator's choice of platinum-based doublet therapy for squamous NSCLC (nab-paclitaxel plus carboplatin or gemcitabine plus carboplatin/cisplatin) and nonsquamous NSCLC (nab-paclitaxel plus carboplatin or pemetrexed plus carboplatin/cisplatin) for 4 cycles.

It is estimated that approximately 350 to 400 patients will be enrolled in the initial therapy phase in order for approximately 250 patients who have not progressed (ie, maintained CR, PR, or SD throughout the initial therapy phase according to Investigator-assessed RECIST 1.1) to be randomized into the maintenance phase of the study (patients completing the initial therapy phase who are not randomized cannot continue durvalumab). Patients will be randomized 1:1 to receive either durvalumab plus placebo or durvalumab plus olaparib maintenance therapy. Randomization will be stratified by histologic subtype (squamous or nonsquamous) and objective response (CR/PR or SD; obtained at the last visit prior to randomization [Cycle 4 scan]) during the initial therapy phase.

Confirmation of eligibility criteria for randomization (eligibility scan and other specific criteria; see Sections 5.1 and 5.2 for criteria that must be met at randomization) will take place 14 to 28 days after Cycle 4 Day 1 of the initial therapy phase. Laboratory assessments for eligibility should be taken after the last dose of chemotherapy in the initial therapy phase. If determined eligible, patients will be randomized within 5 weeks after Cycle 4 Day 1 of the initial therapy phase; every effort should be made to minimize the time between confirmation of eligibility, randomization, and starting maintenance treatment. Patients will receive maintenance treatment until specific discontinuation criteria are met, including clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unacceptable toxicity, and withdrawal of consent. Note that crossover within the study will not be permitted.

Tumor evaluation using RECIST 1.1 will be conducted at screening (within 28 days prior to the first dose of study medication administered during the initial therapy phase), 14 to 28 days after Cycle 2 Day 1 and Cycle 4 Day 1 of the initial therapy phase, and every 8 weeks (q8w) ±1 week during the maintenance phase (for the first 48 weeks, and then q12w ±1 week thereafter) until RECIST 1.1-defined radiological PD plus one or more additional follow-up scans, if clinically feasible.

After treatment discontinuation for any reason other than RECIST 1.1-defined radiological PD, scanning/tumor assessments will continue until RECIST 1.1-defined radiological PD plus one or more additional follow-up scans (if clinically feasible). If treatment is discontinued due to RECIST 1.1-defined radiological PD, one or more additional follow-up scans (if clinically

feasible) will be performed. For patients who are not randomized into the maintenance phase for any reason, follow-up tumor assessments will not be required.

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

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

4.2 Scientific rationale for study design

4.2.1 Rationale for efficacy endpoints

The primary objective of this study is to assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of Investigator-assessed PFS.

This Phase II study will be sized to detect evidence of improved PFS. Conventionally, ORR, PFS, and OS are used as validated measures of clinical benefit. However, given that the study is designed to evaluate the effect of durvalumab plus olaparib combination therapy in the maintenance setting, it is hypothesized that ORR will be modestly improved by the addition of olaparib to durvalumab. Therefore, PFS and OS are the 2 measures that will be used as validated measures of clinical benefit in the maintenance setting. OS is generally regarded as the most reliable cancer endpoint and preferred for studies that can be conducted to adequately assess survival. However, PFS may serve as a surrogate endpoint for OS when differences between treatment arms are of sufficient magnitude and clinically important (FDA Guidance 2015, Pazdur 2008). Therefore, the study will be designed to detect significant improvement in PFS in patients treated with olaparib plus durvalumab combination therapy versus durvalumab monotherapy.

A PFS primary endpoint also affords an earlier understanding of treatment effect than OS. Furthermore, PFS, unlike OS, will not be confounded by cross-over effect of subsequent treatments. Although prior studies in various tumor types have demonstrated OS to be a more robust measure of clinical benefit than PFS with immune-oncology monotherapy (Balar et al 2017, Borghaei et al 2015), the prior clinical experience with PARP inhibitors suggests that PFS is an appropriate measure of clinical benefit for the addition of olaparib to durvalumab (Romero 2017).

Secondary efficacy endpoints, including ORR, DoR, and OS, will be examined in the FAS to further evaluate the antitumor effect of durvalumab plus olaparib combination therapy versus durvalumab monotherapy; Investigator-assessed PFS will also be examined in the HRRm subgroup.

Antitumor activity will be based on Investigator assessment according to RECIST 1.1 guidelines.

4.2.2 Rationale for other study endpoints

The secondary disease-related 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 the patient's perspective and will aid in understanding the benefit/risk evaluation. These PRO questionnaires are well-established instruments that have been previously included in cancer clinical studies.

CCI [redacted]

4.3 Justification for dose

This study will utilize a fixed dose for durvalumab treatment (1500 mg q3w in initial therapy phase and q4w in maintenance phase). Olaparib will be dosed orally at 300 mg BID.

4.3.1 Durvalumab monotherapy dose rationale

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

Pharmacokinetic/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg q2w or 15 mg/kg q3w, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and soluble programmed death-ligand 1 [sPD-L1]), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to

durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUC_{ss} (4 weeks). Median maximum plasma concentration (C_{max}) at steady state is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median trough concentration (C_{trough}) at steady state is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w 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 AUC and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w.

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.

4.3.2 Rationale for fixed dosing of durvalumab

A population PK model was developed for durvalumab using monotherapy data from Study 1108 (N=292; doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). Population PK analysis indicated only minor impact of body 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.

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

and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 therapeutic proteins and peptides 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, it was considered it feasible to switch to fixed dosing regimens. Based on median body WT of approximately 75 kg, a fixed dose of durvalumab 1500 mg (equivalent to 20 mg/kg) is included in the current study.

4.3.3 Rationale for proposed study dose and schedule

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

The safety of a q3w dosing schedule in combination with chemotherapy has been explored in the ongoing Study D419SC00001, where durvalumab 1120 mg q3w plus tremelimumab 75 mg q3w was given concurrently with carboplatin AUC 5 mg/mL/min and etoposide 100 mg/m^2 q3w, followed by durvalumab monotherapy 1120 mg q3w. The combination has been declared tolerable and manageable (see below for more detail). The 1120 mg dose of durvalumab is the q3w equivalent of the standard 1500 mg q4w dose. The tremelimumab dose was not lowered proportionally to 56 mg because 75 mg is the lowest tested biologically effective dose.

In this study, AstraZeneca proposes to use the Phase III fixed dose of durvalumab 1500 mg q3w in combination with chemotherapy. The relative increase in dose density of durvalumab (ie, 1500 mg q3w instead of q4w) is supported by the fact that toxicities attributable to durvalumab do not appear dose dependent and that PK modeling reveals no meaningful differences in drug levels between q3w and q4w dosing, and by the clinical data from the D419MC00004 (POSEIDON), CASPIAN (D419QC00001), and NCT02537418 (CCTG) studies. During the maintenance phase, the dose and schedule of durvalumab will be 1500 mg q4w.

Supportive clinical data

The safety of a q3w dosing schedule of durvalumab (with or without tremelimumab) in combination with chemotherapy has been explored in 2 ongoing studies, D419SC00001 and the CCTG Study NCT02537418.

CCTG Study NCT02537418 (Daaboul et al 2017) is an ongoing Phase Ib study of durvalumab with or without tremelimumab in combination with multiple standard platinum-based chemotherapy regimens in patients with incurable advanced or metastatic cancer. The dose escalation and dose regimens in the study initially included a fixed dose cohort of durvalumab 1125 mg plus tremelimumab 56 mg q3w concurrent with platinum-based doublet chemotherapy and then subsequently a cohort of durvalumab 1500 mg plus tremelimumab 75 mg q3w concurrent with chemotherapy.

At the DCO of October 2016, a total of 111 patients have been dosed with 7 chemotherapy regimens across multiple tumor types and dose levels. Overall, toxicities related to the chemotherapy core regimen appeared as expected in severity and frequency. Across all dose levels, there was no clear dose dependency in any of the reported AEs and there was no DLT reported per protocol-defined criteria (DLT period of 21 days). Toxicities related to durvalumab and tremelimumab were also those expected for these agents, although a number of potential immuno-oncology (IO)-related toxicities such as diarrhea, skin rash, hepatic function changes, or pneumonitis were difficult to differentiate from those reported for cytotoxic agents. As expected, there were more IO-related toxicities reported for dose levels containing tremelimumab. In general, all regimens were tolerable and manageable at all dose levels. The study was presented at the World Conference in Lung Cancer in October 2017 when 13 patients had been exposed to the fixed durvalumab 1500 mg/tremelimumab 75 mg q3w dose. There was no evidence of a dose response including the 1500 mg/75 mg dose cohort in terms of the safety data reported.

Study D419SC00001 is an ongoing study evaluating durvalumab 1120 mg plus tremelimumab 75 mg q3w given concurrently with carboplatin AUC 5 mg/mL/min and etoposide 100 mg/m^2 q3w, followed by durvalumab 1120 mg monotherapy q3w. At the DCO of 6 December 2016, 6 patients with SCLC had completed 4 cycles of treatment. No DLT was reported during the first cycle of treatment (a 21-day period). One patient developed Grade 4 hepatitis with elevation of ALT, AST, and gamma-glutamyl transferase at Cycle 5 Day 1. Although the onset of this event was 1 day after the protocol-defined DLT period of 4 cycles, it was considered as a DLT following discussion with the Investigator. The liver enzymes were normalized within 16 days after steroid use and were confirmed not to be a Hy's law (HL) case. As there was only 1 DLT reported in 6 patients, the safety profile of this combination of durvalumab 1120 mg + tremelimumab 75 mg concurrent with platinum-based doublet chemotherapy using a q3w schedule was declared tolerable and manageable.

In general, the overall safety profile from these 2 studies appears to be consistent with available safety and tolerability data for durvalumab monotherapy. Taken together with the PK data (described further below), the totality of data provided sufficient safety data to support the combination of durvalumab 1500 mg combined with chemotherapy on a q3w schedule and AstraZeneca has started 2 Phase III studies (CASPIAN and POSEIDON)

looking at the combination of fixed dose durvalumab (1500 mg) with or without tremelimumab (75 mg) given q3w concurrent with platinum-based doublet chemotherapy.

Both studies are Phase III randomized studies that are blinded to AstraZeneca. As such, it is not possible to provide safety data specific to a fixed dose of durvalumab 1500 mg q3w in combination with chemotherapy for these studies as the treatment allocation is currently blinded.

However, AstraZeneca has included in both of these studies the use of an IDMC to review the safety data in an unblinded fashion. The IDMC has met and will continue to meet on a regular basis to review unblinded data and will make a recommendation on whether recruitment should continue, be modified, or be held. In addition, the IDMC for the POSEIDON study was convened per protocol to confirm the safety and tolerability of the proposed dose and schedule of durvalumab with or without tremelimumab in combination with SoC chemotherapy at 2 early stages of enrollment. A step-wise approach was adopted. The initial safety review took place when the first 30 patients (10 in each arm) completed the first cycle of treatment and had 21 days of follow-up. A second review utilized an additional 30 patients (10 in each arm) who completed the first cycle of treatment and had 21 days of follow-up, making a total of 60 patients. These 2 reviews were carried out by the IDMC in an unblinded manner. After a review of the unblinded data, the IDMC made a recommendation to continue the study as planned.

The IDMC has met and reviewed unblinded safety data for the POSEIDON and CASPIAN studies on further occasions and has continued to make the recommendation following the safety review meetings for the studies to continue as planned.

Pharmacokinetic modeling

PK modeling and simulation have been conducted to evaluate the switch from q4w dosing to q3w dosing for durvalumab. Simulated PK profiles based on the study design (q3w dosing regimen of durvalumab 1500 mg given at Weeks 0, 3, 6, and 9; durvalumab as a single agent in Week 12 followed by q4w durvalumab monotherapy dosing) were compared with simulated PK profiles of the q4w dosing regimen (q4w dosing regimen of durvalumab 1500 mg given as monotherapy).

Results suggest that for durvalumab, median C_{max} following the 5th dose of the q3w dosing regimen and the 4th dose of the q4w dosing regimen was 689 and 624 µg/mL, median C_{trough} at Week 16 was 125 and 94.5 µg/mL, and $AUC_{0\text{-}16wk}$ was 28726 and 22772 µg•day/mL for the q3w and q4w schedules, respectively.

Therefore, PK modeling suggests that a q3w schedule does not impose a significant increased safety risk based on expected durvalumab and tremelimumab exposures.

Taken together, the totality of data provides sufficient safety data to support the combination of durvalumab 1500 mg q3w with chemotherapy. There is supportive safety data for the combination in a few studies including the CCTG study as well as confirmation from the IDMC for POSEIDON and CASPIAN studies to continue the study as planned. This includes a safety confirmation phase from POSEIDON study. In addition, PK modeling data suggest that there will be a minimal impact on IP exposure if the standard durvalumab dose (1500 mg) is given on a q3w dosing regimen.

4.3.4 Olaparib dose rationale

For combination dosing with durvalumab, olaparib dose selection is based on the results from the National Cancer Institute (NCI) Study ESR-14-10366 and AstraZeneca Study D081KC00001, a Phase I/II study of durvalumab in combination with olaparib in patients with advanced solid tumors. In Study ESR-14-10366 (Lee et al 2017), olaparib was administered at 200 or 300 mg BID, and durvalumab was studied at a fixed dose of 10 mg/kg q2w for the first 2 cohorts. Later in the study, the durvalumab dosing schedule was changed to a dose schedule of q4w. Administration of the durvalumab plus olaparib combination was well tolerated, with no instances of DLT observed. Data from this study formed the basis for the dose selection in Study D081KC00001. Based on these data, the dose of olaparib to be used in this study will be the recommended monotherapy dose of 300 mg BID.

Dose reductions may be required in patients experiencing toxicities related to olaparib treatment (Section 6.5).

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study (ie, DCO for final OS analysis).

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

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

The study may be terminated at individual sites if the study procedures are not being performed according to Good Clinical Practice or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with durvalumab, olaparib, the combination of durvalumab plus olaparib, or the combination of durvalumab plus chemotherapy.

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 may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new informed consent.

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

4.5 Study termination

The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that are as follows:

- Meet individual stopping criteria or are otherwise considered significant
- Assessed as causally related to study treatment
- Not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the electronic case report form (eCRF).

All reasons for discontinuation of treatment must be documented.

4.6 Site closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the Institutional Review Board (IRB)/Independent Ethics Committee or local health authorities, the Sponsor's procedures, or Good Clinical Practice guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

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 enrolled in the initial therapy phase. Eligibility for randomization to the maintenance phase of study treatment will be based on the patient's response to initial therapy (CR, PR, or SD according to Investigator-assessed RECIST 1.1) among other criteria (eg, patient's CrCl; see Sections 5.1 and 5.2 for full list of eligibility criteria). Under no circumstances can there be exceptions to this rule. Patients who receive at least 1 dose of study treatment during the initial therapy phase but are not randomized for any reason are considered initial therapy failures. Patients who do not meet the entry requirements for the initial therapy phase are screen failures, as further described in 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 into the maintenance phase and receive a randomization number.

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

5.1 Inclusion criteria

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

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 CCI [redacted]

The informed consent process is described in Appendix A 3.

Patients must meet the following criteria at screening prior to receiving treatment:

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

5 Histologically or cytologically documented Stage IV NSCLC not amenable to curative surgery or radiation (according to version 8 of the IASLC Staging Manual in Thoracic Oncology; IASLC Staging Manual in Thoracic Oncology 2016).

6 Patients must have tumors that lack activating *EGFR* mutations (eg, exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) and *ALK* fusions. If a patient has squamous histology or is known to have a tumor with a *KRAS* mutation, then *EGFR* and *ALK* testing are not required.

7 World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

8 No prior chemotherapy or any other systemic therapy for Stage IV NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation are eligible, provided that progression has occurred >12 months from end of last therapy.

9 Life expectancy ≥12 weeks at screening.

10 Ability to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening, or otherwise altering the product formulation. Patients should not have GI illnesses that would preclude the absorption of olaparib, which is an oral agent.

11 Patients must also have adequate organ and marrow function without blood transfusions in the past 28 days, defined as follows:

- Hb ≥10 g/dL
- ANC ≥1.5 × 10^9/L
- Platelet count ≥100 × 10^9/L
- Serum bilirubin ≤1.5 × ULN; unless due to Gilbert's syndrome, in which case patients will be allowed in consultation with their physician and AstraZeneca
- ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN
- CrCl ≥51 mL/min calculated by the investigator or designee using the Cockcroft-Gault equation (using actual body WT) or measured by 24-hour urine collection
- Males:
- CrCl = $\frac{\text{WT (kg)} \times (140 - \text{Age})}{72 \times \text{Serum creatinine (mg/dL)}}$ (mL/min)
- Females:
- CrCl = $\frac{\text{WT (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{Serum creatinine (mg/dL)}}$ (mL/min)

12 Patients must have at least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes that must have a short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.

13 All patients must provide a formalin-fixed, paraffin embedded (FFPE) tumor sample for tissue-based immunohistochemistry (IHC) staining and DNA sequencing to determine PD-L1 expression, HRRm status, and other correlatives; either newly acquired or archival tumor samples (<3 years old) are acceptable. If available, a newly acquired tumor biopsy, collected as part of routine clinical practice, is preferred. If not available, an archival sample taken <3 years prior to screening is acceptable. If both an archival sample and a fresh tumor biopsy sample are available, both samples should be submitted for analysis and must be submitted as different samples using different accession numbers. Slides from different blocks cannot be mixed and submitted with the same kit.

14 Tumor lesions used for newly acquired biopsies should not be TLs, unless there are no other lesions suitable for biopsy. Samples with limited tumor content and fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component and should not be decalcified. For additional details on sample requirements, see Section 8.8.1.

15 Body WT >30 kg.

Patients must meet the following criteria to be randomized to maintenance treatment:

16 Patients must have documented radiographic evidence of a timepoint tumor response of CR, PR, or SD according to Investigator-assessed RECIST 1.1 guidelines following the 4 cycles of platinum-based chemotherapy. An objective response does not have to be confirmed in order for the patient to be randomized.

17 CrCl ≥51 mL/min calculated by the investigator or designee using the Cockcroft-Gault equation (using actual body WT) or measured by 24-hour urine collection.

18 Inclusion criterion 10.

5.2 Exclusion criteria

Patients must NOT meet the following criteria at screening prior to receiving treatment:

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

2 Mixed small-cell lung cancer and sarcomatoid variant NSCLC histology.

3 No radiation therapy is allowed, unless it is 1) definitive radiation that had been administered at least 12 months prior, 2) palliative radiation to brain, with associated criteria for stability or lack of symptoms, or 3) palliative radiation to painful bony lesions (this must comprise less than 30% of the bone marrow).

4 Prior exposure to any chemotherapy agents (with the exception of chemotherapy or chemoradiation for non-metastatic disease; see inclusion criterion 8 for full details), PARP therapy, or immune-mediated therapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines and other PARP inhibitors.

5 Any contraindications to platinum-based doublet chemotherapy.

6 Active or prior documented autoimmune or inflammatory disorders (including, but not limited to, inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, Wegener syndrome [granulomatosis with polyangiitis], Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia
- Any chronic skin condition that does not require systemic therapy
- Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
- Patients without active disease in the last 5 years may be included but only after consultation with AstraZeneca.

- Patients with celiac disease controlled by diet alone may be included but only after consultation with AstraZeneca.

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

9 Current or prior use of immunosuppressive medication within 14 days before the first dose of IP. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
- Systemic corticosteroids (that are not excluded according to exclusion criterion 10) at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

10 Concomitant use of known strong cytochrome P450 (CYP) 3A (CYP3A) inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, and telaprevir) or moderate CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, and verapamil). The required washout period prior to starting study treatment is 2 weeks. Concomitant use of known strong (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, and St. John's Wort) or moderate CYP3A inducers (eg, bosentan, efavirenz, dexamethasone, and modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

11 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

12 Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the Investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, QT interval corrected for heart rate using Fridericia's formula [QTcF] value ≥470 ms calculated from 3 ECGs [within 15 minutes at 5 minutes apart], electrolyte disturbances, etc), or patients with congenital long QT-interval syndrome or congestive heart failure.

13 Has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on the baseline brain imaging (please see Appendix F [RECIST] for details on the imaging modality) obtained during the screening period or identified prior to signing the ICF. Patients whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least 4 weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain

metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ≤10 mg/day of prednisone or its equivalent and anti-convulsants for at least 14 days prior to the start of treatment. Brain metastases will not be recorded as RECIST TLs at baseline.

14 Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, or psychiatric illness, or social situations that would limit compliance with study requirements, substantially increase the risk of incurring AEs from IP, or compromise the ability of the patient to give written informed consent.

15 History of allogenic organ transplantation including umbilical cord blood transplantation.

16 Patients with MDS/acute myeloid leukaemia or with features suggestive of MDS/AML

17 History of leptomeningeal carcinomatosis.

18 History of active primary immunodeficiency.

19 Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive hepatitis B virus [HBV] surface antigen [HBsAg] result), **hepatitis C**, or **human immunodeficiency virus** (HIV; 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 hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).

20 Any unresolved toxicity NCI Common Terminology Criteria for Adverse Event (CTCAE) Grade ≥2 from previous anticancer therapy 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 olaparib may be included only after consultation with the Study Physician.

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

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

23 Participation in another clinical study with an IP administered in the last 12 months.

24 Previous IP assignment in the present study.

25 Prior randomization or treatment in a previous durvalumab (and/or olaparib) clinical study regardless of treatment arm assignment.

26 Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later.

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

- CCI

Patients must NOT meet the following criterion to be randomized to maintenance treatment:

29 Inability to complete 4 cycles of platinum-based chemotherapy for any reason or discontinuation of durvalumab during initial therapy. Dose interruptions or delays are not exclusionary.

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 6) from the time of screening throughout the total duration of the study treatment and the drug washout period (90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later). 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, rhythm method, and 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 study treatment and the drug washout period (90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later). Periodic abstinence, rhythm method, and withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 6).

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, and 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 6. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

For administration of SoC (initial therapy), follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for the agents administered.

Table 6 Highly effective methods of contraception (<1% failure rate)

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

[a] This is also considered a hormonal method.

3 All patients: Patients should not donate blood or blood components while participating in this study and through to 90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later or until alternate anticancer therapy is started.

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

5 It is prohibited to consume grapefruit juice while on olaparib/placebo therapy.

5.4 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not begin the initial therapy phase. 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. Patients may be rescreened a single time, but they may not begin the initial therapy phase more than once.

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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Patients who receive at least 1 dose of study treatment during the initial therapy phase but are not randomized for any reason are considered initial therapy failures.

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, olaparib, placebo, and chemotherapy (SoC).

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca will supply durvalumab, olaparib, and placebo. SoC chemotherapy agents will be supplied locally.

Table 7 Study treatments

	Durvalumab	Olaparib	Placebo	Chemotherapy (SoC)
Study treatment name	Durvalumab (MEDI4736)	Olaparib (AZD2281)	Placebo	nab-paclitaxel, carboplatin, cisplatin, gemcitabine, and pemetrexed
Dosage formulation	500-mg vial solution for infusion after dilution, 50 mg/mL	150-mg tablets (2 × 150-mg tablets for 300-mg dose) 100-mg tablet available if dose reductions are required	Matching tablet	As sourced locally (under certain circumstances when local sourcing is not feasible, an SoC treatment may be supplied centrally through AstraZeneca)
Route of administration	IV	Oral	Oral	IV
Dosing instructions	1500 mg q3w (initial therapy phase) and 1500 mg q4w (maintenance phase)[a,b]	Two × 150-mg olaparib tablets should be taken at the same time each day, approximately 12 hours apart with 1 glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food.	Matching placebo for oral tablet BID	Nab-paclitaxel: 100 mg/m^2 on Days 1, 8, and 15 of each 3-week cycle Carboplatin: AUC 5 or 6 on Day 1 of each 3-week cycle Cisplatin: 75 mg/m^2 on Day 1 of each 3-week cycle Gemcitabine: 1000 or 1250 mg/m^2 on Days 1 and 8 of each 3-week cycle Pemetrexed: 500 mg/m^2 on Day 1 of each 3-week cycle
Packaging and labeling	Provided in 500-mg vials, labeled in accordance with GMP Annex 13 and per country regulatory requirements.[c]	Study treatment will be provided in HDPE bottles with child-resistant closures. Each bottle will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.	Study treatment will be provided in HDPE bottles with child-resistant closures. Each bottle will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.	Variable
Provider	AstraZeneca	AstraZeneca	AstraZeneca	Sourced locally by site (under certain circumstances when local sourcing is not feasible, an SoC treatment may be supplied centrally through AstraZeneca)

[a] Subsequent time between 2 consecutive doses of durvalumab cannot be less than 21 days, based on the half-life of durvalumab (see current IB for durvalumab). If there is a dosing delay during the treatment schedule for durvalumab, all future dosing days for durvalumab should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days.

[b] If a patient's WT falls to 30 kg or below, the patient should receive WT-based dosing equivalent to 20 mg/kg of durvalumab q3w (initial therapy phase) or q4w (maintenance phase) until the WT improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q3w/q4w.

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

BID Twice a day; CrCl Creatinine clearance; GMP Good Manufacturing Practice; IB Investigator Brochure; IV Intravenous; q3w Every 3 weeks; q4w Every 4 weeks; SoC Standard of Care.

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. The nominal fill volume is 10.0 mL. IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Durvalumab will be administered to patients during the initial therapy phase for 4 cycles per Table 1, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met. Durvalumab will be administered to patients during the maintenance phase per Table 2 until clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met.

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 the site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

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

A dose of 1500 mg (for patients >30 kg in WT) 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 in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (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.

If WT falls to ≤30 kg, WT-based dosing at 20 mg/kg 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 in-line filter.

Standard infusion time is 60 minutes. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

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

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

6.1.1.2 **Olaparib (AZD2281)**

Olaparib/placebo tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib/placebo will be dispensed to patients on Day 1 of the maintenance phase and at each visit per Table 2 until clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met.

Study treatment is available as a film-coated tablet containing 100 or 150 mg of olaparib or matching placebo.

Patients will be allowed to receive olaparib/placebo maintenance treatment only after meeting the hematology/clinical chemistry requirements specified in Section 1.1 without blood transfusions in the past 28 days. If the patient does not meet these requirements initially, then the hematology and clinical chemistry parameters should be checked at the next cycle. If a patient meets criteria for randomization before being dosed in maintenance but is later found to not meet criteria to start olaparib/placebo before C1D1 dosing, durvalumab as monotherapy may be started, with olaparib/placebo dosing to commence once the patient again meets the hematology/clinical chemistry requirements and conditions specified in Section 1.1. However, the Investigator may check these laboratory results/parameters earlier (eg, mid cycle) at an unscheduled visit. Once olaparib/placebo is administered, these laboratory thresholds are not required for continued olaparib administration. However, patients must continue to be monitored and assessed (eg, lab parameters and toxicities) per Table 2, and dose delays and

modifications for olaparib/placebo should be followed per Sections 6.5 and 8.4.5.2 and Appendix G.

Patients will be administered olaparib/placebo orally at 300 mg BID continually. Olaparib/placebo tablets should be taken at the same time each day, approximately 12 hours apart with 1 glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. IP tablets can be taken with or without food.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

6.1.1.3 Standard of care

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

6.1.2 Dose and treatment regimens

6.1.2.1 Durvalumab (MEDI4736) and platinum-based chemotherapy (initial therapy phase)

During the initial therapy phase, all patients will receive durvalumab 1500 mg via IV infusion q3w for 4 cycles, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met. If a patient's WT falls to 30 kg or below, the patient should receive WT-based dosing equivalent to 20 mg/kg of durvalumab q3w after consultation between Investigator and Study Physician until the WT improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q3w. If there is a dosing delay during the treatment schedule for durvalumab, all future dosing days for durvalumab should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days. The standard infusion time is 60 minutes. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

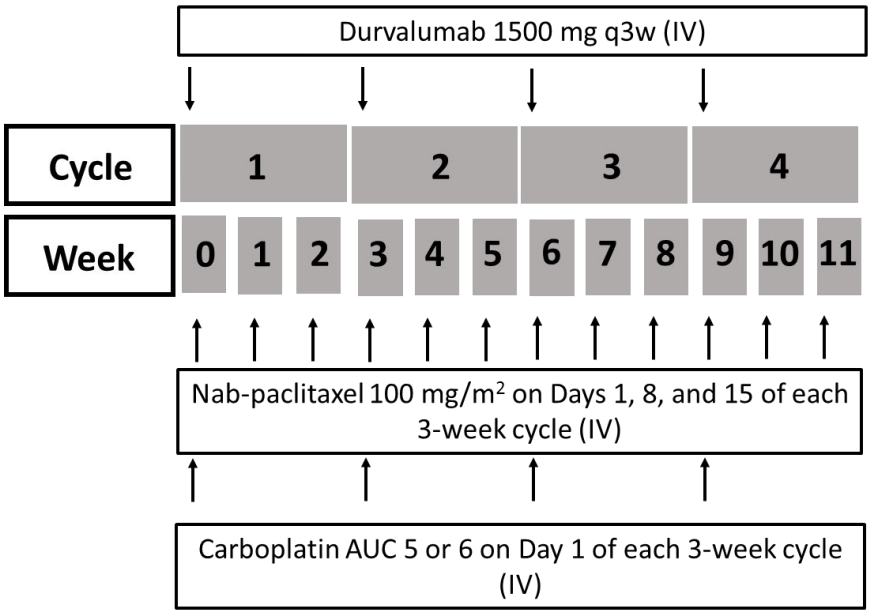
In addition to durvalumab, patients in the initial therapy phase will also receive 1 of the following SoC regimens as part of their treatment regimen (durvalumab will be infused first, followed by the SoC chemotherapy regimen):

- Nab-paclitaxel plus carboplatin (squamous and nonsquamous patients): Nab-paclitaxel 100 mg/m^2 via IV infusion on Days 1, 8, and 15 of each 3-week cycle and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 2).
- Gemcitabine plus carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 3-week cycle and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 3).
- Gemcitabine plus cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 3-week cycle and cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 3).
- Pemetrexed plus carboplatin (nonsquamous patients only): Pemetrexed 500 mg/m^2 and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 4). Pemetrexed maintenance therapy will not be allowed following the initial therapy phase.
- Pemetrexed plus cisplatin (nonsquamous patients only): Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles (Figure 4). Pemetrexed maintenance therapy will not be allowed following the initial therapy phase.

In the event that SoC is delayed during the initial therapy phase, durvalumab administration must also be delayed.

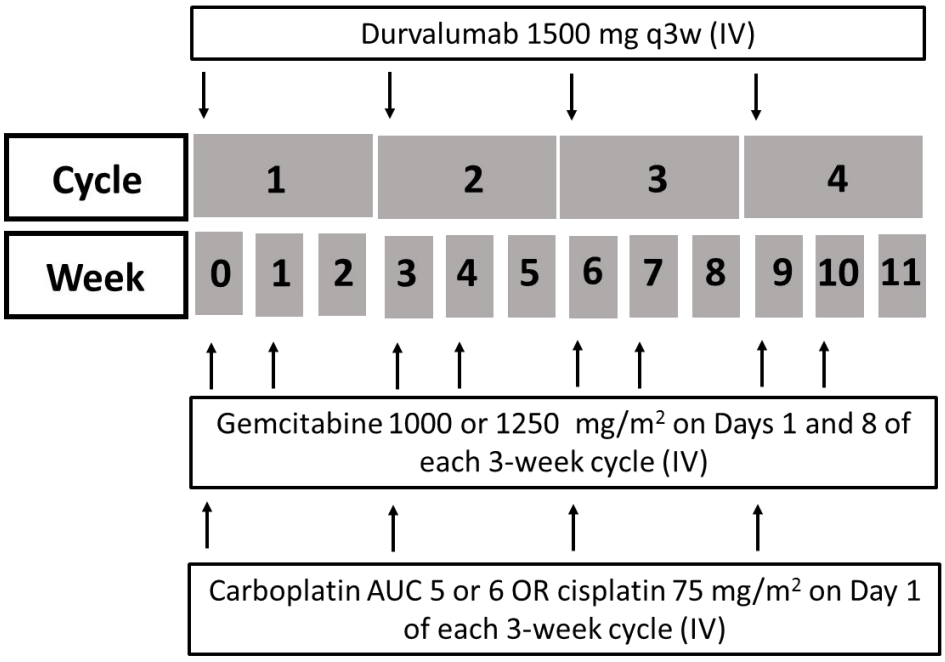
In the event of unfavorable tolerability, patients can switch between cisplatin and carboplatin therapy at any point during the study.

Figure 2 **Dose and treatment regimen for initial therapy phase (durvalumab with nab-paclitaxel plus carboplatin)**



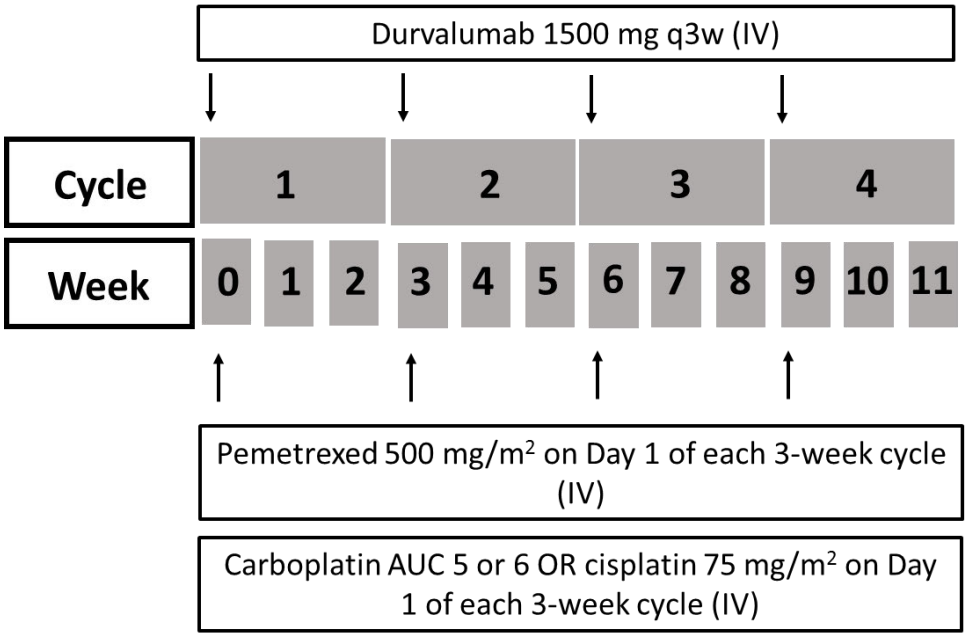
AUC Area under the concentration-time curve; IV Intravenous; Nab Nanoparticle albumin-bound; q3w Every 3 weeks.

Figure 3 **Dose and treatment regimen for initial therapy phase (durvalumab with gemcitabine plus carboplatin/cisplatin)**



AUC Area under the concentration-time curve; IV Intravenous; q3w Every 3 weeks.

Figure 4 **Dose and treatment regimen for initial therapy phase (durvalumab with pemetrexed plus carboplatin/cisplatin)**



Note: Pemetrexed maintenance therapy will not be allowed following the initial therapy phase.
AUC Area under the concentration-time curve; IV Intravenous; q3w Every 3 weeks.

6.1.2.2 Durvalumab monotherapy and durvalumab plus olaparib combination therapy (maintenance phase)

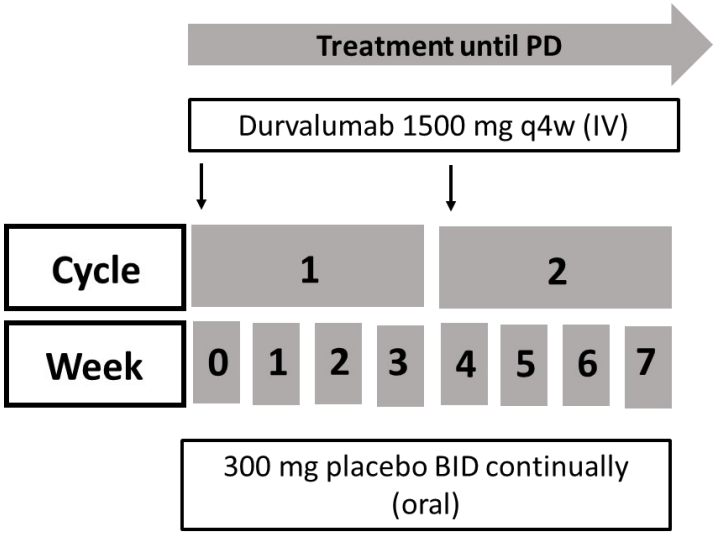
During the maintenance phase, all patients will receive durvalumab 1500 mg via IV infusion q4w. Patients will also receive 300 mg oral olaparib (durvalumab plus olaparib treatment arm) or its matching placebo (durvalumab plus placebo treatment arm) BID continually until clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD (Figure 5 and Figure 6), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met.

Before commencing olaparib/placebo treatment, patients must first meet the hematology/clinical chemistry requirements specified in Section 1.1 without blood transfusions in the past 28 days. If a patient meets criteria for randomization before being dosed in maintenance but is later found to not meet criteria to start olaparib/placebo before C1D1 dosing, durvalumab as monotherapy may be started, with olaparib/placebo dosing to commence once the patient again meets the hematology/clinical chemistry requirements in Section 1.1.

If a patient's WT falls to 30 kg or below, the patient should receive WT-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between Investigator and Study Physician until the WT improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w. If there is a dosing delay during the treatment schedule for durvalumab, subsequent time between 2 consecutive doses of durvalumab cannot be less than 21 days; olaparib/placebo administration may continue as scheduled if durvalumab is delayed. The standard infusion time for durvalumab is 60 minutes. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

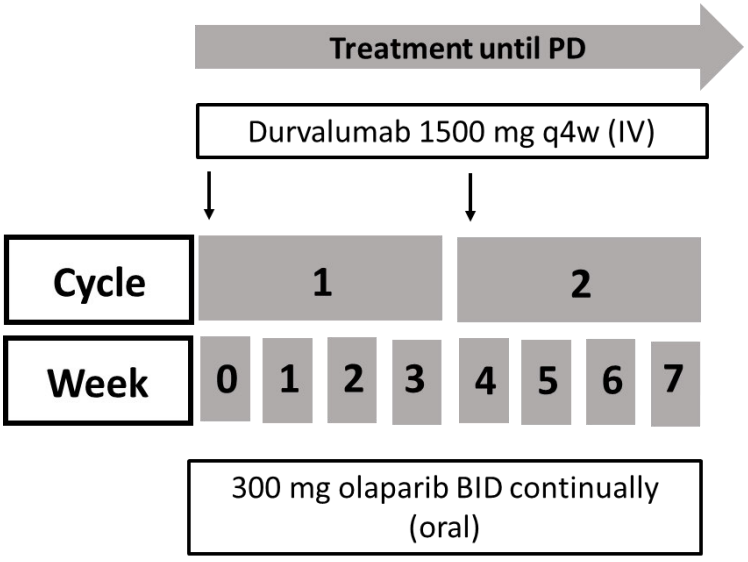
See Section 7.1 for details about discontinuation of either durvalumab or olaparib/placebo in the maintenance phase.

Figure 5 **Dose and treatment regimen for maintenance phase (durvalumab monotherapy)**



BID Twice daily; IV Intravenous; PD Progressive disease; q4w Every 4 weeks.

Figure 6 **Dose and treatment regimen for maintenance phase (durvalumab plus olaparib combination therapy)**



BID Twice daily; IV Intravenous; PD Progressive disease; q4w Every 4 weeks.

6.1.3 Duration of treatment and criteria for treatment through progression

Durvalumab plus chemotherapy will be administered beginning on Day 1 of the initial therapy phase for 4 cycles. Durvalumab plus olaparib/placebo will be administered on Day 1 of the

maintenance phase until clinical disease progression (as assessed by the Investigator) or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion met.

Before commencing olaparib/placebo treatment, patients must first meet the hematology/clinical chemistry requirements specified in Section 1.1 without blood transfusions in the past 28 days.

There is no maximum duration of treatment. Patients with clinical disease progression (as assessed by the Investigator), in the initial therapy or maintenance phase of the study, are not eligible for treatment through progression. Patients who are clinically stable with RECIST 1.1-defined radiological PD at Cycle 2 of the initial therapy phase may continue to receive study treatment at the discretion of the Investigator and patient; however, if the patient continues to show a RECIST 1.1-defined radiological PD at Cycle 4, the patient will not be eligible for the maintenance phase of the study. Patients completing the initial therapy phase who are not randomized cannot continue durvalumab.

During the maintenance phase, patients who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is to be collected after the initial RECIST 1.1-defined radiological PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the Confirmation of Radiological Progression criteria outlined in Appendix F.

Patients with PD in the maintenance phase who continue to receive IP at the discretion of the Investigator and patient (following consultation with AstraZeneca) will have tumor assessments on their regular imaging schedule for the duration of treatment. However, patients will not be permitted to continue immunotherapy or olaparib/placebo if progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) in the TLs to either the initial therapy (durvalumab plus chemotherapy) or maintenance treatment (durvalumab or olaparib/placebo) of the study regardless of the appearance of new lesions. Patients who have discontinued durvalumab will not be permitted to be treated with olaparib/placebo monotherapy after progression.

Patients with rapid tumor progression or with symptomatic progression that require urgent medical intervention (eg, CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) must discontinue durvalumab and olaparib/placebo.

Crossover within the study will not be permitted.

For all patients who are treated through progression (ie, durvalumab with or without olaparib/placebo), the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities related to study treatment that indicate continuing treatment will not further benefit the patient. The patient may not have experienced a toxicity that required permanent discontinuation of study treatment.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression.
- No decline in WHO/ECOG PS
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression or spinal cord compression) requiring urgent alternative medical intervention.
- The patient still fulfills the eligibility criteria for screening (for treatment through progression in the initial therapy phase) or randomization (treatment through progression in the maintenance phase) in this study (see Sections 5.1 and 5.2), with the exception of inclusion criteria 8, 13, and 14 and exclusion criteria 4, 9, 24, and 25.

In addition to the criteria above, written informed consent will be required to continue treatment in the setting of PD. This consent document will specify that treatment beyond initial evidence of PD is not the standard-of-care and that alternative treatment options, either locally licensed treatments or other clinical trials, are available.

Patients who AstraZeneca and the Investigator determine may not continue treatment after RECIST 1.1-defined radiological PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up with tumor assessments until RECIST 1.1-defined radiological PD, plus one or more additional follow-up scans if clinically feasible and followed for survival.

Post final data cut-off

There will be a final DCO defined at the analysis of OS (at approximately 65% maturity; the DCO for this analysis is anticipated to occur approximately 38.5 months after the first patient has been randomized). This will be considered the end of the study. At this timepoint, the clinical study database will close to new data, and after the database lock, all individual patients will be informed of their treatment assignments.

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician consider they are gaining clinical benefit. For patients continuing to receive durvalumab and/or olaparib treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and that the Investigators

monitor the patients' safety laboratory results prior to and periodically during treatment in order to manage AEs in accordance with the durvalumab and olaparib Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5 and Appendix G).

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 and/or olaparib 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

6.1.4.1 Durvalumab

The Investigator, or an approved representative (eg, pharmacist), will ensure that durvalumab is stored in a secured area, in refrigerated temperatures (2°C to 8°C [36°F to 46°F]), and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

6.1.4.2 Olaparib, placebo, and chemotherapy (SoC)

Olaparib, placebo, and chemotherapy (SoC) IPs should be kept in a secure place under appropriate storage conditions. The IP labels specify the appropriate storage.

6.2 Measures to minimize bias: randomization and blinding

6.2.1 Patient enrollment and randomization

All patients will be centrally registered and randomized between study arms using an interactive voice response system/interactive 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 for initial therapy phase (Days -28 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 within 28 days of enrollment. For patients with a single TL, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired. (Informed consent of study procedures may be obtained prior to the 28-day screening window in order to permit tumor biopsy sample acquisition, if necessary.)
- Obtain a unique 7-digit enrollment number (E-code), through the IVRS/IWRS in the format ECCNNXXX (CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center. This number is the patient's unique identifier and is used to identify the patient on the eCRFs.
- Obtain tumor sample. Either newly acquired or archival tumor samples (taken <3 years prior to screening) are acceptable. If available, a newly acquired tumor biopsy, collected as part of routine clinical practice, is preferred. If not available, an archival sample taken <3 years prior to screening is acceptable. If both an archival sample and a fresh tumor biopsy sample are available, both samples should be submitted for analysis. CCI [redacted]
- The sample for centralized PD-L1 testing should be sent only for patients with known *EGFR* and *ALK* status. If a patient has squamous histology or is known to have a tumor with a *KRAS* mutation, then *EGFR* and *ALK* testing are not required (see inclusion criterion 6 [Section 5.1]). If *EGFR* and *ALK* status is unknown, then the tumor sample (archive or fresh, primary or metastatic) should be used first for local *EGFR* mutation and *ALK* fusion testing.
- Tumor samples will be used to retrospectively determine PD-L1 expression status in patients who are enrolled into initial therapy (defined by the Ventana SP263 PD-L1 IHC assay):
  - ≥50% of TC with membrane staining for PD-L1 at any intensity (PD-L1 TC ≥50%)
  - 1% to 49% of TC with membrane staining for PD-L1 at any intensity (PD-L1 TC 1% to 49%)
  - <1% of TC with membrane staining for PD-L1 at any intensity (PD-L1 TC <1%)
- Determine patient eligibility (see Sections 5.1 and 5.2).
- CCI [redacted]
- Record demographic data and other characteristics including date of birth or age, sex, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

At enrollment in the initial therapy phase, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

- Define the Investigator's choice of platinum-based doublet therapy (SoC; based on the most appropriate option for the patient) that the patient will receive during the initial therapy phase. This must be completed for all patients. The information will be recorded in the IVRS/IWRS system.
- Note: For all patients with nonsquamous tumor histology scheduled to receive pemetrexed, folic acid and vitamin B12 should commence prior to treatment initiation for up to 7 days, in line with local practice. This is to ensure treatment can begin on Day 1.

Following the initial therapy phase, patients who have not progressed (ie, maintained CR, PR, or SD, according to Investigator-assessed RECIST 1.1) may be randomized into the maintenance phase of the study after confirming eligibility for the maintenance phase (Sections 5.1 and 5.2). If determined eligible, patients will be randomized within 5 weeks after Cycle 4 Day 1 of the initial therapy phase. After randomization into the maintenance phase, the Investigator or suitably trained delegate will:

- Obtain a unique randomization number via the IVRS/IWRS. Numbers will start at 001 and will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 2 treatment arms: durvalumab plus placebo or durvalumab plus olaparib. Patients will be stratified by histologic subtype (squamous or nonsquamous) and objective response (CR/PR or SD; obtained at the last visit prior to randomization [Cycle 4 scan]) during the initial therapy phase.

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

Patients will begin treatment on Day 1 of the maintenance phase (before commencing olaparib/placebo treatment, patients must first meet the hematology/clinical chemistry requirements specified in Section 1.1 without blood transfusions in the past 28 days). Every effort should be made to minimize the time between confirmation of eligibility, randomization, and starting maintenance treatment. Patients must not be randomized and treated unless all eligibility criteria specified in Sections 5.1 and 5.2 have been met.

6.2.2 Procedures for handling incorrectly enrolled or randomized patients

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

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

Patients will be identified to the IVRS/IWRS per country regulations. Randomization codes will be assigned strictly sequentially, 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 randomization and subsequent treatment visits.

6.2.4 Methods for ensuring blinding (maintenance phase)

The maintenance phase of this study will be conducted in a double-blind manner. The olaparib and placebo tablets will be identical in color and taste to maintain the double-blind conditions. Olaparib/placebo treatment will be blinded to all site staff. The study medication will be labeled using a unique kit ID number, which is linked to the randomization scheme. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the study medication.

No member of the extended study team at AstraZeneca, at the investigational sites, or any blinded contract research organization (CRO) handling data will have access to the randomization scheme until the time of the primary data analysis. At such time, AstraZeneca and any CRO handling data will have access to the randomization scheme. Exceptions are relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package the IP, the drug safety departments at AstraZeneca, and personnel providing the analysis of PK samples.

The randomization code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of

data until all decisions on the evaluability of the data from each individual patient have been made and documented. The IDMC will be provided with unblinded data for their review, but AstraZeneca staff and Investigators involved in the study will remain blinded.

The treatment codes and results will be kept strictly within AstraZeneca to safeguard the integrity of the blinding and hence to minimize any possible bias in data handling.

6.3 Treatment compliance

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

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

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

Treatment compliance will be ensured by reconciliation of site drug accountability logs. The Investigator or Pharmacist must retain records of all study treatment administered at the site (ie, those administered intravenously). The Study Monitor will check these records to confirm the compliance with the protocol administration schedule.

Study site staff will administer chemotherapy (SoC) and durvalumab. Patients will self-administer olaparib/placebo and should be given clear written instructions on how and when to take their study treatment.

All patients will be required to complete an olaparib/placebo dosing diary, which must be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the olaparib/placebo dose(s) is taken on the dosing diary. If a dose is missed, the reason must be noted in the diary. A copy of the dosing diary is provided in the study reference materials.

For olaparib and placebo, study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count, and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the study site until reconciliation is completed by the Study Monitor. All patients must return their bottle(s) of olaparib/placebo at Day 1 of each subsequent cycle, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

The IP Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IPs. The Investigator(s) is responsible for ensuring that the patient has returned all unused IPs.

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 first 3 months of the post-treatment discontinuation period.

The use of any natural/herbal products or other traditional remedies should be discouraged. 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 the following:

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

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

Restricted, prohibited, and permitted concomitant medications are described in Table 8, Table 9, and Table 10. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1 for durvalumab and Section 8.4.5.2 for olaparib). For chemotherapy (SoC) agents, refer to the local prescribing information with regards to warnings, precautions, and contraindications.

Table 8 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. Local treatment of isolated lesions, excluding TLs, for palliative intent is acceptable [eg, by local surgery or radiotherapy]).
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP

Prohibited medication/class of drug	Usage
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the IO infusions. The following are allowed exceptions: Use of immunosuppressive medications for the management of IP-related AEs Short-term premedication for patients receiving SoC (eg, platinum-based chemotherapy), where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions Use in patients with contrast allergies Use of inhaled, topical, and intranasal corticosteroids is permitted A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc). When treating with steroids, the minimum effective dose should be utilized due to the immunosuppressive effects of steroids. Baseline steroid use when starting PD-L1 blockade may be associated with inferior outcomes (Arbour et al 2018)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation *EGFR* TKIs) and increased incidence of transaminase increases (with first-generation *EGFR* TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies, which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

AE Adverse event; CRT Chemoradiation therapy; CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4; *EGFR* Epidermal growth factor receptor; IO Immuno-oncology; IP Investigational product; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1; SoC Standard of care; TKI Tyrosine kinase inhibitor; TL Target lesion.

Table 9 Restricted concomitant medications

Restricted medication/class of drug	Concern
Strong CYP3A inhibitors: Itraconazole, telithromycin, clarithromycin, boosted protease inhibitors (ie, boosted with ritonavir or cobicistat), indinavir, saquinavir, nelfinavir, boceprevir, telaprevir Moderate CYP3A inhibitors: Ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong or moderate CYP3A inhibitors should not be taken with olaparib/placebo. If there is no suitable alternative concomitant medication, then the dose of olaparib/placebo should be reduced for the period of concomitant administration. The dose reduction of olaparib/placebo should be recorded in the eCRF with the reason documented as concomitant CYP3A inhibitor use. Strong CYP3A inhibitors – reduce the dose of olaparib/placebo to 100 mg BID for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. Moderate CYP3A inhibitors - reduce the dose of olaparib/placebo to 150 mg BID for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards. After the washout of the inhibitor is complete, the olaparib/placebo dose can be re-escalated.
Strong CYP3A inducers: Phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide, and St. John's Wort Moderate CYP3A inducers: Bosentan, efavirenz, dexamethasone, and modafinil	Strong or moderate CYP3A inducers should not be taken with olaparib/placebo. If the use of any strong or moderate CYP3A inducers is considered necessary for the patient's safety and welfare, this could diminish the clinical efficacy. If a patient requires use of a strong or moderate CYP3A inducer, then they must be monitored carefully for any change in efficacy.
Effect of olaparib on other drugs	Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2K. Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP2B6. Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are coadministered. Examples of substrates include: CYP3A4 – simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, quetiapine CYP2B6 – bupropion, efavirenz OATP1B1 – bosentan, glibenclamide, repaglinide, statins, valsartan OCT1, OCT2, MATE1, MATE2K – metformin OCT2 – serum creatinine (endogenous substrate) OAT3 – furosemide, methotrexate

Restricted medication/class of drug	Concern
Anticoagulant therapy	Patients who are taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low-molecular-weight heparin are permitted.
Anti-emetics/anti-diarrheals	From initiation of maintenance treatment onward, should a patient develop nausea, vomiting, and/or diarrhea, then these symptoms should be reported as AEs (see Section 8.3) and appropriate treatment of the event should be given.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases or symptomatic pelvic soft tissue mass(es) that were present at baseline (for initial therapy phase), provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Administration of other anticancer agents	Patients must not receive any other concurrent anticancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids (that are not excluded according to exclusion criterion 10 [Section 5.2]) for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning of study treatment.
Subsequent therapies for cancer	Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anticancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

AEs Adverse events; CYP Cytochrome P450; eCRF Electronic case report form; INR International Normalized Ratio; MATE Multidrug and toxin extrusion protein; OAT Organic anion transporter; OATP Organic-anion-transporting polypeptide; OCT Organic cation transporter; OS Overall survival; PARP Poly (ADP ribose) polymerization.

Table 10 Supportive medications

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

NTL Non-target lesion.

6.4.1 Other concomitant treatment

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

6.4.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either preclinically or in patients. As durvalumab is a mAb and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug metabolizing CYP pathways. As a result, there are no expected PK drug-drug interactions, for example, no expected drug-drug interaction with olaparib. 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, steroids and other immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis). AstraZeneca Supply Chain will only be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy related toxicities. These rescue medications must be receipted, controlled, and administered by the pharmacist and stored according to the labeled storage conditions, with temperature excursions reported accordingly by the pharmacist. If

required for use as a result of an imAE, then the IVRS/ IWRS will provide to the pharmacists the kit identification number to be allocated to the patient at the time when the rescue medication is centrally supplied by AstraZeneca supply chain. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS.

6.5 Dose modification

In case a dose reduction is necessary, olaparib/placebo treatment will be administered as follows:

Table 11 Dose reductions for olaparib/placebo to manage adverse events

Initial dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg BID	250 mg BID	200 mg BID

BID twice daily.

Table 12 Dose reduction for olaparib/placebo if patient develops moderate renal impairment

Initial dose	Moderate renal impairment (calculated CrCl either by Cockcroft-Gault equation or based on a 24-hour urine test; ≥31 mL/min but <51 mL/min): Dose reduction
300 mg BID	200 mg BID

BID twice daily; CrCl Creatinine clearance.

Note: No further dose reductions are permitted for patients who receive olaparib/placebo treatment at a dose of 200 mg BID due to moderate renal impairment (≥31 mL/min but <51 mL/min) and who cannot tolerate this dose.

Table 13 Dose reductions for olaparib/placebo if patient has to start taking a strong or moderate CYP3A inhibitor

Initial dose	Strong CYP3A inhibitor	Moderate CYP3A inhibitor
300 mg BID	100 mg BID	150 mg BID

BID twice daily; CYP Cytochrome P450.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided, see Section 6.4.

When olaparib/placebo dose reduction is necessary, patients will take one 150-mg tablet and one 100-mg tablet BID for the 250 mg BID dose or two 100-mg tablets BID for the 200 mg BID dose or one 150-mg tablet BID or one 100-mg tablet BID.

For durvalumab, dose reductions are not permitted. Dose delays are permitted for durvalumab (see link to Dosing Modification and Toxicity Management Guidelines in Section 8.4.5.1). For guidance on dose modifications for management of AEs (including renal impairment) for olaparib and durvalumab, refer to Section 8.4.5.

Investigators should follow local standard clinical practice regarding dose modifications for the SoC treatments (chemotherapy).

6.6 Treatment after the end of the study

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving durvalumab or olaparib monotherapy or durvalumab plus olaparib combination therapy up to the time they discontinue treatment for any reason (see Section 6.1.2).

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

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

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up), unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1 for durvalumab and Section 8.4.5.2 and Appendix G for olaparib) or as defined in the local prescribing information for the SoC agent
- 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 confirmed radiological progression (refer to Appendix F) and Investigator determination that the patient is no longer benefiting from treatment with IP

A patient who discontinues therapy for any reason will have the end of therapy (EOT) recorded as the date of the last dose of IP. The patient should be followed using the schedule of activities outlined in Table 3.

During the initial therapy phase, if SoC chemotherapy is discontinued due to treatment-related toxicity, durvalumab monotherapy may continue at the discretion of the Investigator and patient when toxicity resolves to at least Grade 2 or less (however, these patients will not be allowed to continue into the maintenance phase [Section 5.2]). Similarly, if durvalumab is discontinued due to treatment-related toxicity, SoC may be continued per the study schedule and assessments should be continued according to local practice (however, these patients will not be allowed to continue into the maintenance phase [Section 5.2]). Patients should be monitored per local SoC guidelines and managed using the Dose Modification and Toxicity Management Guidelines (see Section 8.4.5.1) for durvalumab; patients should also follow the recommended schedule in Table 2 for laboratory assessments, physical examinations, ECGs, and AE/SAEs. In these situations, patients cannot be randomized to the maintenance phase of the study.

During the maintenance phase, in the event that durvalumab is discontinued due to treatment-related toxicity, olaparib/placebo may still be administered as scheduled at the discretion of the Investigator and patient (with the understanding that the patient may be receiving placebo, as the study will still be blinded). If olaparib/placebo is discontinued due to treatment-related toxicity, durvalumab may continue at the discretion of the Investigator and patient when toxicity resolves to Grade 2 or less. Note: If the Investigator feels that a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

7.1.1 Procedures for discontinuation of study treatment

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.

All 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 the follow-up period (see the SoA in Table 3).

Patients who permanently discontinue drug for reasons other than RECIST 1.1-defined radiological PD should continue to have RECIST scans performed q8w ±1 week (relative to the date of randomization) for the first 48 weeks and then q12w ±1 week thereafter until

RECIST 1.1-defined radiological PD plus one or more additional follow-up scans, if clinically feasible, as defined the SoAs. Please note, for patients who are not randomized into the maintenance phase for any reason, durvalumab will be discontinued and follow-up tumor assessments will not be required.

If a patient is discontinued for RECIST 1.1-defined radiological PD, then the patient should have one or more additional follow-up scans performed (if clinically feasible).

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 end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets (SAF) 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 eCRF modules will be updated.)
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available), where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable eCRF modules will be updated.)

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 survival follow-up, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. The patient may be offered additional tests or tapering of treatment to withdraw safely.

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

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

- All further participation in the study including any further follow-up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples (see Section 8.8.6)

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

The Investigator will ensure the accuracy, completeness, 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 SoAs, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria (patients must also meet added eligibility criteria for the maintenance phase prior to randomization). 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 (for initial therapy phase) purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoAs.

8.1 Efficacy assessments

This study will evaluate the primary endpoint of PFS (Investigator-assessed). Secondary efficacy endpoints include ORR, DoR, and OS in the FAS, and PFS (Investigator-assessed) in the HRRm subgroup. Efficacy assessments of PFS (Investigator-assessed), ORR, and DoR will be derived using RECIST 1.1 assessments.

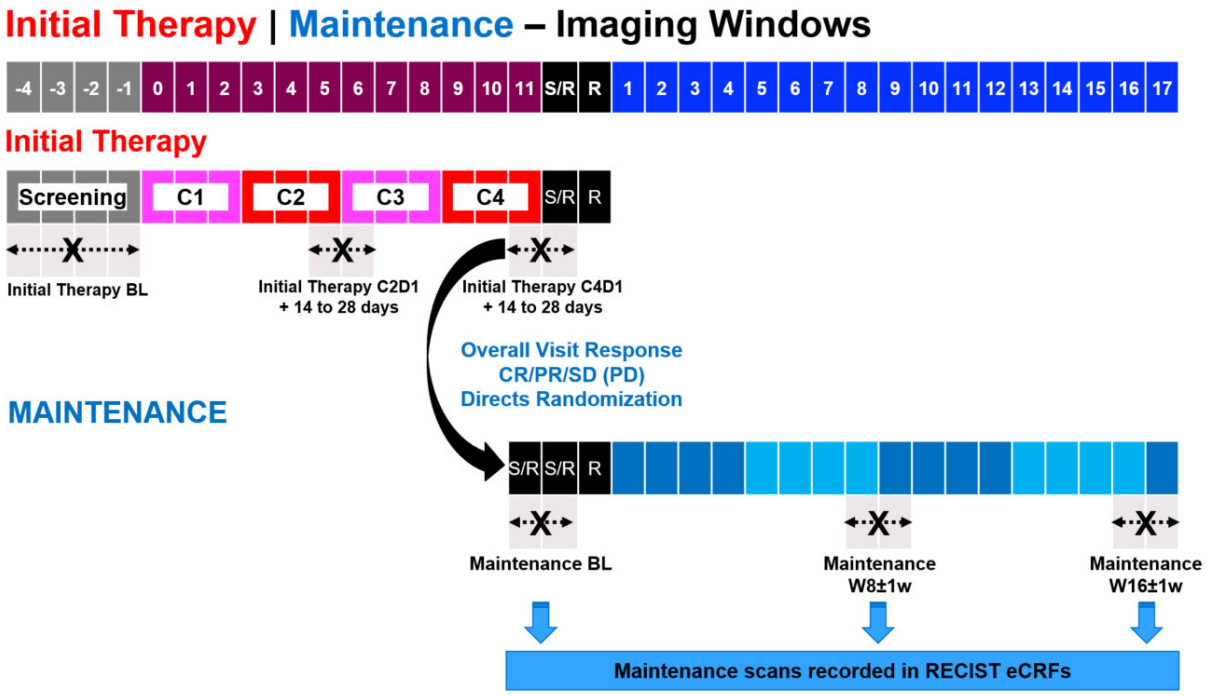
Radiological efficacy will be assessed by RECIST 1.1 on IV contrast-enhanced CT or MRI scans of the chest and abdomen (including the entire liver and both adrenal glands). There will be 2 baseline assessments, the first for the initial therapy period and the second for the maintenance period. A first "Initial Therapy Baseline" scan should be collected during screening (Days -28 to -1) for disease staging and for use as a RECIST 1.1 baseline scan for the initial therapy phase on-study scans (collected 14 to 28 days after Cycle 2 Day 1 and Cycle 4 Day 1 of the initial therapy phase [Table 1]). A patient's diagnostic scan may be used as a baseline scan for the initial therapy phase only if taken within 28 days of first-dose administration and in accordance with the scan acquisition requirements (ie, chest and abdomen [including the entire liver and both adrenal glands] IV contrast-enhanced CT/MRI) outlined in Appendix F. The scan at 14 to 28 days after Cycle 4 Day 1 of the initial therapy phase will be compared with the initial therapy baseline scan to determine eligibility for the maintenance phase and will also be the "Maintenance Baseline" scan for the assessment of response during the maintenance phase (for those patients eligible for randomization into the maintenance phase) with new RECIST 1.1 baseline assignment of TLs/NTLs (Table 2). If determined eligible, patients will be randomized within 5 weeks after Cycle 4 Day 1 of the initial therapy phase; every effort should be made to minimize the time between confirmation of eligibility, randomization, and starting maintenance treatment. During the maintenance phase, on-study tumor assessments occur q8w ±1 week relative to the date of randomization beginning 8 weeks after randomization for the first 48 weeks and then q12w ±1 week thereafter until RECIST 1.1-defined radiological PD (plus one or more additional follow-up scans if clinically feasible), the end of study, study discontinuation, or Sponsor decision, whichever comes first. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoAs). If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to resume subsequent assessments according to the original imaging visit schedule (relative to the date of randomization).

For patients who discontinue treatment due to toxicity or other reasons in the absence of RECIST 1.1-defined radiological PD, tumor assessments should be continued until

RECIST 1.1-defined radiological PD plus one or more additional follow-up scans if clinically feasible.

Figure 7 depicts the tumor assessment schedule for both the initial therapy and maintenance phases.

Figure 7 Tumor assessment schedule for initial therapy and maintenance phases



[a] During the initial therapy phase, 1 cycle is 21 days in duration, unless there are SoC dosing delays (eg, for toxicity reasons). If there is a dosing delay during the treatment schedule for durvalumab, all future dosing days for durvalumab should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days.

Note: Maintenance phase on-study tumor assessments occur q8w ±1 week relative to the date of randomization beginning 8 weeks after randomization for the first 48 weeks and then q12w ±1 week thereafter until RECIST 1.1-defined radiological PD plus one or more additional follow-up scans if clinically feasible.

BL RECIST 1.1 baseline scan; C Cycle; D Day; R Randomize; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; S/R Scan, analyze, randomize; W Week; X Scan timepoint.

8.1.1 Central reading of scans

All radiological scans, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed CRO for quality control and storage. Guidelines for image acquisition, de-identification, storage at the study site as source data, and transfer to the imaging CRO for central review 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 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').

The BICR of radiological scans will be analyzed as a sensitivity analysis for the primary endpoint of PFS (Investigator-assessed). Only Investigator assessments will be captured in the RAVE system in RECIST folders.

8.1.2 Survival assessments

Assessments for survival must be made every 2 months following treatment discontinuation. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

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

8.1.3 Clinical outcome assessments

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

The PRO instruments will be completed by the patients using a site-based, electronic patient-reported outcome (ePRO) device. All assessments should be completed without assistance from anyone according to the assessment schedules (Table 2 and Table 3).

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/quality of life (QoL) (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, and nausea and vomiting); a 2-item global QoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the

disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population (see Appendix H).

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, sore mouth, dysphagia, peripheral neuropathy, alopecia, and pain medication (see Appendix H).

CCI [redacted]

8.1.3.5 Administration of the patient-reported outcome questionnaires

Patients will perform the PRO assessments using an electronic tablet (ePRO) during clinic visits.

Each site must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be administered and completed at the clinic as per the SoAs (Table 2 and Table 3).

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

- PRO questionnaires should be completed prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.
- PRO questionnaires must be completed in private by the patient.
- Patients should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is confidential. Therefore, if the patient has any medical problems, he/she should discuss them with the doctor or research nurse separately from the PRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided in the ePRO device.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items. The patient should not receive help from relatives, friends, or clinic staff in answering the PRO questionnaires.

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

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the SoAs (Table 1, Table 2, and Table 3).

8.2.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs [Table 1, Table 2, and Table 3]). During the initial therapy phase, laboratory assessments should be performed according to local standard clinical practice for SoC; if these items are performed on Day 8 or 15 of each cycle per local standard clinical practice, results do not need to be recorded in the clinical database unless abnormal results are associated with AEs and SAEs.

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). If pregnancy test results are positive, the patient is ineligible for the study/must be discontinued from study treatment immediately.

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 14 (clinical chemistry), Table 15 (hematology), and Table 16 (urinalysis).

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

The following laboratory variables will be measured:

Table 14 Clinical chemistry

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

[a] Tests for ALT, AST, alkaline phosphatase, and TBL must be conducted and assessed concurrently. If TBL is ≥2 × ULN (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured, either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, CrCl, gamma glutamyltransferase, magnesium, testing are to be performed at screening, on Day 1 of initial therapy phase (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), on Day 1 of maintenance phase, and as clinically indicated (except for CrCl, which is also measured at Day 1 of each cycle during the maintenance phase).

[d] CrCl will be calculated by the investigator or designee using Cockcroft-Gault equation (using actual body WT) or based on a 24-hour urine test.

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

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

ALT Alanine aminotransferase; AST Aspartate aminotransferase, CrCl Creatinine clearance; T3 Triiodothyronine; T4 Thyroxine; TBL Total bilirubin; TSH Thyroid-stimulating hormone; ULN Upper limit of normal; WT Weight.

Table 15 Hematology

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

Note: For coagulation parameters, activated partial thromboplastin time and INR are to be assessed at screening (initial therapy phase) and as clinically indicated (in both the initial therapy and maintenance phases). Patients who are taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

[a] Can be recorded as absolute counts or as percentages. Total white cell count therefore has to be provided.

INR International Normalized Ratio.

Table 16 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin (TBL) ≥2 × ULN, refer to Appendix E for further instructions on cases of increases in liver biochemistry and evaluation of HL. These cases should be reported as SAEs per criteria specified in Appendix E.

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 Table 3).

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

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

8.2.1.1 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities, as defined in Appendix G.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the Investigator for documentation on the Patient Safety database. These data are not required to be entered into eCRF.

8.2.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see Table 1, Table 2, and Table 3). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at 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 Table 1, Table 2, and Table 3. Body WT is also recorded at each visit along with vital signs.

First infusion of durvalumab

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

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

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

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

Subsequent infusions of durvalumab

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

During the initial therapy phase, on days where SoC is administered without durvalumab, patients will be monitored pre-dose and as clinically indicated before every infusion or administration.

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

8.2.4 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.

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 Early patient review for safety

During the initial therapy phase, patients will be evaluated 7±2 days after the first dose of each cycle of chemotherapy with durvalumab (Day 8 ±2 days) to ensure early identification and management of toxicities. It is strongly recommended for any patient experiencing Grade 3 or 4 neutropenia that granulocyte colony-stimulating factor is administered according to local practice.

Following the initial therapy phase, patients are to be contacted 2 weeks ±2 days after receiving the first dose of each of the first 2 cycles of olaparib/placebo maintenance therapy to ensure early identification and management of toxicities. For the maintenance phase, the form of contact and procedures conducted will be at the Investigator's discretion.

8.2.6 WHO/ECOG performance status

WHO/ECOG PS will be assessed at the times specified in the assessment schedules (see Table 1, Table 2, and Table 3) based on the following:

0 Fully active; able to carry out all usual activities without restrictions
1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)
2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair
5 Dead

Any significant change from baseline for the initial therapy or maintenance phases must be reported as an AE.

8.2.7 Other safety assessments

If new or worsening pulmonary symptoms (eg, dyspnea or cough) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended, and further diagnostic workup should be performed to exclude pneumonitis. The differential diagnosis should include the possibility of both immune-related and non-immune-related processes. AEs of pneumonitis are of interest for AstraZeneca as pneumonitis has been observed with use of both anti-PD-1 and anti-PD-L1 mAbs, and instances of pneumonitis have been reported in patients undergoing olaparib treatment.

Initial workup should consider the inclusion of a clinical evaluation, high-resolution CT scan, ruling-out infection, pulse oximetry, and other appropriate laboratory workup. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-related AEs including pneumonitis are provided in the Dose Modification and Toxicity Management Guidelines (see Section 8.4.5.1).

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

Pneumonitis (ILD) investigation

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

- Physical examination
  - Signs and symptoms (cough, shortness of breath, pyrexia, etc) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD markers (KL-6, SP-D) and β-D-glucan
    (ii) Tumor markers: particular tumor markers that are related to disease progression.
    (iii) Additional Clinical chemistry: CRP, LDH

8.3 Collection of adverse events

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

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

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 signing the informed consent throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later; Table 3). 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 Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.3.2.1 Adverse events after the safety follow-up period

For pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the follow-up period (as defined in Section 8.3.2) should be reported to AstraZeneca Patient Safety regardless of Investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow-up for OS if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he or she considers that there is a reasonable possibility that the event is causally related to the IP, the Investigator should notify AstraZeneca Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment after DCO and/or after study completion, then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (ie, after any scheduled post-treatment follow-up period has ended), there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post-treatment follow-up period.

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 SAEs and AEs of special interest (as defined in Section 8.3.12), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated (this may be beyond 90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo), but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- Date when the AE started and stopped
- Maximum CTCAE grade reported
- Changes in CTCAE grade (report all changes in 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
- AE caused patient's withdrawal from study (yes or no)
- Outcome

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

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

8.3.5 Causality collection

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

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

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

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

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

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

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

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

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 TBL ≥2 × ULN may need to be

reported as SAEs. Refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increase in any of 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, which are unequivocally due to disease progression should not be reported as an AE during the study.

8.3.10 New cancers

The development of a new cancer should be reported as an AE (see Section 8.3.12.2) and would in most cases meet seriousness criteria (with the exception of some non-melanoma skin cancers). 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. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

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 post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow-up period and the

event is considered to be due to a late onset toxicity to 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 IP and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of these IPs.

8.3.12.1 Adverse events of special interest for durvalumab

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

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

AESIs/imAEs observed with anti PD-L/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis,myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

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

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see link in

Section 8.4.5.1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

8.3.12.2 Adverse events of special interest for olaparib

AESIs for olaparib are the important potential risks of the following:

- MDS/AML
- New primary malignancy (other than MDS/AML)
- Pneumonitis

Any event of MDS/AML, new primary malignancy, or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE (eg, non-melanoma skin cancer) or SAE, and regardless of Investigator assessment of causality. These AEs must be reported according to the timelines for reporting an SAE (see Section 8.4.1) to allow timely safety monitoring.

A questionnaire will be sent to any Investigator reporting an AESI as an aid to provide further detailed information on the event. During the study, there may be other events identified as AESIs that require the use of a questionnaire to help characterize the event and gain a better understanding regarding the relationship between the event and study treatment.

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

For patients continuing to receive study 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 in order to manage AEs in accordance with the Dose Modification and Toxicity Management Guidelines (see Section 8.4.5 and Appendix G). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving study treatment (or within the follow-up period [Section 8.3.2]) 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 eCRF.

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

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

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

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

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

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except 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 IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the first dose of study treatment until 90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later, 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 inform the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he/she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all 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 eCRF is used to report the pregnancy, and the PREGOUT is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later. Please follow the local prescribing information relating to contraception and the time limit for such precautions for SoC agents.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the first dose of study treatment until 90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo, whichever is later, if possible, should 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)/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 Table 3).

8.4.3 Overdose

8.4.3.1 Durvalumab and olaparib

Olaparib and durvalumab must only be used in accordance with the dosing recommendations in this protocol. Use of durvalumab or olaparib in doses in excess of that specified in the protocol is reported as an overdose. There is currently no specific treatment in the event of overdose of durvalumab or olaparib, and possible symptoms of overdose are not established.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

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

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

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

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

8.4.3.2 Standard of care

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

8.4.4 Medication error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an

SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

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

8.4.5 Management of IP-related toxicities

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, or infections). This includes SoC-induced toxicity. In the event that toxicities are clearly attributed to chemotherapy, both SoC and durvalumab should be delayed (note that if SoC is delayed for any reason, durvalumab administration must be delayed as well).
- In the event that durvalumab is discontinued or delayed as part of the toxicity management guidance, SoC may still be administered as scheduled.
- In the event that SoC chemotherapy is discontinued due to treatment-related toxicity, durvalumab monotherapy may continue at the discretion of the Investigator and patient when toxicity resolves to at least Grade 2 or less. Note: if the Investigator feels that a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

If unsure how to manage a patient, please contact the Study Physician at AstraZeneca to discuss individual cases. All toxicities will be graded according to NCI CTCAE, version 5.0.

8.4.5.1 Durvalumab

Comprehensive toxicity management guidelines (TMGs) 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). 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 (ie, antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific

instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with 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. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Please contact the clinical study associate for information on how to gain access to this website.

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

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

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

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

8.4.5.2 **Olaparib**

Potential olaparib-related toxicities observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions (see Appendix G). Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed.

For patients with CrCl ≥51 mL/min dosed with 300 mg BID, study treatment can be dose reduced to 250 mg BID as a first step and to 200 mg BID as a second step. If the reduced dose of 200 mg BID is not tolerable, no further dose reduction is allowed and olaparib/placebo should be discontinued.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A inhibitors; see Section 6.4).

No further dose reductions are permitted for patients who receive olaparib treatment at a dose of 200 mg BID due to moderate renal impairment (≥31 mL/min but <51 mL/min) and who cannot tolerate this dose.

8.4.5.3 SoC

Investigators should follow local standard clinical practice regarding dose modifications for SoC. For specific information regarding the individual agent used in this study, refer to the local prescribing information for the relevant agent.

In the event of unfavorable tolerability, patients can switch between cisplatin and carboplatin therapy at any point during the study.

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

In the event that SoC is delayed, durvalumab administration must also be delayed.

Every effort should be made to ensure that patients receive 4 cycles of SoC during the initial therapy phase, if conditions allow.

8.5 Pharmacokinetics

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

8.5.1 Collection of samples

Blood samples for determination of durvalumab concentration in serum will be obtained according to Table 1, Table 2, and Table 3.

Samples for determination of durvalumab 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.

8.5.1.1 Collection of samples to measure for the presence of ADAs

The presence of ADA will be assessed in serum samples taken according to Table 1, Table 2, and Table 3.

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for durvalumab 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-naïve validation samples will be employed.

8.5.2 Storage and destruction of pharmacokinetic/ADA samples

Durvalumab PK and ADA samples will be destroyed within 5 years of CSR finalization.

PK and ADA samples may be disposed of or destroyed and 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 AstraZeneca-designated biobank; see details in the Laboratory Manual).

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

CCI [redacted]

CCI [redacted]

8.7.2 CCI [redacted]

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.

Pretreatment tumor tissue will be submitted for PD-L1 expression in all enrolled patients. Data will be compared between arms to determine if baseline PD-L1 status is prognostic and/or predictive of outcomes associated with IP. Baseline tumor requirements are briefly described in Section 8.8.1.

CCI [redacted]

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

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy as described in Section 8.8.2.

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

8.8.1 Collection of tumor samples for biomarkers assessments

To accomplish biomarker assessments, the following samples will be collected from all patients, including screen failures, wherever possible.

The FFPE tumor sample provided at baseline will ideally be a sample close to the time of study entry; either newly acquired or archival tumor samples (<3 years old) are acceptable. If available, a newly acquired tumor biopsy, collected as part of routine clinical practice, is preferred. If not available, an archival sample taken <3 years prior to screening is acceptable. If both an archival sample and a fresh tumor biopsy sample are available, both samples should be submitted for analysis. CCI

Tumor lesions used for newly acquired biopsies should not be TLs, unless there are no other lesions suitable for biopsy. Samples with limited tumor content and fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component and should not be decalcified.

Patients will be given the option to consent to an optional tumor biopsy (FFPE tumor sample) at progression. This should be performed as soon as possible after disease progression is confirmed. The treating physician will judge the feasibility of such a procedure.

8.8.1.1 HRR mutation testing

Patient tumor samples will be provided at screening to determine HRR mutation status by a central laboratory (details of HRR mutation assessment follow below and in the Laboratory Manual). The anticipated prevalence of HRR mutations in the NSCLC patient population is approximately 12.5% based on analysis of TCGA data; it is expected to be approximately between 15% and 20% in this study population given that patients with platinum-sensitive NSCLC may be enriched for HRRm. Sites will be blinded to the result of the central assessment. If available, full results from the HRR mutation test will be provided to the Investigator upon individual request for randomized patients who received treatment upon disease progression and treatment discontinuation.

The newly acquired or archival tumor sample (<3 years old) provided at baseline (Section 8.8.1.1) will be used for tissue-based HRR genes mutation testing. The analysis will be performed at a central laboratory testing service using the DNA extracted from FFPE tissue.

The tumor sample will be tested for loss of function and alterations in specific HRR genes that have not yet been determined. If the test results indicate that the patient has at least 1

qualifying mutation in any of these genes, the patient will be considered HRRm. No local testing results are permitted. All tumor samples will be analyzed for a range of cancer-related genes to explore correlations between clinical response and DNA alterations.

CCI [redacted]

CCI [redacted]

CCI [redacted]

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

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. CCI [redacted]

8.8.4 Labeling and shipment of biological samples

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

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

8.8.5 Chain of custody of biological samples

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

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

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

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

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

8.8.6 Withdrawal of informed consent for donated biological samples

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

The Principal Investigator will:

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

CCI [redacted]

9. STATISTICAL CONSIDERATIONS

All personnel involved with the analysis of the study will remain blinded until database lock for the analysis of PFS, with all protocol violators identified. A comprehensive statistical analysis plan (SAP) will be finalized before database lock.

Analyses will be performed by AstraZeneca or its representatives.

The primary objective of this study is to assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy during the maintenance phase in terms of PFS as determined by Investigator assessment according to RECIST 1.1 in all

randomized patients. Secondary efficacy variables include ORR, DoR, and OS in the FAS, and PFS as determined by Investigator assessment according to RECIST 1.1 in the HRRm subgroup. Sensitivity analyses for the primary endpoint will be performed, including analyzing PFS according to BICR in the FAS.

9.1 Statistical hypotheses

The primary objective is to assess the efficacy of durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS (Investigator-assessed) for patients who are in the FAS. The formal statistical analysis will be performed to test the following main hypotheses:

- H01: No difference between durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS for the FAS
- H11: There is a difference between durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of PFS for the FAS

If a statistically significant difference is observed in the study, ie, reject the null hypothesis of no difference in favor of H11, then the following hypotheses can also be tested:

- H20: No difference between durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of OS for the FAS
- H21: There is a difference between durvalumab plus olaparib combination therapy compared with durvalumab monotherapy in terms of OS for the FAS

9.2 Sample size determination

The study is sized to characterize the PFS benefit of durvalumab in combination with olaparib versus durvalumab monotherapy in patients with Stage IV NSCLC whose disease has not progressed after 4 cycles of durvalumab with platinum-based first-line chemotherapy.

Approximately 350 to 400 patients will be enrolled in the initial therapy phase of the study. Approximately 250 patients globally who have not progressed will be randomized in a 1:1 ratio to either the durvalumab plus olaparib treatment arm or the durvalumab plus placebo treatment arm, approximately 125 patients per arm. The randomization will be stratified based on objective response to durvalumab plus chemotherapy (CR/PR or SD; obtained at the last visit prior to randomization [Cycle 4 scan]) and histology (squamous or nonsquamous).

The DCO for the primary analysis of PFS will occur when approximately 163 PFS events have occurred across the durvalumab plus olaparib treatment arm and durvalumab plus placebo treatment arm (approximately 65% maturity). CCI

CCI

CCI

9.3 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 17.

Table 17 Summary of outcome variables and analysis populations

Outcome variables	Populations
Efficacy data	
PFS (Investigator-assessed)	FAS (ITT population) and HRRm subgroup
OS, ORR, DoR	FAS (ITT population)
PRO	FAS (ITT population)
Demography	FAS (ITT population)
PK data	PK analysis set
Safety data	
Exposure	SAF
AEs	SAF
Laboratory measurements	SAF
Vital signs	SAF

AE Adverse event; DoR Duration of response; FAS Full analysis set; HRRm Homologous recombination repair related gene mutation; ITT Intent to treat; ORR Objective response rate; OS Overall survival; PFS Progression-free survival.; PK Pharmacokinetics; PRO Patient-reported outcome; SAF Safety analysis set.

9.3.1 Full analysis sets

9.3.1.1 Full analysis set (FAS) for the initial therapy phase

The FAS for the initial therapy phase will include all patients who received at least 1 dose of durvalumab and/or chemotherapy in the study. It will be used to summarize patient disposition and demographic characteristics for all patients receiving treatment in the study. It will also be used to summarize the tumor response as reported by investigators in the initial therapy phase.

9.3.1.2 Full analysis set (FAS)

The FAS for the maintenance phase will include all randomized patients (ie, intent-to-treat population). The FAS will be used for all efficacy analyses (including PROs). Treatment arms will be compared based on randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently proceed to receive study treatment are included in the analysis in the treatment arm to which they were randomized.

9.3.2 Safety analysis sets

9.3.2.1 Safety analysis set for initial therapy phase

The SAF for the initial therapy phase will consist of all patients who received at least 1 dose of durvalumab during the initial therapy phase of the study. Minimal safety data will be summarized for the initial therapy phase only (not including post-randomization data for randomized patients), unless unexpected safety signals are observed.

9.3.2.2 Safety analysis set for maintenance phase (SAF)

The SAF for the maintenance phase will consist of all patients who received at least 1 dose of any study treatment (durvalumab and/or olaparib/placebo) during the maintenance phase of the study. Safety data will not be formally analyzed but summarized using the SAF according to the treatment received, that is, erroneously treated patients will be summarized according to the treatment they actually received (ie, those randomized to durvalumab plus placebo who receive one or more doses of olaparib in error will be reported in the durvalumab plus olaparib arm).

9.3.3 Pharmacokinetic analysis set

All patients who receive at least 1 dose of durvalumab 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.

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of efficacy variables

9.4.1.1 RECIST 1.1-based endpoints

The analyses of the primary endpoint (PFS in the FAS) and secondary endpoints (ORR and DoR in the FAS, and PFS in the HRRm subgroup) will be based on site Investigator assessments using RECIST 1.1. In addition, OS in the FAS will also be evaluated. Sensitivity analyses for the primary endpoint will be performed, including analyzing PFS according to BICR in the FAS.

Investigator RECIST 1.1-based assessments

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

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the Investigator-reported status of their disease compared with baseline (Section 9.5) and previous assessments. 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).

Refer to Appendix F for the definitions of CR, PR, SD, PD, and NE.

Blinded independent central review RECIST 1.1-based assessments

As described in Section 8.1.1, a BICR of radiological scans will be performed for the sensitivity analysis of the primary endpoint in the FAS. The BICR will be performed on all radiological scans of all patients.

All images will be collected centrally. Prior radiotherapy reports will also be provided to the BICR to allow the selection of appropriate TLs. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). PFS according to BICR will be derived from the overall visit response date and the scan dates.

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

9.4.1.2 Progression-free survival

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

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

- For Investigator assessments, the date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates progression.
- For BICR assessments, date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans that indicates progression for the adjudicated reviewer selecting PD, or of either reviewer where both reviewers select PD as a timepoint response, and there is no adjudication for central review (BICR) data.
- 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.

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 (where possible to do so under applicable local laws).

9.4.1.4 Objective response rate

ORR (per RECIST 1.1 using Investigator's assessments) is defined as the percentage of patients with at least 1 visit response of CR or PR after randomization and who have

measurable disease at randomization. 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.

Categorization of objective tumor response assessment will be based on the RECIST criteria of response: CR, PR, SD, PD, and NE. TL progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study from the time of randomization). In the absence of a best response of progression, tumor response (CR, PR, or SD) will be calculated in comparison with the tumor measurements used to determine eligibility for the maintenance phase obtained prior to randomization.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time from randomization up to and including the defined analysis cut-off point. For each treatment arm, the ORR is the number of CR and PR divided by the number of patients in the FAS with measurable disease at time of randomization.

9.4.1.5 **Duration of response**

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

DoR will not be defined for those patients who do not have documented response.

9.4.2 **Calculation or derivation of safety variables**

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and physical examination findings. These will be collected for all patients and summarized separately for the initial therapy and maintenance phases. Data from all cycles of treatment will be combined in the presentation of safety data.

9.4.2.1 **Adverse events**

AEs and SAEs for both treatment arms will be collected throughout the study, from the date of signing the informed consent throughout the treatment period and including the follow-up period (90 days following discontinuation of durvalumab or 30 days following discontinuation of olaparib/placebo, whichever is later). The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute CTCAE Version 5.0.

Any AE occurring before starting study treatment will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within the follow-up period may be included in the AE summaries, but the majority of the AE summaries will omit the AEs observed after a patient has received further therapy for cancer. This will more accurately depict AEs attributable to study treatment only as a number of AEs up to the end of the follow-up period are likely to be attributable to subsequent therapy. Any AE that occurs after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

For the durvalumab plus olaparib arm and the durvalumab plus placebo arm, in the event of the components being administered separately, then the date of first dose/last dose will be considered as the earliest/latest dosing date of either component.

The SAF in the initial therapy phase will be used for the reporting of safety data in the initial therapy phase, and the SAF in the maintenance phase will be used for the reporting of safety data in the maintenance phase.

A separate data listing of AEs occurring more than 90 days after discontinuation of durvalumab and more than 30 days after discontinuation of olaparib/placebo, whichever is later, will be produced for both the initial therapy and maintenance phases. These events will not be included in AE summaries.

9.4.2.2 **Safety assessments**

For the change from baseline summaries during the maintenance phase for vital signs, laboratory data, and physical examinations, the baseline value will be the latest result obtained prior to the start of randomized study treatment.

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) using the following formula:

QTcF = QT/RR^(1/3), where RR is in seconds.

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

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

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

For example:

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

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

9.4.3 Calculation or derivation of patient-reported outcome variables

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

9.4.3.1 EORTC QLQ-C30 and EORTC QLQ-LC13

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

An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, the functional scales, and the global health status/QoL scale according to the EORTC QLQ-C30 Scoring Manual (Fayers et al 2001) and EORTC QLQ-LC13 instructions.

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

Changes in score compared with baseline (Section 9.5)will be evaluated. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically relevant change is defined as a change in the score from baseline of ≥10 for scales/items from the QLQ-C30 and the QLQ-LC13 (Osoba et al 1988). For example, a clinically relevant deterioration or worsening in chest pain (as assessed by QLQ-LC13) is defined as an increase in the score from baseline (defined as Day 1, pre-dose) of ≥10. A clinically relevant improvement in fatigue (as assessed by QLQ-C30) is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable, or worsening as shown in Table 18.

Table 18 Visit responses for symptoms and health-related quality of life

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

QLQ-C30 30-Item core quality-of-life questionnaire; QLQ-LC13 13-Item lung cancer quality-of-life questionnaire; QoL Quality of life.

Time to symptom and health-related QoL/function deterioration, based on the clinically meaningful cutoffs, will be evaluated.

Health-related QoL/function and symptom improvements will be evaluated.

CCI [redacted]

CCI [redacted]

9.4.3.4 Definition of compliance and evaluability rates

Compliance rates for the PRO questionnaires should be 85%; this rate will be monitored as the trial goes on. Compliance with the EORTC QLQ-C30 and EORTC QLQ-LC13 will be calculated separately for each questionnaire:

$$\text{Compliance rate} = \frac{\text{number of evaluable forms}}{\text{number of expected forms}} \times 100$$

Evaluability rates for the EORTC QLQ-C30 and EORTC QLQ-LC13 will also be calculated separately for each questionnaire:

$$\text{Evaluability rate} = \frac{\text{number of evaluable forms}}{\text{number of received forms}} \times 100$$

An expected form = a questionnaire that is expected to be completed at a scheduled assessment time, that is, a questionnaire from a patient who has not withdrawn from the study at the scheduled assessment time but excluding patients in countries with no available translation.

An evaluable form = a questionnaire with a completion date and at least 1 subscale that is non-missing.

A received form = a questionnaire that has been received and has a completion date and at least 1 individual item completed.

9.4.4 Calculation or derivation of pharmacokinetic variables

9.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model may be developed using a non-linear mixed-effects modeling approach. The impact of physiologically relevant patient characteristics (covariates) and disease on PK may be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints may be evaluated. The results of such an analysis will be reported in a separate report. The PK, 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 methods.

9.4.4.2 Pharmacokinetic analysis

PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. The following PK parameters will be determined after the first and steady-state doses: C_{max} and C_{trough} (as data allow). Samples below the lower limit of quantification will be treated as missing in the analyses.

9.4.4.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, efficacy, and safety may be evaluated, if the data allow.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

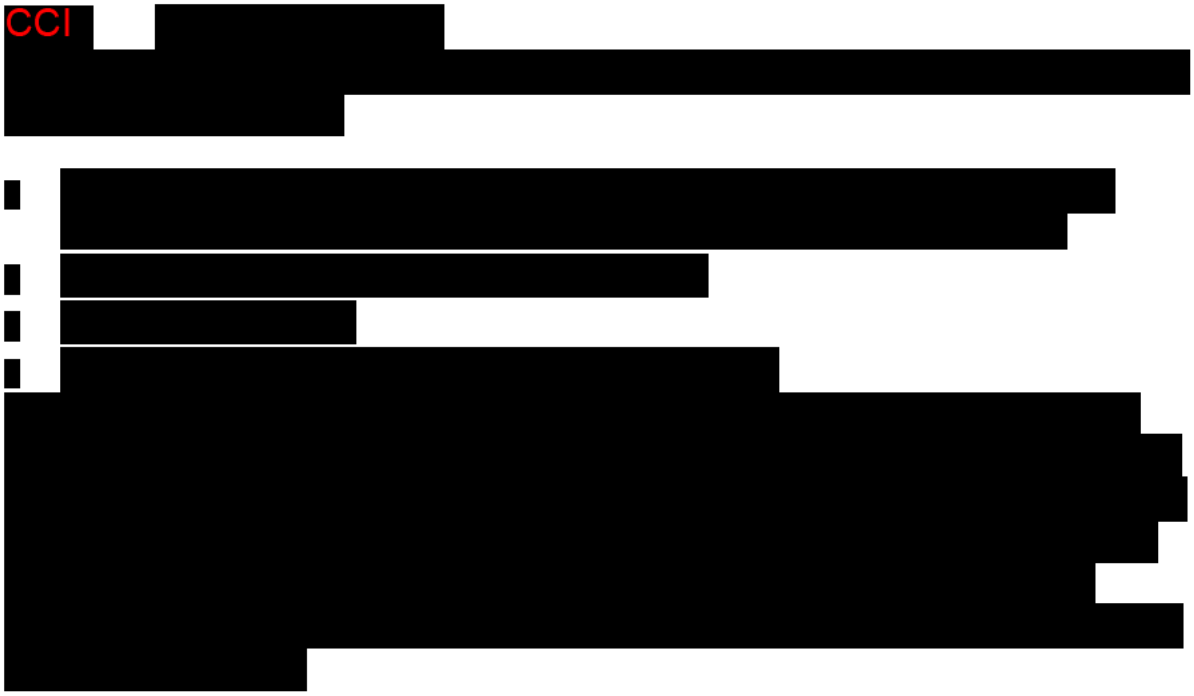
CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]



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, secondary, and exploratory endpoints. Any deviations from this plan will be reported in the CSR.

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

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

Efficacy and PRO data will be summarized and analyzed based on the FAS. Efficacy will also be summarized for the HRRm subgroup of the FAS. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized based on the appropriate SAF.

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

9.5.1 Efficacy analyses

Efficacy data will be summarized and analyzed using the FAS. All outputs will be summarized by treatment arm and where required for all randomized patients within the HRRm subgroup.

Table 19 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 that all endpoints compare durvalumab plus olaparib combination therapy versus durvalumab monotherapy, unless otherwise indicated. The 2 stratification factors are histology (squamous or nonsquamous) and objective response to durvalumab plus chemotherapy obtained at the last visit prior to randomization (CR/PR or SD [Cycle 4 scan]; response does not have to be confirmed). These factors will be covariates in logistic regression and mixed-effect model repeated measure models.

Table 19 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank tests for: Primary analysis using Investigator RECIST 1.1 assessments Sensitivity analysis using BICR RECIST 1.1 assessments Sensitivity analyses using Investigator RECIST 1.1 assessments • Interval censored analysis – evaluation time bias • Analysis using alternative censoring rules – attrition bias Secondary analysis using Investigator RECIST 1.1 assessments (HRRm subgroup)
Overall survival	Stratified log-rank test Secondary analysis
Objective response rate	Logistic regression for: Secondary analysis using Investigator assessments (RECIST 1.1)
Duration of response	Summary statistics and KM plot by treatment arm for: Secondary analysis using Investigator assessments (RECIST 1.1)
Time to deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Stratified log-rank test
Change from baseline in symptoms (EORTC QLQ-C30 and QLQ-LC13 endpoints)	MMRM analysis
HRQoL/Function and symptom improvement rate (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Logistic regression

BICR Blinded independent central review; EORTC European Organisation for Research and Treatment of Cancer; HRRm Homologous recombination repair related gene mutation; MMRM Mixed-effect model repeated measure; PFS Progression-free survival; QLQ-C30 30-item Core Quality of Life Questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1.

9.5.1.1 Primary endpoint: progression-free survival

The primary analysis of PFS will occur when it is expected that approximately 163 PFS events have occurred (approximately 65% maturity) in the FAS. The analysis will be performed for patients in the FAS using a stratified log-rank test adjusting for objective response to durvalumab plus chemotherapy (CR/PR or SD; obtained at the last visit prior to randomization [Cycle 4 scan]) and histology (squamous or nonsquamous) for generation of the p-value, and using a method that corresponds to the Breslow approach for handling ties (Breslow 1974).

The effect of durvalumab + olaparib versus durvalumab + placebo will be estimated by the HR together with its 95% CI from a stratified Cox model (an HR less than 1 will favor durvalumab in combination with olaparib). The CI will be calculated using a profile likelihood approach. The stratified Cox model will be fitted using PROC PHREG (in SAS) with the EFRON method to control for ties and the strata variables included in the strata statement.

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

The primary analyses will be based on Investigator-recorded assessment of disease progression using RECIST 1.1 criteria.

Stratification variables will be defined according to data from the IVRS/IWRS. If there are any patients who are mis-stratified, a sensitivity analysis will be carried out using the baseline data collected in the eCRF.

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

The primary analysis will be based on programmatically derived PFS based on Investigator assessments and using all scans regardless of whether they were scheduled or not.

The number of patients prematurely censored will be summarized by treatment arm together with baseline prognostic factors of the prematurely censored patients. A patient is defined as prematurely censored if they had not progressed and the latest scan prior to DCO was more than 1 scheduled tumor assessment interval (+2 weeks) prior to the DCO date.

9.5.1.2 Analysis of the secondary variables

The analyses of OS in the FAS, and of PFS as assessed by the site Investigator in the HRRm subgroup, will use the same methodology as specified for PFS as assessed by the site Investigator in the FAS (see Section 9.5.1.1).

For OS, 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. KM plots will be presented by treatment arm.

ORR in the FAS will be analyzed using logistic regression models adjusting for the same factors as the primary endpoint (histology and objective response to durvalumab plus chemotherapy). The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

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

9.5.1.3 Sensitivity analysis

Summary statistics for the number of weeks between the time of progression and the last evaluable RECIST assessment prior to progression will be presented for each treatment arm.

BICR

The analysis of PFS as assessed by BICR in the FAS will use the same methodology as specified for PFS as assessed by the site Investigator in the FAS (see Section 9.5.1.1).

Evaluation time bias

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analyzed using a stratified 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). This approach will use the Investigator RECIST assessments.

Attrition bias

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 KM plot of the time to censoring where the censoring indicator of the PFS analysis is reversed. This approach will use the Investigator RECIST 1.1 assessments.

9.5.1.4 Subgroup analyses

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

- Sex (male or female)
- Age at randomization (<65 or ≥65 years of age)
- PD-L1 status (<1%, 1% to 49%, ≥50%)
- Histology (squamous or nonsquamous)
- Objective response to initial therapy (CR/PR or SD)
- Smoking (smoker or non-smoker [never smoker])
- Race (Asian or non-Asian)
- HRRm status (yes, no, unknown)
- Investigator's choice of chemotherapy (cisplatin doublet versus carboplatin doublet; nab-paclitaxel doublet versus pemetrexed doublet versus gemcitabine doublet)

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

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.

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

Additionally, for each subgroup, the HR (durvalumab plus olaparib combination therapy:durvalumab monotherapy) 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 FAS.

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 across both treatment groups in a subgroup), the relationship between that subgroup and PFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

9.5.1.5 Patient-reported outcomes

EORTC QLQ-C30 and QLQ-LC13

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

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

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

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score, and each functional domain will be reported by assessment timepoint for each treatment group. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each assessment timepoint for each ordinal item (in terms of the proportion of patients in the categories of improved, stable, and worsened as defined in Table 18) will also be produced for each treatment group.

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

Time to deterioration will be analyzed for each of the symptom scales/items, function scales, and global health status/QoL using a stratified log-rank test as described for the primary analysis of PFS. The HR and 95% CI for each scale/item will be presented graphically on a forest plot.

For each of the symptom scales/items, functional scales, and global health status/QoL, time to deterioration will be presented using a Kaplan-Meier plot. Summaries of the number and percentage of patients experiencing a clinically relevant deterioration as well as who are censored will also be provided along with the medians for each treatment group.

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

CCI

CCI

CCI

9.5.2 Safety analyses

Safety and tolerability will be presented overall for the initial therapy phase and by treatment arm for the maintenance phase.

A brief overview of safety data during the initial therapy period will be summarized using the initial therapy phase SAF; details of these summaries will be provided in the SAP.

For the maintenance phase SAF, data from all cycles will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number and percentage of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced. Any safety summaries examining retreatment with durvalumab will be produced separately as described in the SAP.

Other safety data will be assessed in terms of physical examination, serum chemistry, hematology, urinalysis, vital signs, and ECGs. Exposure to each study treatment, time on study, dose delays, and dose reductions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.5.3 Pharmacokinetic data

PK concentration data for durvalumab will be listed for each patient and each PK sampling timepoint, 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 anti-durvalumab antibodies. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab antibodies.

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

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]

[redacted]

9.5.8 Methods for multiplicity control

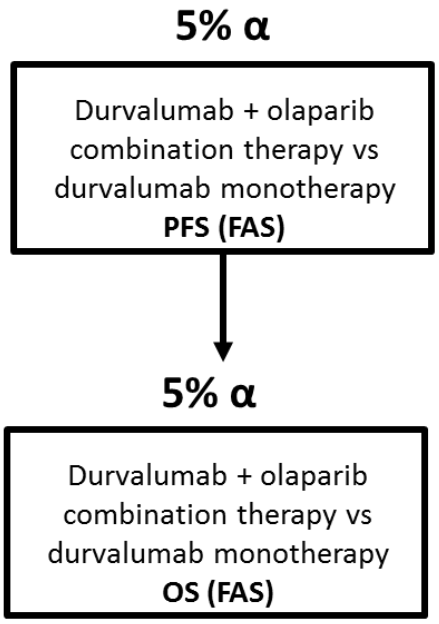
The multiple testing procedure (as shown in Figure 8) will define which significance levels should be applied to the interpretation of the raw p-values for the primary endpoint of Investigator-assessed PFS and the key secondary endpoint intended for label claims.

The overall 5% type I error rate will first be allocated to test the primary endpoint of PFS for durvalumab plus olaparib combination therapy versus durvalumab monotherapy (FAS). If the primary analysis of PFS is significant, 5% alpha will be recycled to the lower level in the hierarchy, where the 5% alpha will be used for the test of OS for durvalumab plus olaparib combination therapy versus durvalumab monotherapy (FAS) (5% alpha).

The primary endpoint of PFS (FAS) will be tested at 1 primary analysis of PFS. The key secondary endpoint, OS (FAS), will be tested at 2 timepoints: 1 interim analysis and 1 final analysis. The test at the primary analysis of PFS (FAS) (ie, shown in Box 1 in Figure 8) will be considered as 1 test family, as will the tests for the interim analysis and final analysis of OS. As long as 1 test in the family can be rejected, the family is rejected. Thus, the assigned total alpha to the family will be recycled to the next MTP level. Details of the interim analyses are provided in Section 9.6.

Figure 8 shows the multiple testing framework. The details of the multiple testing procedure will be provided in the SAP.

Figure 8 Multiple testing procedure



FAS Full analysis set; OS Overall survival; PFS Progression-free survival.

9.6 Interim analyses

A primary analysis for PFS will occur at approximately 163 events. If the PFS analysis occurs at exactly 163 events, a significant result will be declared if the OS HR is 0.74. Assuming non-uniform randomization, a median PFS of 8 months for the durvalumab monotherapy arm and an exponential distribution, randomization of 250 patients in 15 months would be expected to yield 163 PFS events approximately 25 months after the first patient is randomized.

There will be 1 interim analysis performed for OS. The OS interim will occur at the time of the primary analysis for PFS. It is anticipated that approximately 67% of the OS events will be available for this OS IA (approximately 109 of 163 OS events). With an alpha level of 5% and

if 67% of the OS events required at the time of the final OS analysis are available at the time of the interim (109/163 OS events have occurred) and the final analysis occurs once 163 OS events are reached, then the 2-sided significance levels of 0.012 and 0.046 will be applied to the interim and final analysis for OS, respectively. If the interim analysis occurs at exactly 109/163 OS events and the final analysis for OS occurs once 163 OS events are reached, a significant result will be declared if the OS HR is 0.62 at the interim or 0.73 at the final analysis.

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

The SAP will describe the planned interim analyses in greater detail.

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.

An IDMC will be established to perform an assessment of the safety of durvalumab plus olaparib therapy combinations in this population on an ongoing basis. The IDMC will be comprised of independent experts. The committee will meet at a frequency outlined in the IDMC Charter.

IDMC members will be consulted to ensure appropriate frequency. Following each meeting, the IDMC will report to AstraZeneca and may recommend changes in the conduct of the study.

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.

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 et al 2016
Antonia SJ, Kim SW, Spira AI, Ahn MJ, SHI Ou, Stjepanovic N et al. Safety and clinical activity of durvalumab (MEDI4736), an anti-PD-L1 antibody, in treatment-naïve patients with advanced non–small-cell lung cancer. J Clin Oncol 2016;34 (suppl; abstr 9029).

Arbour et al 2018
Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, et al. Deleterious effect of baseline steroids on efficacy of PD-(L)1 blockade in patients with non-small cell lung cancer. Poster presented at: ASCO Annual Meeting 2018.

Balar et al 2017
Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389(10064):67-76.

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: relationships with clinical outcomes. J Natl Cancer Inst. 2009;101(23):1624-32.

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

Borghaei et al 2015
Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627-39.

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.

Breslow 1974
Breslow N. Covariance analysis of censored survival data. Biometrics. 1974 Mar;30(1):89-99.

Carbone et al 2017
Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-line nivolumab in stage IV or recurrent non–small-cell lung cancer. N Engl J Med 2017;376:2415-26.

Chatzinikolaou et al 2014
Chatzinikolaou G, Karakasilioti I, Garinis GA. DNA damage and innate immunity: links and trade-offs. Trends Immunol 2014;35(9):429-35.

Ciuleanu et al 2009
Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small cell lung cancer: a randomized, double-blind, phase 3 study. Lancet 2009;374:1432-40.

Daaboul et al 2017
Daaboul N, Gauthier I, Tu D, Brown-Walker P, Sun X, Hao D, et al. Immune related adverse events (irAE) with platinum chemotherapy (CT) with durvalumab (D) ± tremelimumab (T): CCTG IND226. J Clin Oncol 2017;35(15_suppl):3058.

D'Addario et al 2010
D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2010;21(suppl 5):116-9.

Domchek et al 2018
Domchek SM, Postel-Vinay S, Bang YJ, Park YH, Alexandre J, Delord JP, et al. An open-label, multitumor, Phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline BRCA-mutated (gBRCAm) HER2-negative metastatic breast cancer (MBC). San Antonio Breast Cancer Symposium. 5-9 December 2017.

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

CCI [redacted]

Evers et al 2008
Evers B, Drost R, Schut E, de Bruin M, van der Burg E, Derksen PW, et al. Selective inhibition of BRCA2-deficient mammary tumor cell growth by AZD2281 and cisplatin. Clin Cancer Res 2008;14:3916-25.

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 tumors. J Clin Oncol, 2014 ASCO Annual Meeting Abstracts;32:5s (suppl; abstr 2602).

Farmer et al 2005
Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434(7035):917-21.

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 2015
Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of non-small cell lung cancer drugs and biologics [2015 Apr]. Available from: URL: http://www.fda.gov/downloads/Drugs/Guidances/UCM259421.pdf. Accessed 26 Jun 2018.

Fidias et al 2009
Fidias PM, Dakhil SR, Lyss AP, Loesch DM, Waterhouse DM, Bromund JL, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009;27(4):591-8.

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.

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

Gandhi et al 2018
Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; Epub 16 April 2018.

Garassino et al 2016
Garassino MC, Vansteenkiste J, Kim J-H, Lena H, Mazieres J, Powderly J. et al. Durvalumab in ≥3rd-line locally advanced or metastatic, EGFR/ALK wild-type NSCLC: results from the Phase 2 ATLANTIC study. IASLC 17th World Conference on Lung Cancer. 2016.

GLOBOCAN 2012
GLOBOCAN. Lung cancer, estimated incidence, mortality, and prevalence worldwide in 2012. International Agency for Research on Cancer, World Health Organization; Lyon, 2012. Available from: URL: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

Helleday 2011
Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. Mol Oncol 2011;5(4):387-93.

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.

Howlander et al 2017
Howlander N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, et al, editors. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER website, April 2017.

Huang et al 2015
Huang J, Wang L, Cong Z, Amoozgar Z, Kiner E, Xing D, et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. Biochem Biophys Res Commun 2015;463(4):551-6.

IASLC Staging Manual in Thoracic Oncology 2016
Rami-Porta R, ed. Staging manual in thoracic oncology (2nd edition; includes 8th edition tumor, node, and metastasis 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.

Jotte et al 2018
Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Abreu DR, Hussein M, et al. IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. Poster presented at: ASCO Annual Meeting 2018.

Juergens et al 2017
Juergens R, Hao D, Laurie S, Mates M, Tehfe M, Bradbury P, et al. MA09.03 Cisplatin/Pemetrexed + Durvalumab +/- Tremelimumab in Pts with Advanced Non-Squamous NSCLC: A CCTG Phase IB Study – IND.226. J Thorac Oncol 2017;12(1):S392-S393.

Karzai et al 2018
Karzai F, Madan RA, Owens H, Couvillon A, Hankin A, Williams M, et al. A phase 2 study of olaparib and durvalumab in metastatic castrate-resistant prostate cancer (mCRPC) in an unselected population. J Clin Oncol 2018;36(suppl 6):163.

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.

Krebs et al 2017
Krebs M, Ross K, Kim S, De Jonge M, Barlesi F, Postel-Vinay S, et al. An open-label, multitumor phase II basket study of olaparib and durvalumab (MEDIOLA): results in patients with relapsed SCLC. P1.15-004. International Association for the Study of Lung Cancer (IASLC) 18th World Conference on Lung Cancer (WCLC). 15-18 October 2017.

Kroemer et al 2013
Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013;31:51-72.

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

Ledermann et al 2012
Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382–92.

Lee et al 2017
Lee JM, Cimino-Matthew A, Peer CJ, Zimmer A, Lipkowitz S, Annunziate CM, et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in women's cancers: a dose-escalation, phase I study. J Clin Oncol 2017;35(19):2193-2202.

Litwin et al 1998
Litwin MS, Lubeck DP, Henning JM, Carroll PR. 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.

Lopes et al 2018
Lopes G, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab vs platinum-based chemotherapy as first-line therapy for advanced/metastatic NSCLC with a PD-L1 TPS ≥1%: Open-Label, Phase 3 KEYNOTE-042 study. Poster presented at: ASCO Annual Meeting 2018.

Malhotra et al 2017
Malhotra J, Jabbour SK, Aisner J. Current state of immunotherapy for non-small cell lung cancer. Transl Lung Cancer Res 2017;6(2):196-211.

Mulligan et al 2014
Mulligan JM, Hill LA, Deharo S, Irwin G, Boyle D, Keating KE, et al. Identification and validation of an anthracycline/cyclophosphamide-based chemotherapy response assay in breast cancer. J Natl Cancer Inst 2014;106(1):djt335.

Murai et al 2012
Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res 2012;72(21):5588-99.

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.

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.

Okazaki and Honjo 2007
Okazaki T, Jonjo 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 1988
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.

Oza et al 2015
Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, Sonke GS, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: A randomised phase 2 trial. Lancet Oncol 2015;16(1):87-97.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

Paz-Ares et al 2013
Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:2895-902.

Paz-Ares et al 2018
Paz-Ares L, Luft A, Tafreshi A, Gumus M, Mazières J, Hermes B, et al. KEYNOTE-407: Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel with or without pembrolizumab for metastatic squamous NSCLC. Poster presented at: ASCO Annual Meeting 2018.

Pazdur 2008
Pazdur R. Endpoints for assessing drug activity in clinical trials. Oncologist 2008;13(suppl 2):19-21.

Pérol et al 2012
Pérol M, Chouaid C, Pérol D, Barlési F, Gervais R, Westeel V, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30(28):3516-24.

Pisters and LeChevalier 2005
Pisters KM, LeChevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol 2005;23:3270-8.

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
Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. Cancer Med 2016;9:2169-70.

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(19):1823-33.

Rizvi et al 2015a
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 non-small cell lung cancer (NSCLC). J Clin Oncol 2015;33:abstract 8032.

Rizvi et al 2015b
Rizvi N, Hellman MD, Snyder A, Kvistborg P, Makarov V, Havel J, et al. Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. Science 2015;348:124-8.

Romero 2017
Romero D. Breast cancer: olaparib improves PFS. Nat Rev Clin Oncol 2017;14(8):460. doi: 10.1038/nrclinonc.2017.93. Epub 20 June 2017.

Rottenberg et al 2008
Rottenberg S, Jaspers JE, Kersebergen A, van der Burg E, Nygren AO, Zander SA, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci USA 2008;105(44):17079-84.

Sandler et al 2006
Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355(24):2542-50.

Scagliotti et al 2008
Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.

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.

Socinski et al 2018
Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288-2301.

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.

Tang et al 2014
Tang ML, Khan MK, Croxford JL, Tan KW, Angeli V, Gasser S. The DNA damage response induces antigen presenting cell-like functions in fibroblasts. Eur J Immunol 2014;44(4):1108-18.

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.

CCI [redacted]

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.

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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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 serious adverse events 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

A 2 Financial disclosure

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

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

CCI [redacted]

If a patient's partner becomes pregnant during the study or within 90 days after the last dose of durvalumab or 30 days after the last dose of olaparib/placebo (whichever is later), 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.

CCI [redacted]

A 4 Data protection

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

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

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

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

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

A 5 Committees structure

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

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic case report form 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 case report form (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.

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

A 8 Source documents

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

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

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

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

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical treatment to prevent 1 of the outcomes listed above.

Regulatory reporting requirements for serious adverse event

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

The Sponsor has a legal responsibility to notify both local authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

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

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 an SAE, 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 judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous 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 National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) latest version will be utilized for all events with an

assigned CTCAE grading. For those events without assigned CTCAE grades, the criteria recommended in the CTCAE manual that converts severity levels into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A guide to interpreting the causality question

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

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

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

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error (eg, medication prepared incorrectly, even if it was not actually given to the participant)
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (eg, kept in the fridge when it should be at room temperature)
- Wrong participant received the medication (excluding interactive voice response system [IVRS]/interactive web response system [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 1 of the above listed events that would otherwise have been a medication error

- Participant accidentally missed drug dose(s) (eg, forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

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

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

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

The 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 arrival.

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

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

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

C 2 Withdrawal of informed consent for donated biological samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

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

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

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

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action is documented and the study site is informed.

C 3 International Airline Transportation Association 6.2 guidance document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

containment standards are encouraged wherever possible when road or rail transport is used.

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

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 (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

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 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 case report form (CRF)

E 4 Follow-up

E 4.1 Potential Hy's law criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's law criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- 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 and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the 3 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.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

- 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 'Potential Hy's Law') 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 amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 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)?

If **No**: Follow the process described in Appendix E 4.1 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 4.

#A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Appendix F Guidelines for evaluation of objective 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. Additional special guidance is provided for determination of confirmation of radiological progression.

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.
- Previously irradiated lesions[3]
- 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).

[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).
[3] Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

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 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.

Only patients with measurable target disease at baseline should be included in the study.

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):

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 20.

Table 20 Summary of imaging modalities for tumor assessment

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

CT Computed tomography; FDG-PET/CT 18F-Fluoro-deoxyglucose positron emission tomography/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 timepoint.

FDG-PET/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography/CT (FDG-PET/CT) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[4] 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.

[4] 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.

Tumor response evaluation

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TL at baseline. 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 21).

Table 21 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

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 22).

Table 22 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.

Table 22 Evaluation of non-target lesions

Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

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

New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as 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 23.

Table 23 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	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; NA Not applicable (only relevant if there were no target and/or non-target lesions at baseline); NE Not evaluable; NED No evidence of disease; PD Progression of disease; PR Partial response; SD Stable disease.

Confirmation of Radiological Progression

A follow-up scan is collected after the initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD, and the Confirmation of Radiological Progression criteria described below are applied for tumor assessments of this follow-up scan. Patients with confirmed radiological PD who continue to receive study treatment at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit, and will continue to have tumor assessments on their regular imaging schedule for the duration of treatment.

Confirmation of radiological progression guidelines are set for the following reasons:

- For patient management and treatment decisions
- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression.
- When scans are evaluated by Investigator and by blinded independent central review (BICR), additional scans can reduce informative censoring by Investigator assessments (if the Investigator assesses PD but collects no follow-up scans, and the BICR reviewer does not identify RECIST PD among the available scans, then this patient would be censored for PFS by BICR).

Confirmation of Radiological Progression Criteria:

An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if any of the following criteria are met in the subsequent follow-up scan (acquired preferably at the next regularly scheduled imaging visit but no sooner than 4 weeks after the RECIST 1.1-defined PD scan):

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits, each with an absolute increase of at least 5 mm in sum of diameters compared to nadir (as per RECIST 1.1 definition)
- *and/or* significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint (as per RECIST 1.1 definition)
- *and/or* significant progression (worsening) of pre-existing new lesions at the follow-up scan timepoint compared with the immediate prior timepoint (unique definition)
- *and/or* additional (brand) new unequivocal lesions at the follow-up scan timepoint (as per RECIST 1.1 definition)

NOTE: In order to have confirmed radiological progression, there should be two consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the Confirmation of Radiological Progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, in the absence of significant clinical deterioration, then the patient may continue with assessments until the next PD by RECIST 1.1, which will also require a follow-up scan evaluated using the Confirmation of Radiological Progression criteria. **If the first PD (by RECIST 1.1) is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

Central Review

All radiological scans, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed contract research organization (CRO) for quality control and storage. Guidelines for image acquisition, de-identification, storage at the study site as source data, and transfer to the imaging CRO for central review 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 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 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 new lesions.

For standard RECIST 1.1 assessments, it is recommended that IV contrast-enhanced CT examinations of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis will be used to assess tumor burden at baseline and follow-up visits. It is strongly encouraged to acquire follow-up scans using the same modality (CT/MRI) and acquisition parameters that were used at baseline. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV MRI contrast of the abdomen and pelvis is appropriate. In patients who develop sensitivity to both CT and MRI IV contrast or severely compromised renal function, a non-contrast CT examination of the chest, abdomen, and pelvis is appropriate. Any other areas of disease involvement (eg, brain) should be additionally imaged based on the signs and symptoms of individual patients. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast-enhanced CT.

CT and MRI scans – General Guidance

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. The most critical CT and MRI image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

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 preferably with fat suppression along with T1 weighted imaging with fat suppression following IV injection of gadolinium-based contrast agent is 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 scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans for each patient. Body scans should be performed with breath-hold scanning techniques if possible. For these reasons, CT is the imaging modality of choice.

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. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) with ≤5 mm slice thickness for optimal lesion measurements. 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.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

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 Olaparib toxicity management instructions

Management of hematological toxicity

Management of anemia

Table 24 Management of anemia

Hemoglobin	Action to be taken
Hb <10 g/dL but ≥8 g/dL (CTCAE Grade 2)	First occurrence (after patient has initiated olaparib/placebo treatment): Give appropriate supportive treatment, and investigate causality. Investigator judgment to continue olaparib with supportive treatment (eg, transfusion) or interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to >9 g/dL. Subsequent occurrences: If Hb <10 g/dL but ≥9 g/dL, Investigator judgment to continue olaparib with supportive treatment (eg, transfusion) or interrupt dose (for a maximum of 4 weeks), and upon recovery dose reduction may be considered (to **250** mg BID as a first step and to **200** mg BID as a second step). If Hb <9 g/dL but ≥8 g/dL, interrupt dose (for a maximum of 4 weeks) until Hb ≥9 g/dL and upon recovery dose reduction may be considered (to **250** mg BID as a first step and to **200** mg BID as a second step).
Hb <8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (eg, transfusion), and investigate causality. Interrupt olaparib for a maximum of 4 weeks, until improved to Hb ≥9 g/dL. Upon recovery reduce dose to 250 mg BID as a first step and to 200 mg BID as a second step in the case of repeat Hb decrease.

BID Twice daily; CTCAE Common Terminology Criteria for Adverse Events; Hb Hemoglobin.

Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies, and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or worse anemia and/or development of blood transfusion dependence), refer to guidance later in this section for management.

Management of neutropenia, leukopenia, and thrombocytopenia

Table 25 Management of neutropenia, leukopenia, and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grades 1-2	Investigator judgment to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation.

Toxicity	Study treatment dose adjustment
CTCAE Grades 3-4	Dose interruption until recovered to CTCAE Grade 1 or better for a maximum of 4 weeks. If repeat CTCAE Grades 3-4 occurrence, reduce olaparib to 250 mg BID as a first step and 200 mg BID as a second step.

BID Twice daily; CTCAE Common Terminology Criteria for Adverse Events.

Adverse events (AEs) of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow-up and interruption of study drug if neutropenia CTCAE Grade 3 or worse occurs.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. However, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or worse), refer to guidance later in this section for management.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as the following:

- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse neutropenia (absolute neutrophil count $<1 \times 10^9$/L)
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets $<50 \times 10^9$/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to at least CTCAE Grade 1 within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome (MDS) or other clonal blood disorder should be reported as a serious AE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or acute myeloid leukemia is confirmed.

Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this, the Study Monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment dose can be reduced to 250 mg twice daily (BID) as a first step and to 200 mg BID as a second step. Treatment must be interrupted if any National Cancer Institute CTCAE Grade 3 or 4 AE occurs that the Investigator considers to be related to administration of study treatment.

Management of new or worsening pulmonary symptom

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high-resolution computed tomography [CT] scan) should be performed to exclude pneumonitis. Please also refer to the durvalumab toxicity management guidelines below.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE Grade 1 or 2) in severity, intermittent, and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (European Society for Medical Oncology and National Comprehensive Cancer Network), generally a single-agent anti-emetic should be considered (eg, dopamine receptor antagonist, antihistamines, or dexamethasone).

Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AstraZeneca Study Physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the electronic case report form.

Olaparib treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of olaparib treatment is required for any needle biopsy procedure.

Olaparib treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Olaparib treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue, and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Table 26 Dose reductions for study treatment

Initial dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg BID	250 mg BID	200 mg BID

BID - Twice daily.

Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated creatine clearance (CrCl) falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated CrCl either by Cockcroft-Gault equation or based on a 24-hour urine test) of ≥31 mL/min but <51 mL/min for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg BID.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to ≥31 mL/min but <51 mL/min, the Investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (≤30 mL/minute) or end-stage renal disease; if patients develop severe impairment or end-stage disease it is recommended that olaparib be discontinued.

Appendix H Patient-reported outcomes

This appendix includes example copies of the following patient-reported outcome (PRO) questionnaires:

- European Organisation for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire
- EORTC 13-item Lung Cancer Quality of Life Questionnaire
- CCI t
- CCI
- CCI

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?

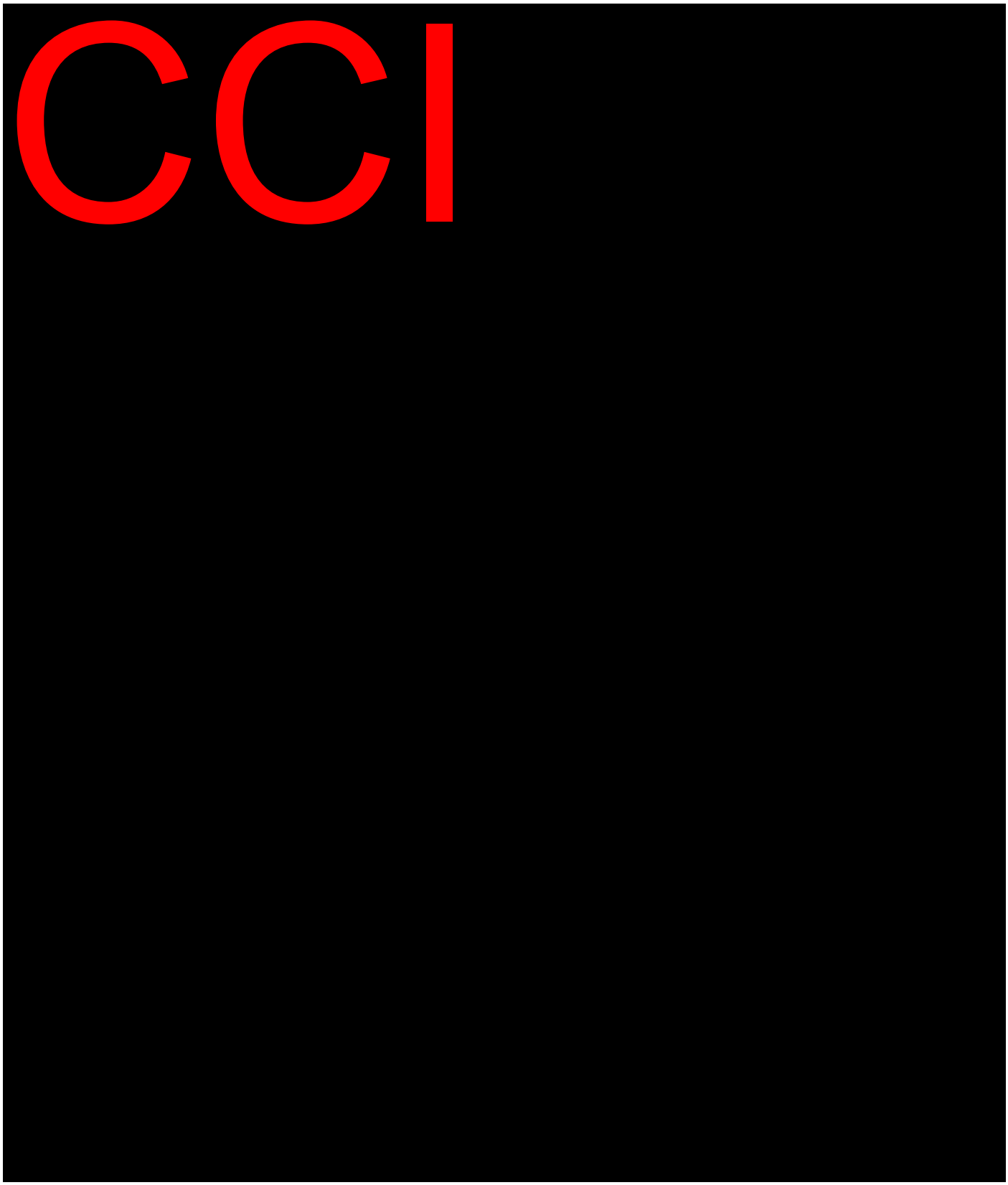
1 2 3 4 5 6 7

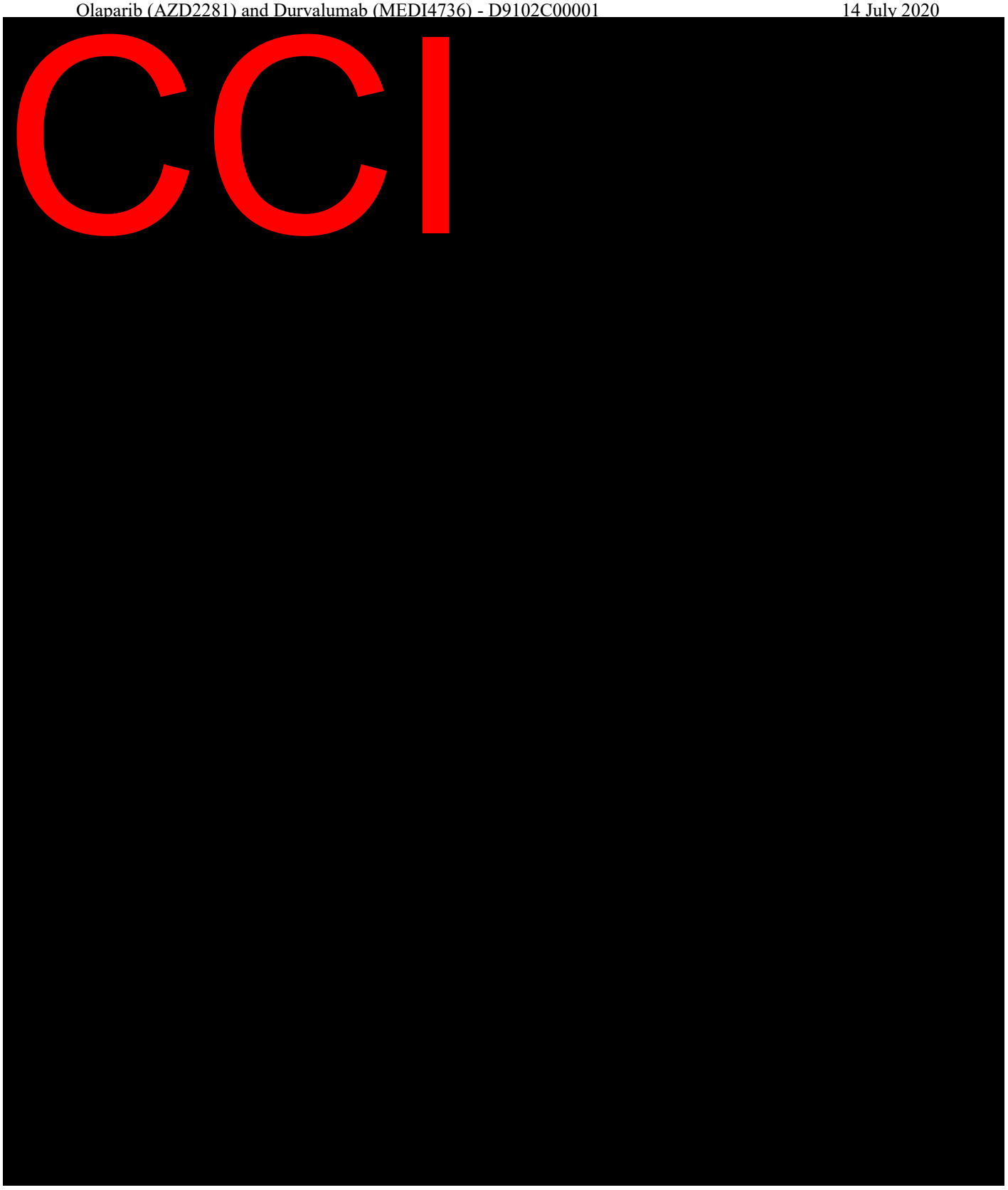
Very poor Excellent

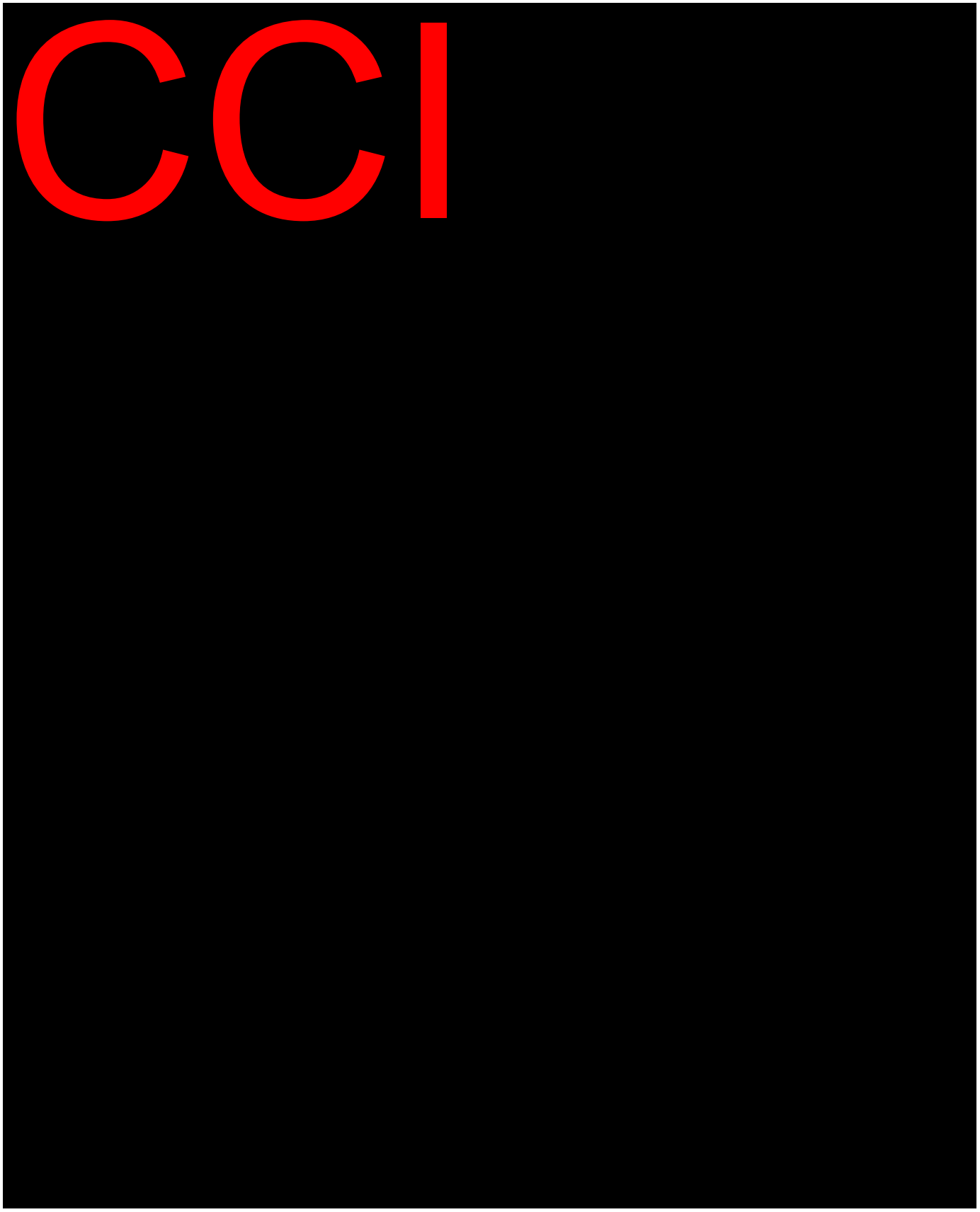
EORTC QLQ - LC13

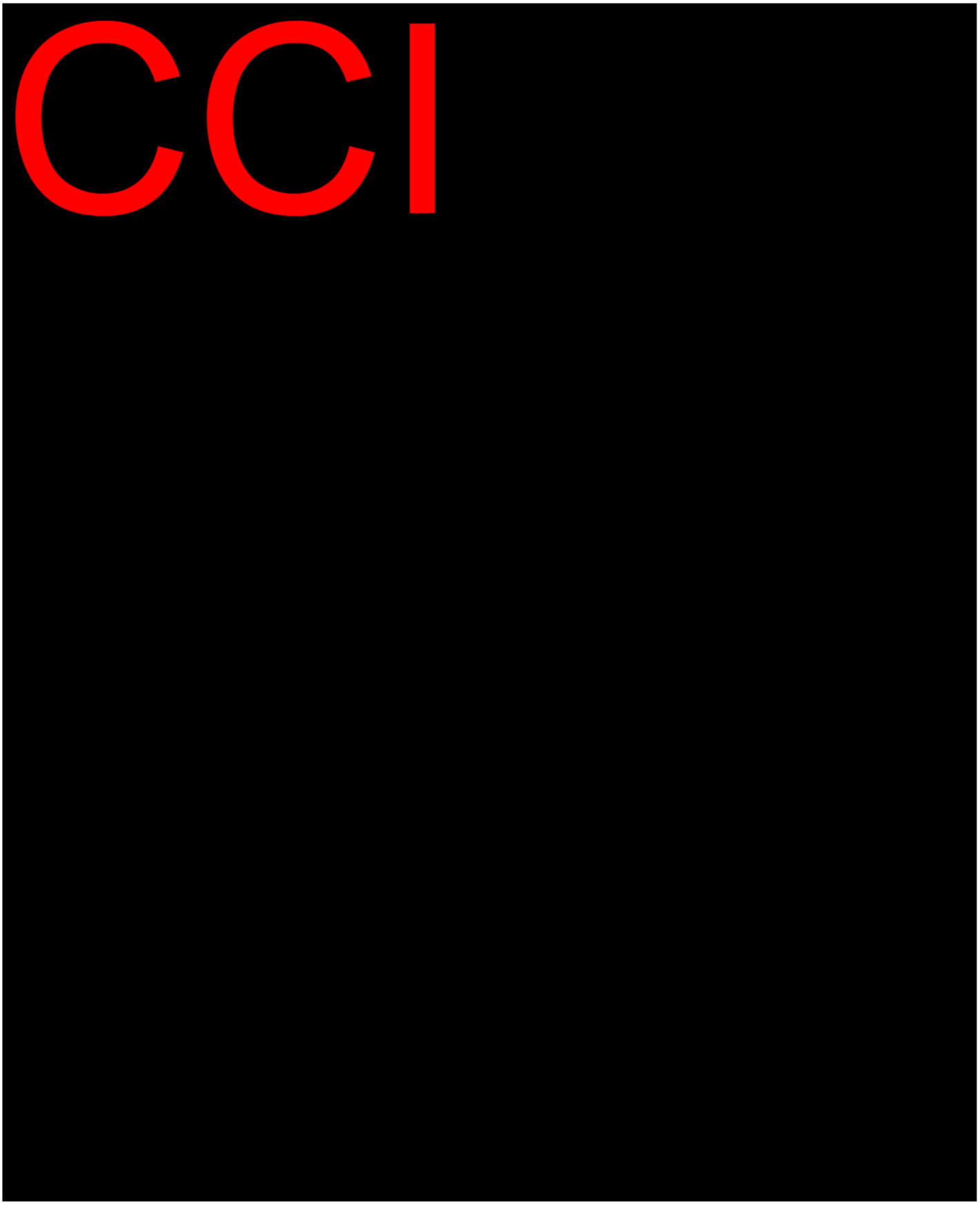
Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

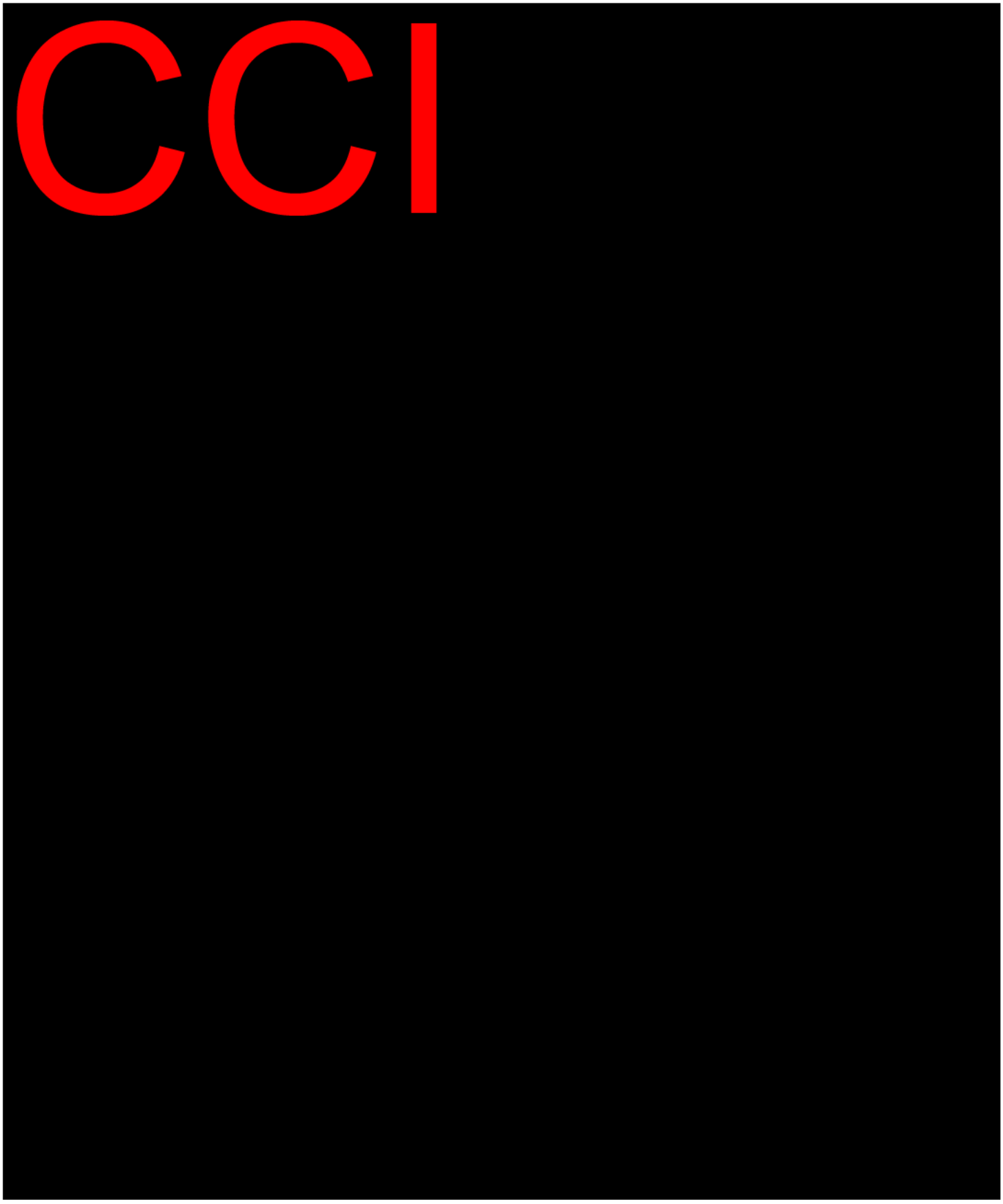
During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	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

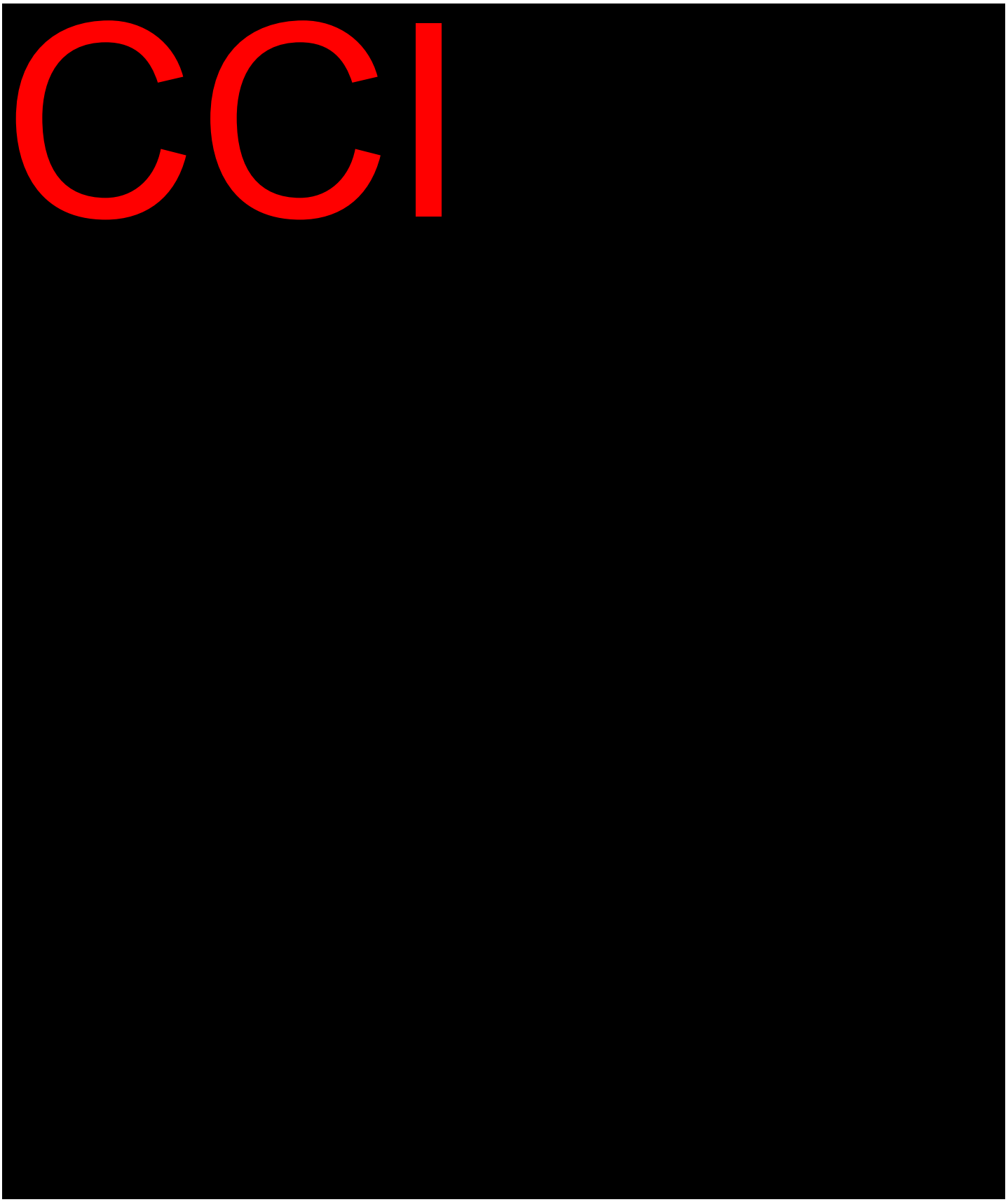

CCI


CCI


CCI


CCI


CCI


CCI

Appendix I Abbreviations

Abbreviation or special term	Explanation
1L	first line
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BICR	blinded independent central review
BID	twice daily
BP	blood pressure
BRCA	breast cancer susceptibility gene
*BRCA*m	*BRCA* gene mutation
C	cycle
CCTG	Canadian Cancer Trials Group
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum plasma concentration
CNS	central nervous system
COA	Clinical Outcome Assessment
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRT	chemoradiation therapy
CSR	clinical study report
CT	computed tomography

Abbreviation or special term	Explanation
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CCI	[redacted]
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
C_{trough}	trough concentration
CYP	cytochrome P450
D	day
DCO	data cut-off
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DoR	duration of response
DSB	double strand break
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDoR	expected duration of response
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of therapy
ePRO	electronic patient-reported outcome
CCI	[redacted]
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin embedded
g*BRCA*m	germline *BRCA* mutation
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GMP	Good Manufacturing Practice
H0	null hypothesis
H1	alternative hypothesis

Abbreviation or special term	Explanation
Hb	hemoglobin
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hy's Law
CCI	[redacted]
HR	hazard ratio
HRQoL	health-related quality of life
HRR	homologous recombination repair
HRRm	homologous recombination repair related gene mutation
IASLC	International Association for the Study of Lung Cancer
IATA	International Airline Transportation Association
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
CCI	[redacted]
IHC	immunohistochemistry
ILD	interstitial lung disease
IM	intramuscular
imAE	immune-mediated adverse event
INR	International Normalized Ratio
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.
IO	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system

Abbreviation or special term	Explanation
KM	Kaplan-Meier
LFT	liver function test
LIMS	laboratory information management system
mAb	monoclonal antibody
MATE	multidrug and toxin extrusion protein
MDS	myelodysplastic syndrome
MEDI4736	durvalumab
MMRM	mixed-effect model repeated measure
MOA	mechanism of action
MRI	magnetic resonance imaging
CCI	[redacted]
NA	Not applicable
Nab	Nanoparticle albumin-bound
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of disease
NSCLC	non-small cell lung cancer
NTL	Non-target lesion
OAT	organic anion transporter
OATP	organic-anion-transporting polypeptide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PARP	polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase
CCI	[redacted]
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PFS	progression-free survival
CCI	[redacted]
PHL	potential Hy's Law
PI	Principal Investigator
PK	pharmacokinetic(s)

Abbreviation or special term	Explanation
PR	partial response
PRO	patient-reported outcome
PS	performance status
q12w	every 12 weeks
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q8w	every 8 weeks
QLQ-C30	30-item Core Quality of Life Questionnaire
QLQ-LC13	13-item Lung Cancer Quality of Life Questionnaire
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
R	Randomization
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SAF	safety analysis set
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SoAs	schedule(s) of activities
SoC	standard of care
sPD-L1	soluble programmed death-ligand 1
S/R	scan, analyze, randomize
SSB	single strand break
T3	triiodothyronine
T4	thyroxine
TBL	total bilirubin
TC	tumor cells
TKI	tyrosine kinase inhibitor
TL	target lesion
CCI	[redacted]
TMG	toxicity management guideline
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone

Abbreviation or special term	Explanation
ULN	upper limit of normal
US	United States
VAS	visual analog scale
w	week
WBDC	Web Based Data Capture
WHO	World Health Organization
WT	weight
w/v	weight/volume