Clinical Study Protocol	
Drug Substance	Durvalumab+Olaparib: Imfinzi™ (durvalumab; MEDI4736) plus Lynparza™ (olaparib; AZD2281; KU 0059436)
Study Codes	D9311C00001; GOG-3041; ENGOT-EN10
Version	CCI
Date	24 January 2023

A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E)

Sponsors: AstraZeneca AB, 151 85 Södertälje, Sweden
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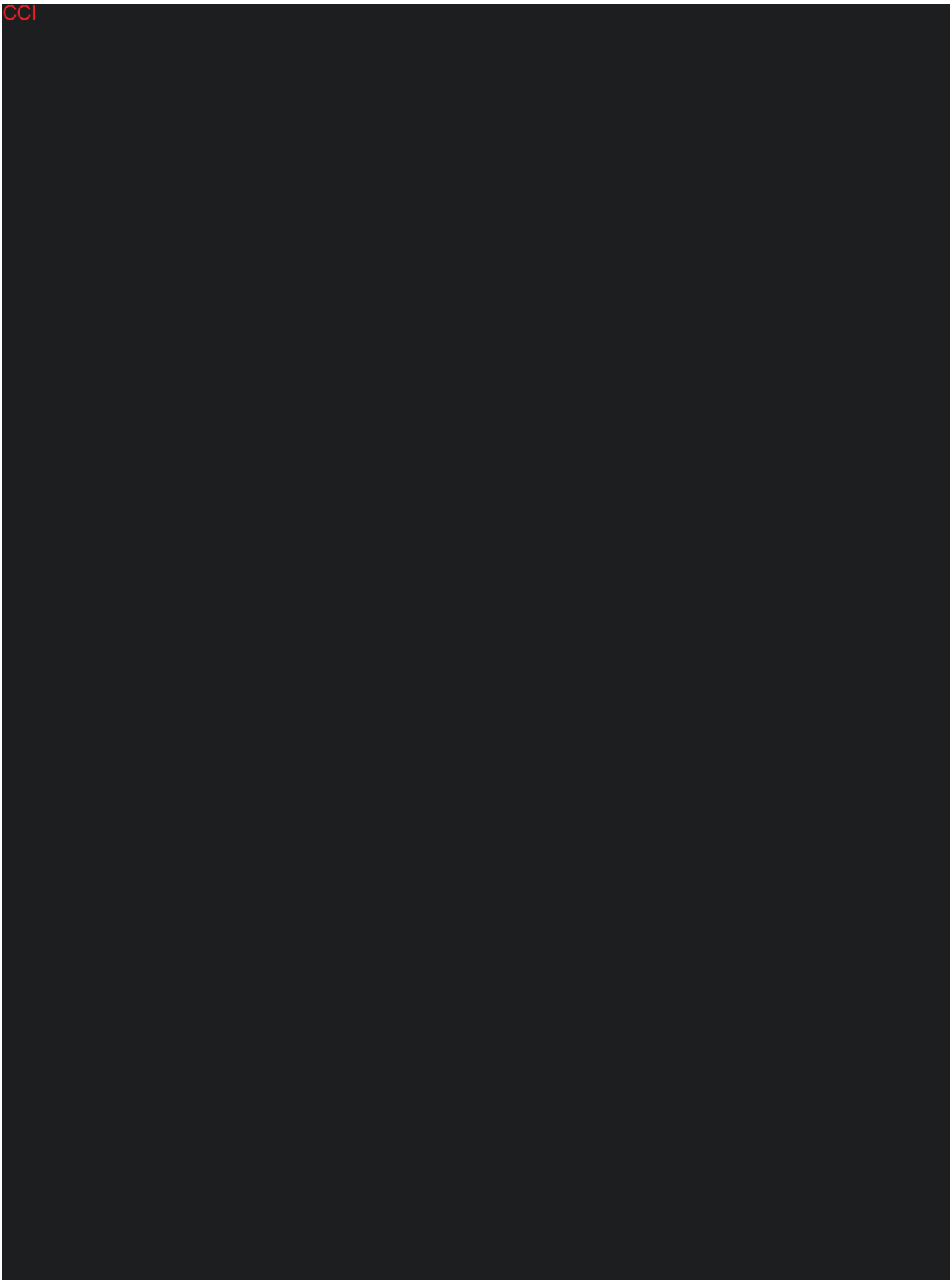
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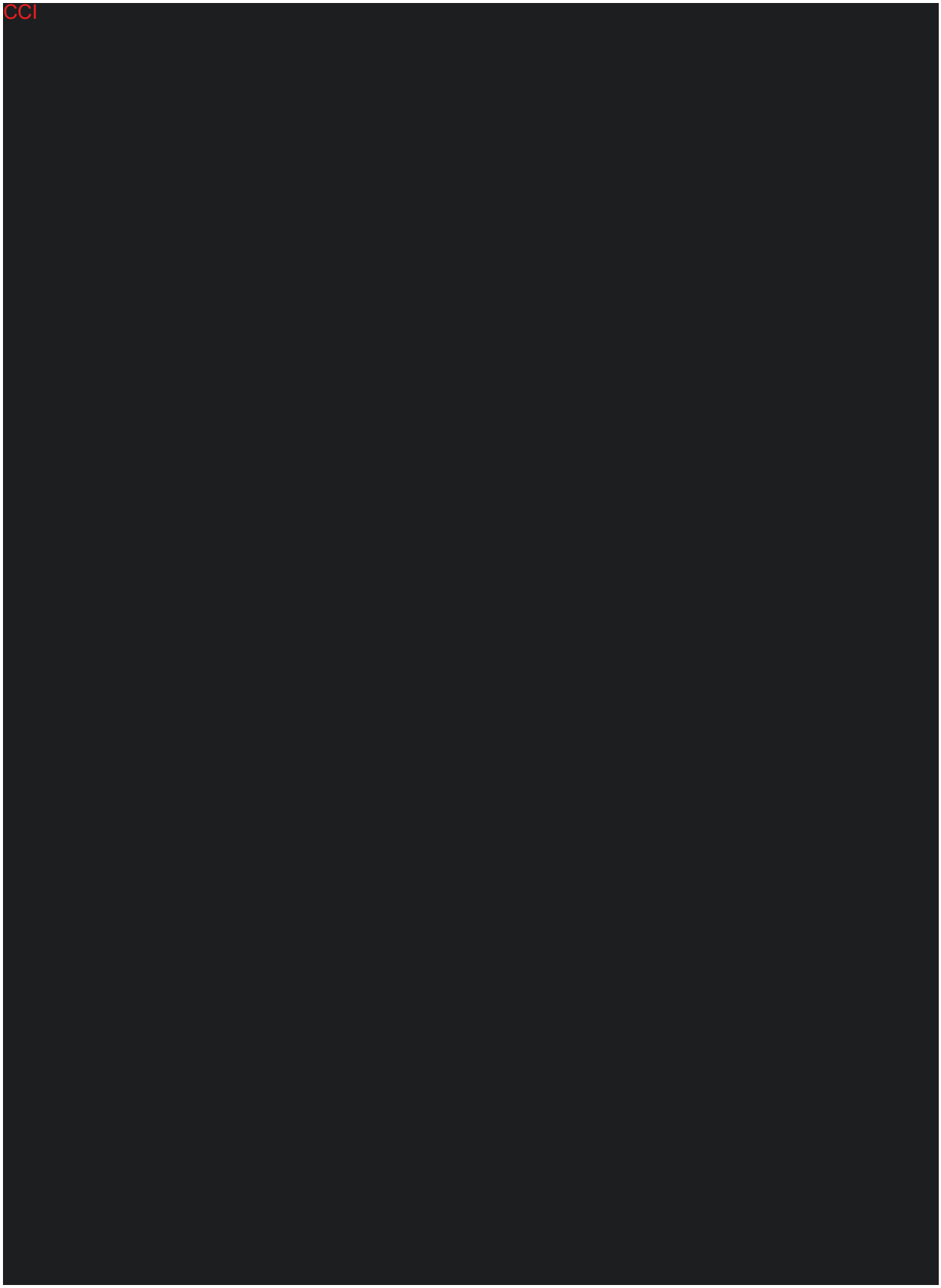
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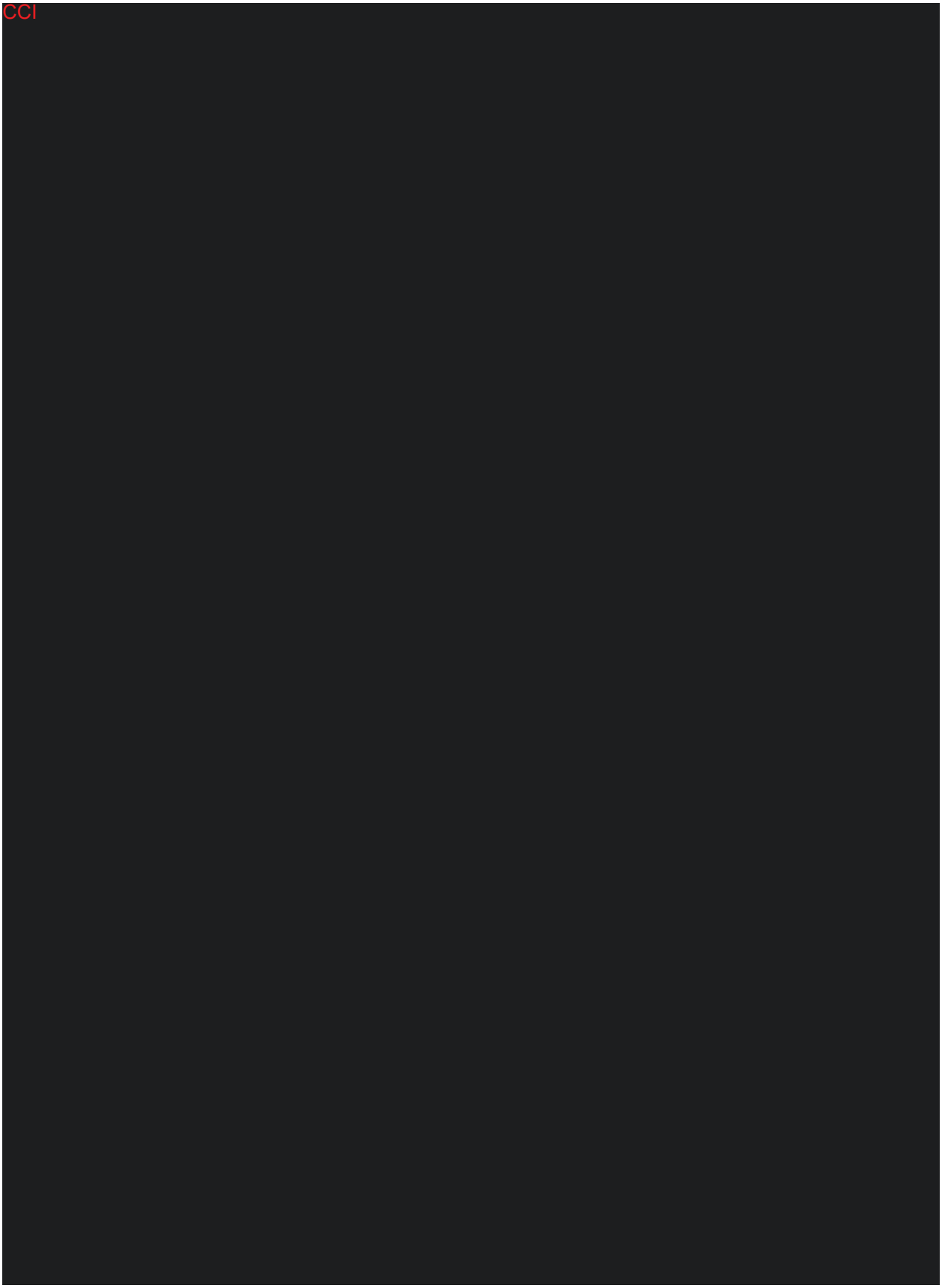
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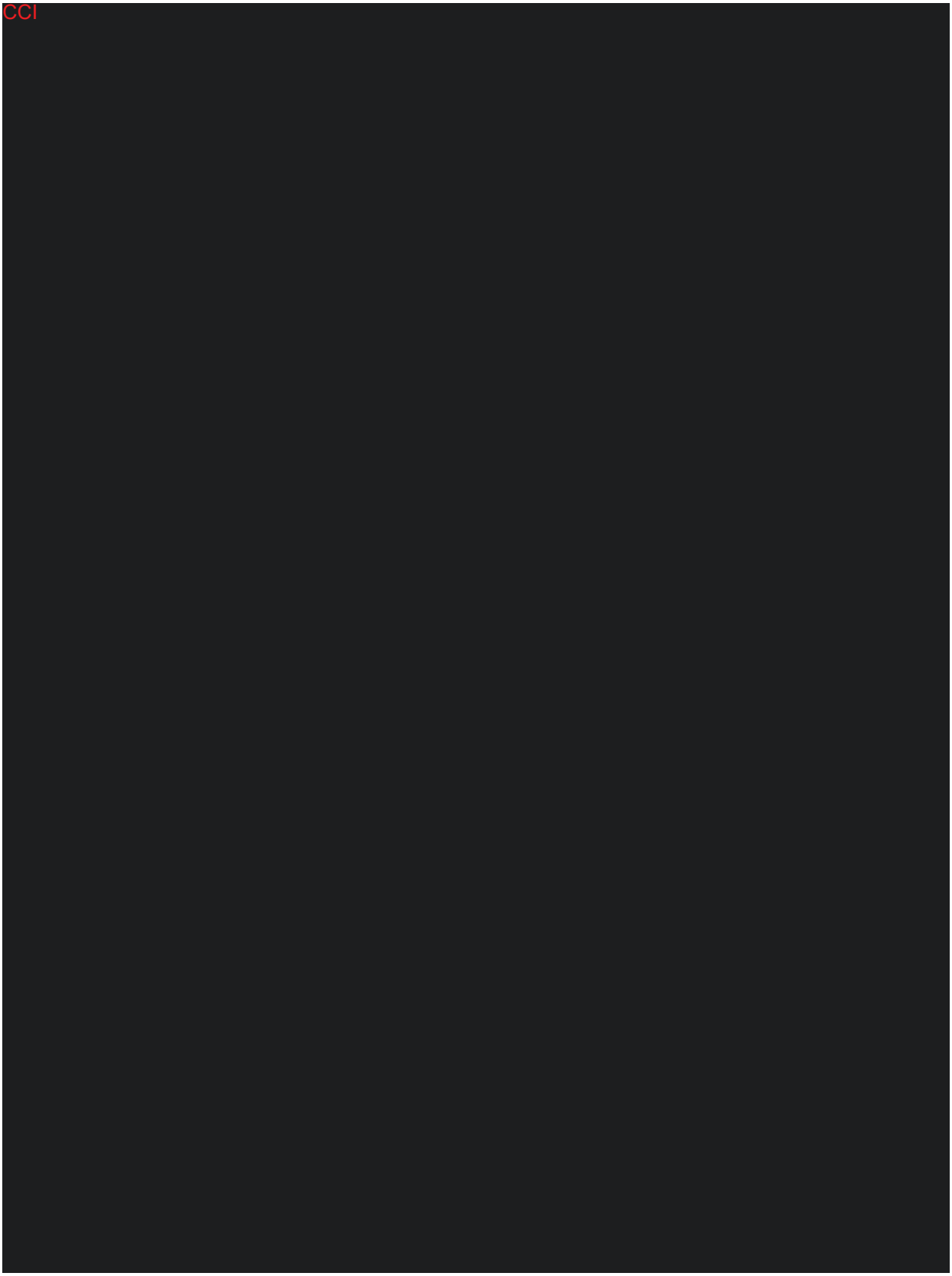
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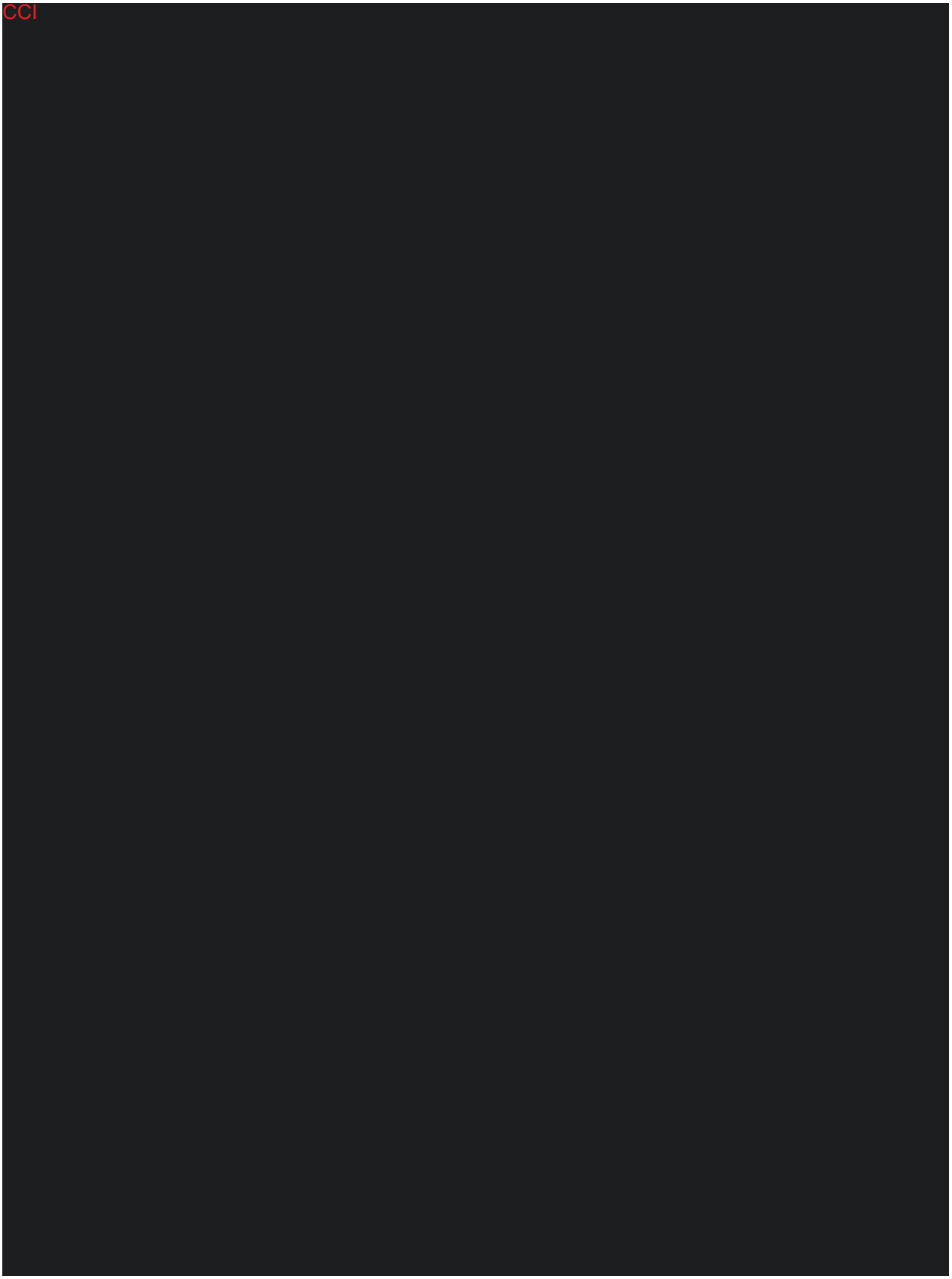
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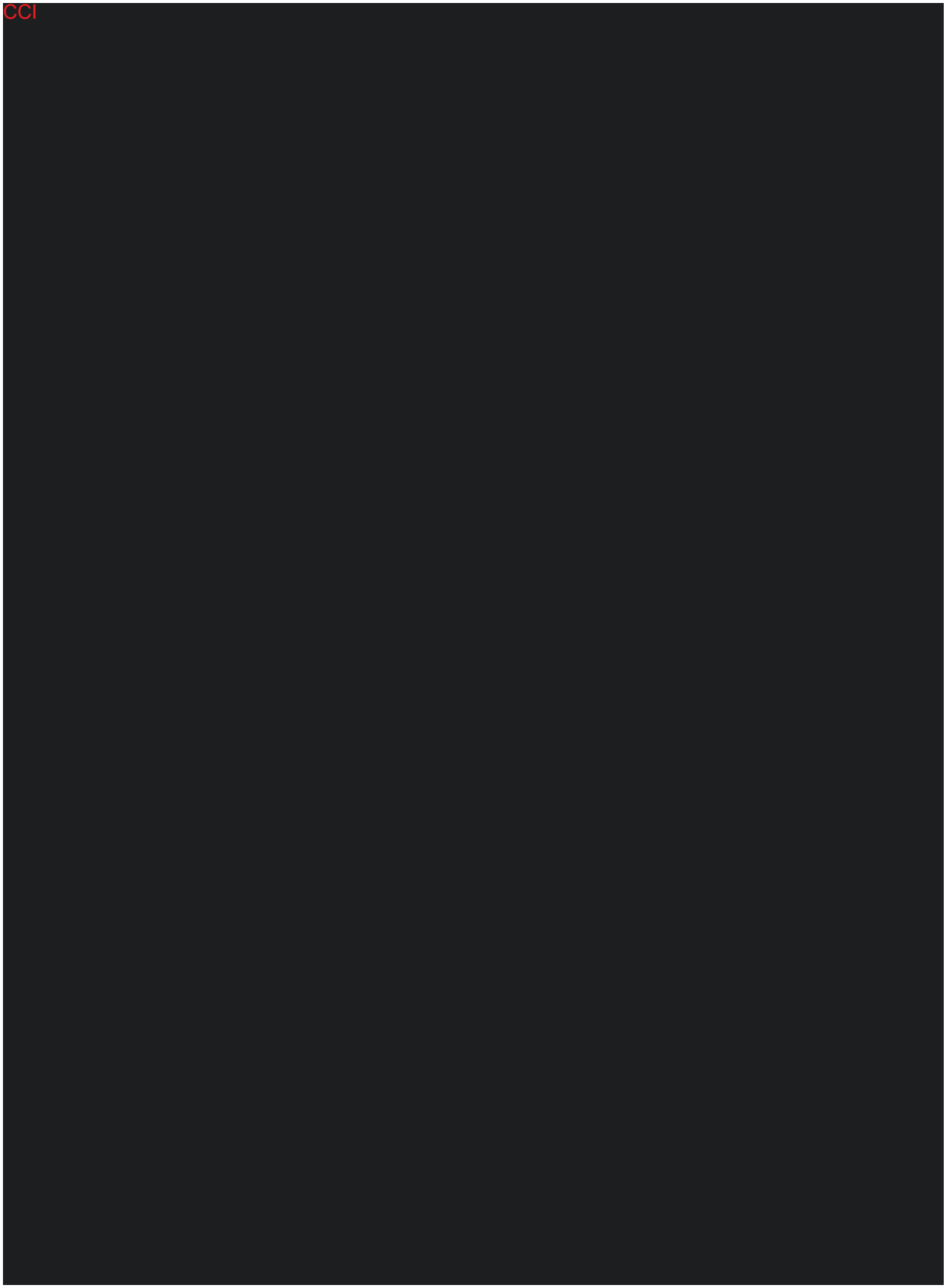
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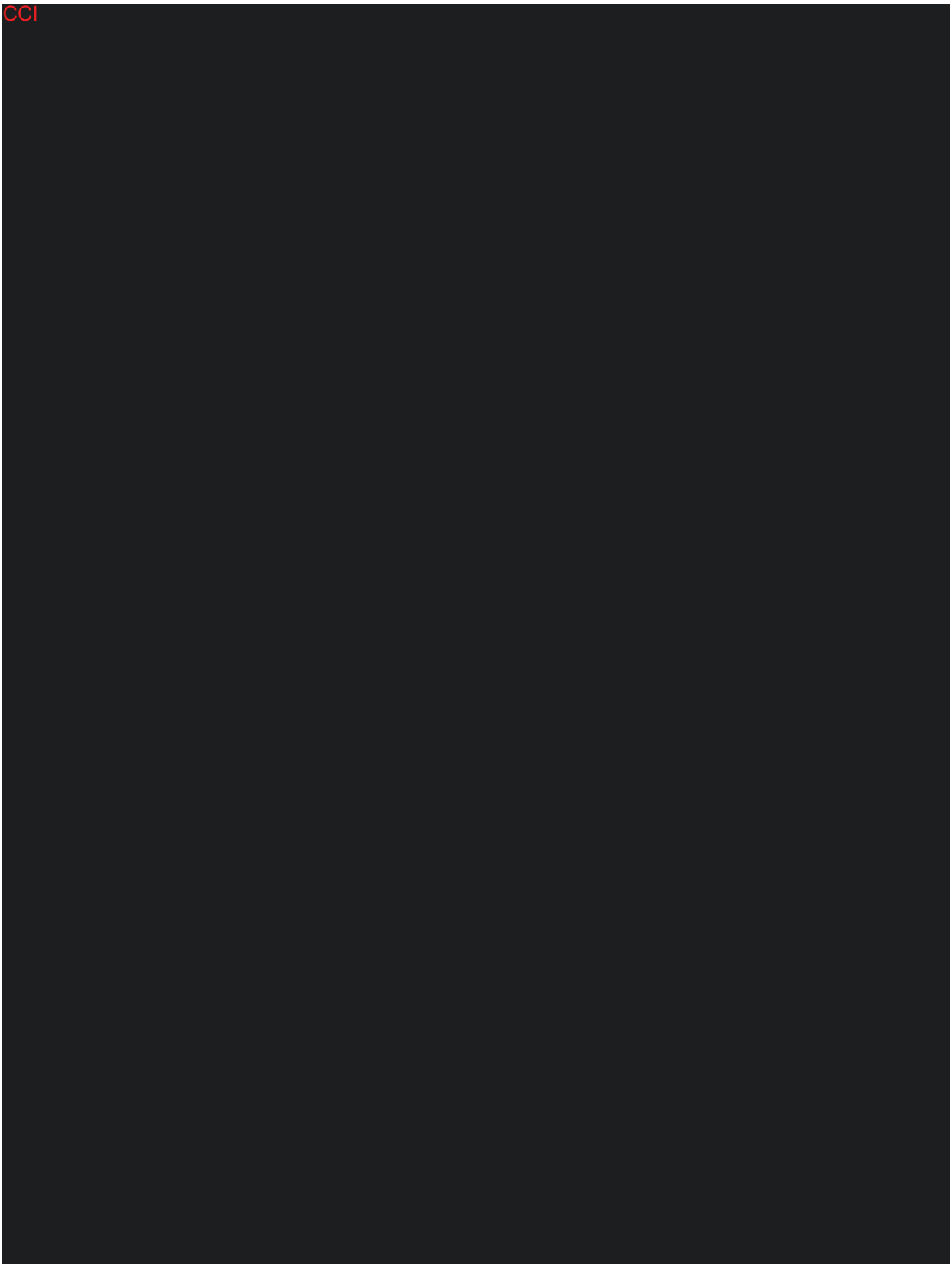
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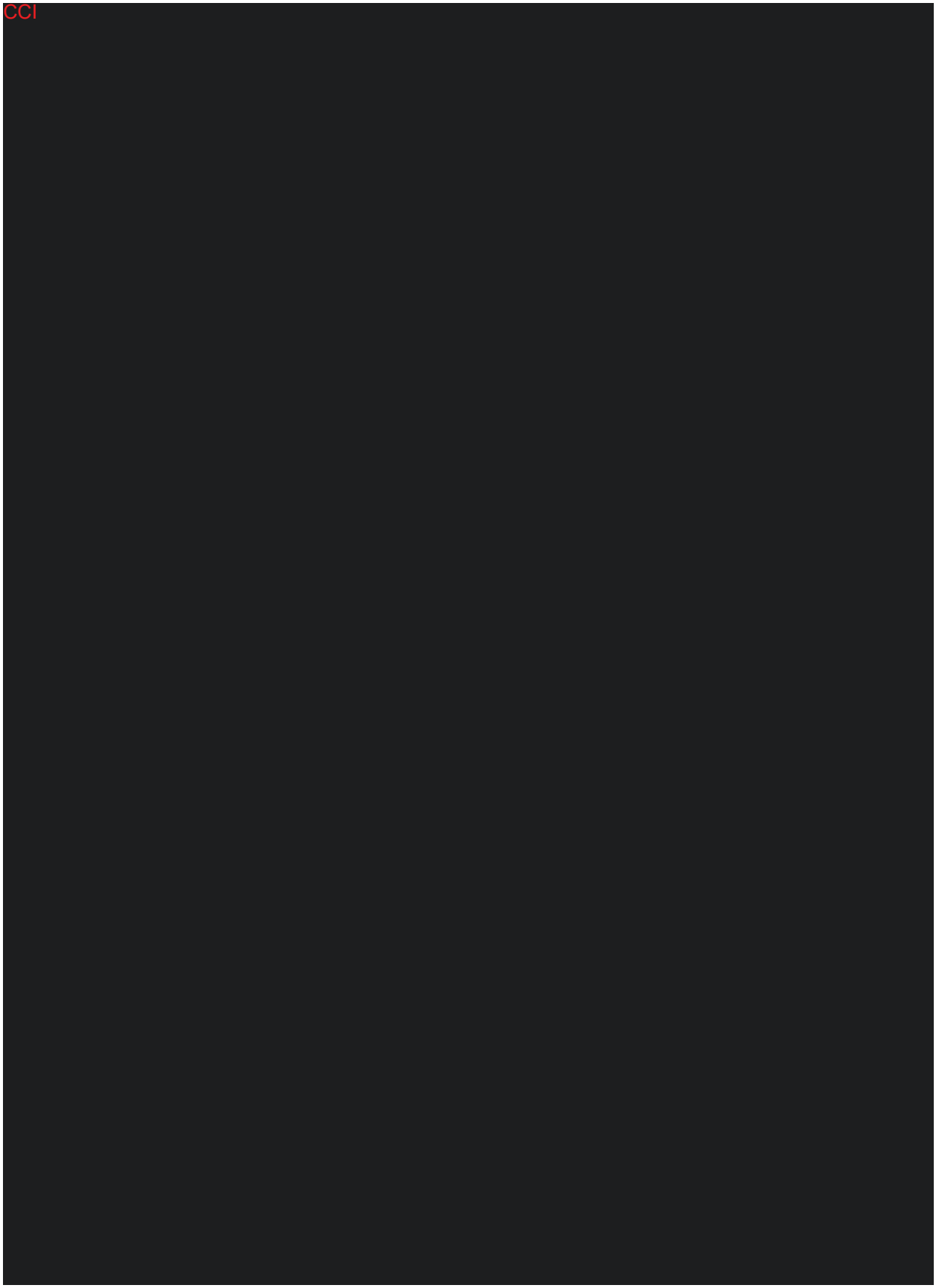
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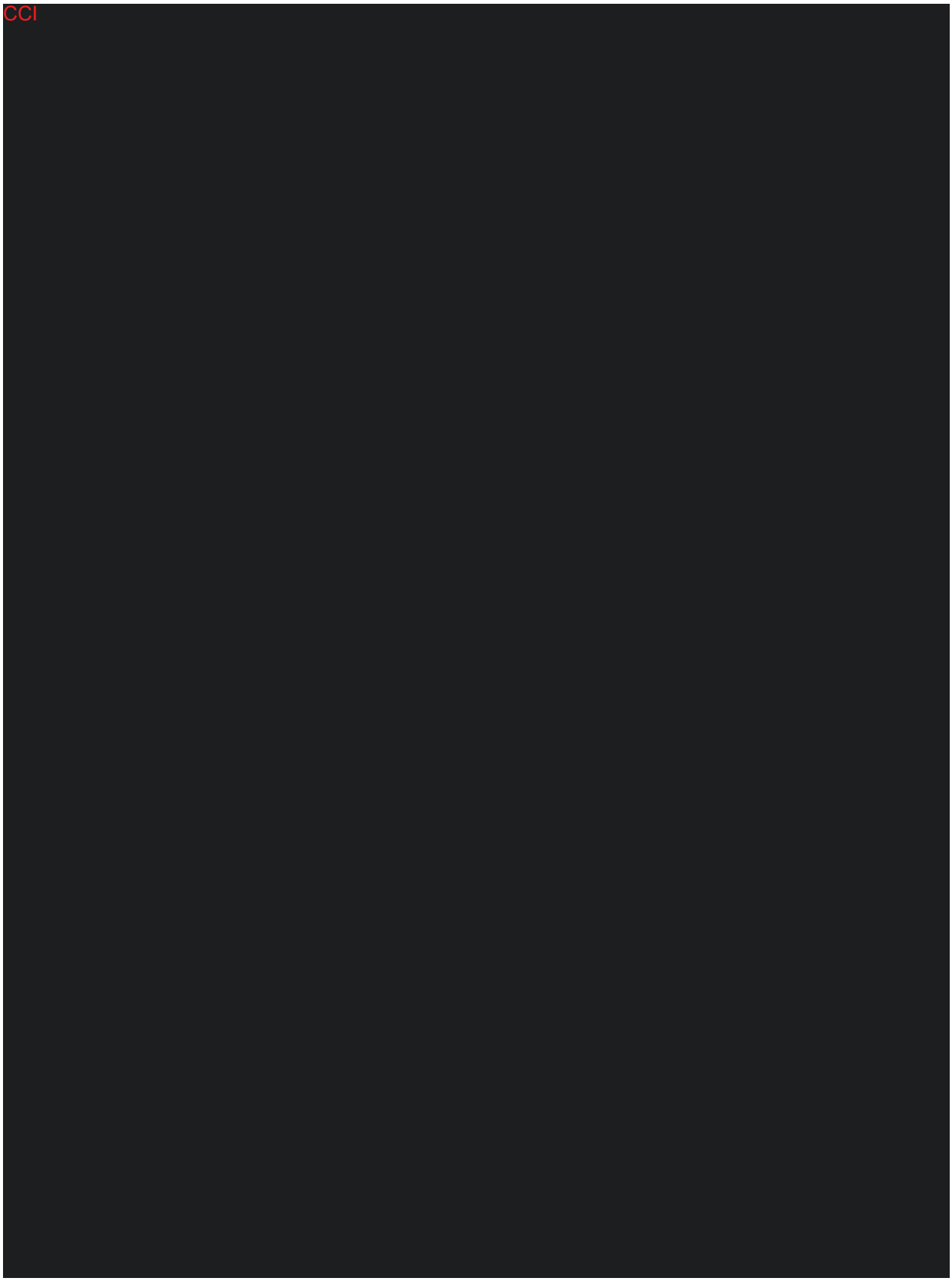
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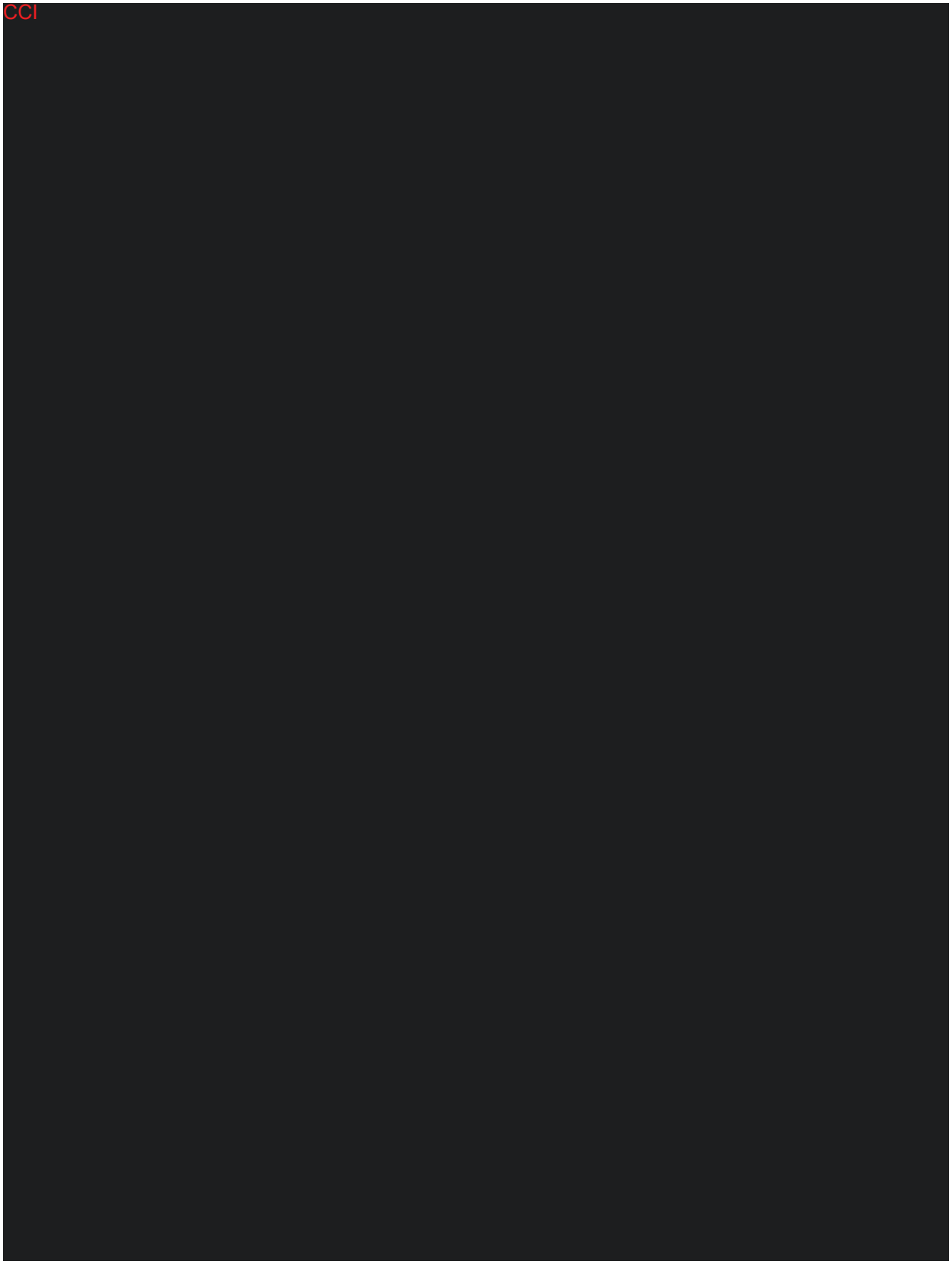
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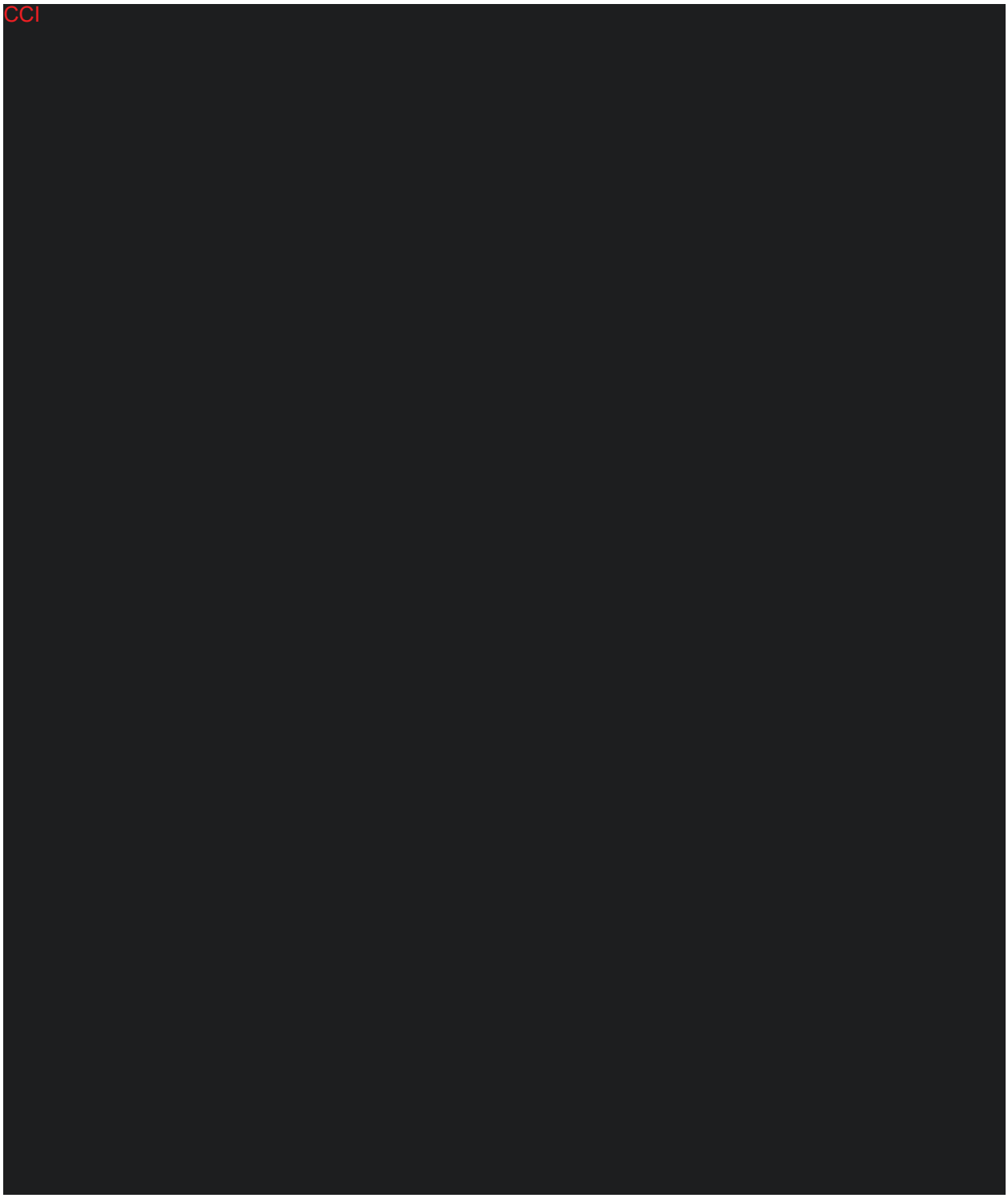
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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

This Phase III study will assess the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin) followed by maintenance durvalumab with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer.

Target patient population: Adult female patients with histologically confirmed diagnosis of epithelial endometrial carcinoma (excluding sarcomas): newly diagnosed Stage III (measurable disease per Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), newly diagnosed Stage IV (with or without disease following surgery or diagnostic biopsy), or recurrent (measurable or non-measurable disease per RECIST 1.1) endometrial cancer.

1.1 Schedule of activities (SoA)

The procedures for the screening, treatment and follow-up periods in this study are presented in Table 1, Table 2 and Table 3, respectively.

All patients must sign the pre-screen informed consent form (ICF) for biomarker testing including prospective tumour tissue-s mismatch repair (MMR) status analysis, followed by the main ICF. Central assessment of MMR status (proficient or deficient) is required for randomisation, so the pre-screen ICF must be signed first so that tissue for MMR status determination can be completed on time. The main ICF should be signed once the tissue for MMR testing has been shipped. See Section 8.8.1 for details on central MMR testing.

Additional screening procedures can be conducted during the main screening period while awaiting results for the MMR status analysis. Screening activities should be performed prior to randomisation on Cycle 1 Day 1, as shown in Table 1.

Whenever patient reported outcomes (PROs), electrocardiograms (ECGs), vital signs and/or blood draws are scheduled for the same visit, the assessments should ideally occur in the following order: (1) PROs, (2) ECG, (3) vital signs and (4) blood draws.

For durvalumab (or corresponding placebo)

Patients may delay dosing under certain circumstances.

- Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (TMGs) (see Section 6.6.1), due to either an immune- or a non-immune-mediated AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

For olaparib (or corresponding placebo)

Dose reductions are permitted under certain circumstances (see Section 6.6.2).

- To manage adverse events (AEs).
- If the patient develops moderate renal impairment.
- If the patient starts taking a strong or moderate CYP3 inhibitor.

For chemotherapy (Cycles 1 to 6)

Patients may delay 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.

Table 1 Screening schedule of activities

Visit	Pre-screening	Screening	
Day		**-28 to 0**	**For details, see**
Informed consent for tumour biomarker testing including MMR testing (pre-screen ICF; mandatory) [a]	X		Section 8.8.1
Informed consent for study procedures (main ICF; mandatory) [b]		X	Section 5.4
Informed consent for Genomics Initiative blood sample (optional ICF)		X[m]	Section 5.4
E-code assigned	X		Section 6.3.1
Verify inclusion/exclusion criteria	X (all * criteria) [c]	X	Sections 5.4 and 5.5
Study procedures			
Ship tumour sample to central laboratory for MMR status and other biomarkers (mandatory) [a]	X		Section 8.8.1
Demography		X	
Family history of cancer		X	
Medical and surgical history [d]		X	
Prior cancer therapies including radiotherapy [e]		X	
History of blood transfusions [f]		X	
Concomitant medications		X	Section 5.6.4
Physical examination [g]		X	Section 8.2.2
Vital signs (includes blood pressure, pulse, body weight, height, and temperature)		X	Section 8.2.3
12-lead resting ECG		X	Section 8.2.4
ECOG Performance Status (0-1)		X	Section 8.2.5
SAEs (from time of signing the main consent form)		X	Section 8.3
Pregnancy test (serum or urine) [h]		X	Section 8.2.6.1
Haematology, coagulation and clinical chemistry [i]		X	Section 8.2.1
Thyroid function tests (TSH, T3 [reflex], T4 [reflex]) [j]		X	Table 12
Screen for HBV, HCV and HIV		X	Section 5.5
Urinalysis		X	Table 14

Visit	Pre-screening	Screening	
Day		**-28 to 0**	**For details, see**
Tumour imaging (CT or MRI; RECIST version 1.1) [k]		X	Section 8.1.1
Central MMR status (proficient or deficient) available – mandatory prior to randomisation [a]		X	Section 8.8.1
Blood sample for retrospective specified genetic testing [l]		X	Section 8.7.1
Blood sample for cfDNA analysis		X	Section 8.8.2
Blood sample for peripheral chemokines and cytokines		X	Section 8.8.2
Blood sample for Genomics Initiative (optional, separate consent required)		X [m]	Section 8.7.2 and Appendix D

Abbreviations: CCI CT = computed tomography; cfDNA = cell-free DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; CCI ; ICF = informed consent form; IHC = immunohistochemistry; *MLH1* = MutL homologue 1; *MSH2* = MutS protein homologue 2, *MSH6* = MutS protein homologue 6; MMR = mismatch repair; MRI = magnetic resonance imaging; CCI PMS2 = PMS1 protein homologue 2; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; CCI T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

[a] The pre-screen informed consent for the tumour sample must be obtained prior to the main informed consent, in order to acquire and ship the tumour sample for MMR analysis. The tumour sample must be shipped prior to signing the main informed consent. MMR status is mandatory for randomisation; patients with unknown MMR status at randomisation will be considered screen failures. Patients should not be pre-screened based on prior or local MMR status results. Note that all patients, regardless of whether or not they already know their MMR status based on prior/local testing, MUST sign the pre-screen ICF and undergo central MMR testing. If the original MMR testing cannot be completed by the end of the 28-day screening period due to technical failure, patients must be re-screened to ensure adequate time for MMR re-testing (see Sections 5.7 and 8.8.1 for details). If a new sample has to be shipped, randomisation will not occur until the new MMR test result is available. With remaining tissue, CCI and other exploratory tumour biomarkers will also be assessed. The baseline biopsied tumour site should not be assessed as target lesions as part of the RECIST assessments if there are other lesions available.

[b] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any screening/baseline procedures and evaluations. Informed consent for study procedures from screening onwards (main ICF) should be obtained after the MMR tumour sample has been shipped to the central laboratory and within 28 days prior to randomisation on Day 1. **Note:** that the MMR result does not need to be known prior to signing the main consent form, but is required prior to randomisation.

[c] See Sections 5.4 and 5.5 for marked (*) eligibility criteria.

[d] Including disease characteristics such as stage, grade, pathology, hormone receptor status (only if known/available, not required for study entry), history of primary debulking surgery, and other relevant medical history.

[e] All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigator's opinion of response to them.

[f] Include all blood transfusions within 120 days prior to starting study treatment and the reasons, eg, bleeding or myelosuppression.

[g] If the pelvic examination is abnormal, it can be repeated at the time of the baseline scan.

[h] Pregnancy tests on serum or urine samples will be performed for women of childbearing potential within 28 days prior to starting study treatment. Details of the pregnancy tests must be recorded in the patient's medical records.

[i] For a list of all required laboratory tests, please refer to Section 8.2.1.

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

k RECIST baseline assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis. Any other areas of disease involvement should also be imaged based on the signs and symptoms of the individual patient. Baseline assessments should be performed no more than 28 days before randomisation and ideally should be performed as close as possible to randomisation.

l Sample for evaluation of germline mutations in CCI and the Lynch Syndrome related genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*) CCI CCI if required. These samples should ideally be taken at screening, however, samples taken later will be acceptable. Please refer to Section 8.7.1.

m Consent for provision of a blood sample for the Genomics Initiative programme is optional for all patients, and will be obtained via a separate optional Genomics Initiative ICF. If the Genomics Initiative blood sample cannot be collected during screening period, it can be collected any time after starting study treatment.

Table 2 On-treatment schedule of activities

	Chemotherapy Phase (Cycles 1 to 6)						Maintenance Phase				Study Treatment Discont-inuation visit (when all study treatments have been discontinued)	For details, see
Cycle	**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7D1**	**C8D1**	**C9D1**	**≥C10D1 to PD**		
Visit frequency		**Q3W**					**Q4W**					
Study week	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**22**	**26**	**30 to PD**		
Day (visit window +3 days from C2D1 onwards in the Chemotherapy Phase, and ±3 days in Maintenance Phase)	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**155**	**183**	**211 to PD**		
Check screening assessments complete	X											Table 1
Check eligibility criteria	X						X					Section 5.2 & 5.3
Randomisation [a]	X											Section 6.3.1
Patient diary for olaparib/placebo – issue and review							X (start of olaparib/ placebo)	X	X	X		Section 6.4
Concomitant medications and blood transfusions	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Study treatments												
Chemotherapy [b]	X	X	X	X	X	X [c]						Section 6.1.2
Durvalumab or placebo (IV infusion) [b, d]	X	X	X	X	X	X	X	X	X	X (until PD) [e]		Section 6.1.1
Olaparib or placebo (oral tablets)							Twice daily (until PD) [e, f]					Section 6.1.1
Safety assessments												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Physical examination [g]	X [o]	X	X	X	X	X	X	X	X	X	X	Section 8.2.2
Blood samples for haematology and clinical chemistry [h, i]	X [j]	X	X	X	X	X	X [k]	X	X	X	X	Section 8.2.1
Thyroid function tests (TSH, T3 [reflex], T4 [reflex]) [l, i]	X [m]		X		X		X	X	X	X	X	Table 12
Cancer antigen 125 [i]	X [n]		X		X		X	X	X	X	X	Section 8.2.1.4
Urinalysis	X [o]	As clinically indicated										Table 14
Pregnancy test [p, i]	X [j]	X	X	X	X	X	X	X	X	X	X	Section 8.2.6.1

	Chemotherapy Phase (Cycles 1 to 6)						Maintenance Phase				Study Treatment Discontinuation visit (when all study treatments have been discontinued)	For details, see
Cycle	**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7D1**	**C8D1**	**C9D1**	**≥C10D1 to PD**		
Visit frequency		**Q3W**					**Q4W**					
Study week	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**22**	**26**	**30 to PD**		
Day (visit window +3 days from C2D1 onwards in the Chemotherapy Phase, and ±3 days in Maintenance Phase)	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**155**	**183**	**211 to PD**		
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.5
Vital signs (includes blood pressure, pulse and temperature) [q]	X [o]	X	X	X	X	X	X	X	X	X	X	Section 8.2.3
12-lead resting ECG	X [o]	As clinically indicated										Section 8.2.4
Efficacy assessments												
Tumour imaging (RECIST 1.1) [r]	Q9W (±1 week) for the first 18 weeks relative to randomisation and then Q12W (±1 week) until RECIST 1.1-defined radiological progression (PD)											Section 8.1.1
Pharmacokinetic assessments												
Durvalumab PK blood sample [s]					X				X			Section 8.5
Durvalumab ADA blood sample [s]	X (pre-dose)				X				X			Section 8.5.1.1
Other assessments												
Tumour biopsy (optional)											X [t]	Section 8.8.1
Blood sample for cfDNA [u]	X	X	X				X	X	X		X [v]	Section 8.8.2
Blood sample for peripheral gene expression profiling [u]	X	X	X				X	X			X [v]	Section 8.8.2
Blood sample for peripheral cytokines/chemokines [u]	X	X	X				X	X			X [v]	Section 8.8.2
Allocate ePRO device [w]	X											Section 8.1.3
ePRO device training [x]	X											Section 8.1.3

	Chemotherapy Phase (Cycles 1 to 6)						Maintenance Phase				Study Treatment Discontinuation visit (when all study treatments have been discontinued)	For details, see
Cycle	**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7D1**	**C8D1**	**C9D1**	**≥C10D1 to PD**		
Visit frequency		**Q3W**					**Q4W**					
Study week	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**22**	**26**	**30 to PD**		
Day (visit window +3 days from C2D1 onwards in the Chemotherapy Phase, and ±3 days in Maintenance Phase)	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**155**	**183**	**211 to PD**		
EORTC QLQ-C30 [y]	X [z]	Q3W (±3 days) for the first 18 weeks relative to Cycle 1 Day 1, and then Q4W (±3 days) until PFS2. Patients will also be assessed at the study treatment discontinuation visit (+2 days) unless completed within 3 days prior to the visit, and for those who discontinue for reasons other than PD, also at the PD visit (+2 days) unless completed within 3 days prior to the visit. *Note patients should have a PRO assessment at the start of maintenance therapy visit unless completed within 3 days prior to the visit.										Section 8.1.3.1
EORTC QLQ-EN24 [y]	X [z]											Section 8.1.3.1
EQ-5D-5L [y]	X [z]											Section 8.1.3.2
PGIS [y]	X [z]											Section 8.1.3.4
PGIC [y]												Section 8.1.3.5
PGI-TT [y]	X [z]	Q3W (±3 days) for the first 18 weeks relative to Cycle 1 Day 1 and then Q4W (±3 days). Patients will also be assessed at the study treatment discontinuation visit (+2 days) unless completed within 3 days prior to the visit and 4 weeks (±3 days) after the study treatment discontinuation visit.										Section 8.1.3.6
PRO-CTCAE [y]	X [z]	*Note patients should have a PRO assessment at the start of maintenance therapy visit unless completed within 3 days prior to the visit.										Section 8.1.3.3
PGI-BR [v]		At weeks 12, 15 and 18 (each ±3 days) relative to Cycle 1 Day 1, and then Q8W (±3 days). Patients will also be assessed at the study treatment discontinuation visit (+2 days) unless completed within 3 days prior to the visit, and for those who discontinue for reasons other than PD, also at the PD visit (+2 days) unless completed within 3 days prior to the visit. *Note patients should have a PRO assessment at the start of maintenance therapy visit unless completed within 3 days prior to the visit.										Section 8.1.3.7
Healthcare resource use (HOSPAD)											X	Section 8.9

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; C = cycle; cfDNA = cell-free DNA; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients 30; EORTC QLQ-EN24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer 24; ePRO = electronic patient reported outcomes; EQ-5D-5L = EuroQoL five dimensions, five level health state utility index; HRQoL = health-related quality of life; IV = intravenous; PD = progressive disease; PFS2 = time from randomisation to second progression or death; PGI-BR = patient global impression of benefit/risk; PGIC = patient global impression of change (in symptoms); PGIS = patient global impression of severity; PGI-TT = patient global impression of treatment tolerability; PK = pharmacokinetics; PRO = patient reported outcomes; PRO-CTCAE = Patient Reported Outcomes Common Terminology Criteria for Adverse Event; RECIST = Response Evaluation Criteria in Solid Tumours; QxW = every x weeks; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

[a] Patients should begin treatment on the day of randomisation (in the event of logistical challenges, treatment should start no later than 3 calendar days following randomisation). Every effort should be made to minimize the time between randomisation and starting treatment.

[b] The order of infusions for the chemotherapy phase should be durvalumab/placebo, followed by paclitaxel, and then carboplatin.

[c] Chemotherapy should continue for a maximum of 6 cycles. If required due to toxicity, 4 cycles of platinum-based chemotherapy may be given as a minimum. Patients must have a minimum of 4 cycles of platinum-based chemotherapy to continue into the maintenance phase. Patients completing chemotherapy must start maintenance treatment within 9 weeks of last dose of last cycle of chemotherapy and meet the criteria to start maintenance treatment. See Section 5.3.

[d] Following completion of chemotherapy, the durvalumab/placebo dosing schedule will change to durvalumab 1500 mg Q4W/durvalumab placebo. See Section 5.3 and Table 5 for more information.

[e] Study treatment will be administered until radiological disease progression per RECIST 1.1 as assessed by the investigator (refer to Appendix G), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. If there is doubt regarding the radiological disease progression, patients may continue to receive study treatment for the purpose of confirming disease progression with a follow-up scan in no less than 4 weeks if, in the opinion of the investigator, they do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment would not further benefit the patient. See Section 6.1.3.

[f] Olaparib treatment will be self-administered and will start after chemotherapy is completed (a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion).

[g] Limited physical examination - clinically directed based on signs and symptoms. Complete physical examination is not required on each visit during the study treatment phase. If clinically significant changes are found, they should be recorded as AEs. See Section 8.2.2.

[h] For a list of all required laboratory tests please refer to Section 8.2.1. Coagulation test should also be performed if clinically indicated.

[i] Starting at Cycle 2, regular blood laboratory assessments can be conducted 1-3 days before infusions. Not all clinical chemistry tests are required to be conducted at every visit; see Table 12 for more details. Serum or plasma clinical chemistry (including liver function test monitoring) and haematology may be performed more frequently if clinically indicated.

[j] If assessed within 3 days prior to starting study treatment, they do not need to be repeated at Day 1 of study treatment, unless the investigator believes that results are likely to have changed significantly.

[k] Patients must have adequate organ and bone marrow function, and creatinine clearance >51 mL/min as determined by the Cockcroft-Gault formula within 3 days prior to starting olaparib/placebo maintenance treatment (see Section 5.3). Patients should have reticulocyte count performed once prior to starting olaparib/placebo in the maintenance phase (see Table 13).

[l] 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.

[m] If TSH has been measured within 14 days prior to starting study treatment, it does not need to be repeated at Day 1 of study treatment unless the investigator believes that results are likely to have changed significantly.

[n] If CA-125 levels have been measured within 28 days prior to starting study treatment, it does not need to be repeated at Day 1 of study treatment unless the investigator believes that results are likely to have changed significantly.

[o] If assessed within 7 days of starting study treatment and meets the stated eligibility criteria (if applicable), it does not need to be repeated on Day 1 of study treatment, unless the investigator believes that the results are likely to have changed significantly.

[p] Pregnancy tests on serum or urine samples will be performed for women of childbearing potential on Day 1 of Cycle 1 prior to commencing treatment, at the time points shown during study treatment, and at the 30 day follow up visit. If results are positive, the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

[q] Blood pressure, pulse and temperature should be measured on the day of treatment and prior to the start of the infusion. In addition, for the first infusion of durvalumab/placebo, blood pressure and pulse will be measured before, during and after the infusion – see Section 8.2.3.1 for timings.

[r] RECIST assessments will be performed using CT or MRI scans of chest, abdomen and pelvis, and any area where disease was identified at baseline. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Note: Scans MUST be performed according to the time since randomisation, not necessarily aligned to the treatment schedule (which may be delayed).

[s] Samples for PK and ADA should be collected within 1 hour prior to the durvalumab/placebo infusion.

[t] Only applicable to patients who discontinue due to objective disease progression per RECIST 1.1. Optional for tumours that are assessable without putting the patient at risk, if the patient provides consent. Sample should be from a progressing lesion.

[u] Samples to be taken pre-dose.

[v] Mandatory, but only applicable to patients who discontinue due to objective disease progression per RECIST 1.1. If treatment discontinuation occurs due to reasons other than disease progression, these samples should still be taken at the time of disease progression (see Table 3 for further details).

[w] The handheld device should be charged and set up for the patient prior to their arrival at the site for their baseline PRO assessments, to ensure it is functioning properly and ready for use, in accordance with device training.

[x] The patient should be trained on the use of the device, including the importance of completing the PRO questionnaires throughout the study in accordance with the schedule.

[y] PRO questionnaires will be completed electronically at site visits or at home. For completion during site visits, PRO questionnaires must be completed prior to treatment administration and ideally before any discussions of health status, to avoid biasing the patient's response to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures such as collection of laboratory samples, to further minimise bias.

[z] PROs should be completed on Day 1, but if first dose of treatment is delayed, PROs will be accepted if first dose is administered within 3 days of completing the PROs.

Table 3 Schedule of assessments during the post-discontinuation follow-up phase

Visit	Time since last dose of IP						
Evaluation	30 days (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)	Month 4 (± 1 week)	6 (± 1 week) and then every 6 months (± 2 weeks) [g]	At PD per RECIST 1.1 (if treatment discontinued for reasons other than PD)	For details, see
Concomitant medications and blood transfusions	X	X	X				Section 6.5
Subsequent cancer therapy following discontinuation of study treatment [a]	<----------					---------->	Section 6.5.3
Safety assessments							
Adverse events [b]	X	X	X				Section 8.3
Physical examination [c]	X	X	X				Section 8.2.2
Weight	X	X	X		X (only 6 months)		
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X						
Pregnancy test (serum or urine) [d]	X	As clinically indicated					Section 8.2.6.1
Clinical chemistry and haematology [e]	X	X	X				Section 8.2.1
Thyroid function tests (TSH, T3 [reflex], T4 [reflex]) [f]	X	X	X				Table 12
Efficacy assessments							
Survival status [g]	X	X	X	X	X (every 2 months [± 2 weeks)		Section 8.1.2
Tumour imaging (RECIST 1.1) [h]	On-study tumour assessments begin Q9W (±1 week) for the first 18 weeks relative to randomisation and then Q12W (±1 week) until RECIST 1.1-defined radiological progression (PD)						Section 8.1.1
Second progression assessment [i]	Following RECIST 1.1-defined radiological progression, patients will be assessed Q12W (± 2 weeks) for a second progression (using the patient's status at first progression as the reference for assessment of second progression).						
EORTC QLQ-C30	Q3W (±3 days) for the first 18 weeks relative to Cycle 1 Day 1, and then Q4W (±3 days) until PFS2						Section 8.1.3.1
EORTC QLQ-EN24							Section 8.1.3.1
EQ-5D-5L							Section 8.1.3.2
PGIS							Section 8.1.3.4
PGIC							Section 8.1.3.5

Visit	Time since last dose of IP						
Evaluation	30 days (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)	Month 4 (± 1 week)	6 (± 1 week) and then every 6 months (± 2 weeks) [g]	At PD per RECIST 1.1 (if treatment discontinued for reasons other than PD)	For details, see
PGI-TT	X						Section 8.1.3.6
PRO-CTCAE							Section 8.1.3.3
Cancer Antigen 125						X	Section 8.2.1.4
Tumour biopsy on progression (optional) [j]						X	Section 8.8
Blood sample for cfDNA on progression						X	Section 8.8.2
Blood sample for peripheral gene expression profiling on progression						X	Section 8.8.2
Blood sample for peripheral cytokines/chemokines on progression						X	Section 8.8.2
ECOG performance status [k]	X	X	X		X (only 6 months)		Section 8.2.5
Pharmacokinetic assessments							
Durvalumab PK blood sample [l]			X				Section 8.5
Durvalumab ADA blood sample [l]			X		X[l] (only 6 months)		Section 8.5.1.1

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients 30; EORTC QLQ-EN24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer 24; EQ-5D-5L = EuroQoL five dimensions, five level health state utility index; IP = investigational product; PFS2 = time from randomisation to second progression or death; PGIC = patient global impression of change (in symptoms); PGIS = patient global impression of severity; PGI-TT = patient global impression of treatment tolerability; PK = pharmacokinetics; PRO-CTCAE = Patient Reported Outcomes Common Terminology Criteria for Adverse Event; QxW = every x weeks; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

[a] Including all anti-cancer treatments (including, but not limited to, surgery, chemotherapy and targeted agents) and the investigator's opinion of response to them. At minimum, collect the start date and description of the subsequent anticancer therapy. Reasons for any blood transfusions should also be recorded.

[b] All ongoing adverse events/serious adverse events (AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow-up period after last dose of olaparib/placebo or during the 90 calendar days follow-up period after last dose of durvalumab/placebo (whichever is later) must be followed to resolution.

[c] Limited physical examination - clinically directed based on signs and symptoms. Complete physical examination is not required on each visit during the post-discontinuation follow-up phase. If clinically significant changes are found, they should be recorded as AEs. See Section 8.2.2.

[d] Pregnancy tests on serum or urine samples will be performed for women of childbearing potential. Details of the pregnancy tests must be recorded in the patient's medical records.

[e] Coagulation test should be performed if clinically indicated.

[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] Following RECIST 1.1-defined radiological progression, patients must be followed for survival status every 2 months (±2 weeks), up to the final analysis, provided they have not withdrawn consent to do so.

[h] For patients who have discontinued treatment in the absence of RECIST 1.1-defined radiological progression. Patients should continue to undergo tumour assessments.

[i] Second progression assessments will be performed by the investigator following the first RECIST progression (PFS1; ±2 weeks). Second progression assessments will be defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death.

[j] Optional for tumours that are assessable without putting the patient at risk, if the patient consents. Progression biopsy should be from a progressing lesion.

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

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

1.2 Synopsis

International Co-ordinating Investigator

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Protocol Title: A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E)

Short Title: Durvalumab with or without Olaparib as Maintenance Therapy after First-Line Treatment of Advanced and Recurrent Endometrial Cancer (DUO-E)

Rationale

A major limitation of the current standard chemotherapy treatment is that most patients can only tolerate chemotherapy for a limited time due to associated toxicities and there are no approved maintenance treatment options available for patients with advanced endometrial cancer. This is compounded by the fact that there are currently no standard treatment options in the second-line setting or beyond, aside from salvage chemotherapy or participation in clinical trials. Further, the relative lack of development of new targeted therapies for endometrial cancer highlight the unmet need for patients with advanced endometrial cancer. In particular, new treatment options in the maintenance setting could build on the initial activity of carboplatin/paclitaxel, providing the potential to prolong the progression-free interval and the interval between lines of chemotherapy. Combining programmed death-ligand 1 (PD-L1) inhibitors with agents aimed at increasing the immunogenicity of tumours is a potential approach for the treatment of endometrial cancer. In various models, chemotherapy has been shown to alter the immune profile of tumours and their microenvironment, which may result in upregulation of PD-L1 expression, increasing antigen presentation and expansion of neoantigen repertoires, all of which have the potential to increase clinical responses to immune checkpoint inhibition. It therefore follows that durvalumab and chemotherapy have potentially synergistic effects, and that durvalumab may provide an option for maintenance treatment in patients with advanced endometrial cancer after chemotherapy. The potential increased activity from combining a polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase (PARP) inhibitor, such as olaparib, with PD-L1 is based on the hypothesis that chemotherapy and/or pharmacological inhibition of PARP by olaparib will result in enhanced immunogenicity which can be further enhanced with an immune checkpoint inhibitor such as durvalumab. This study was therefore designed

to investigate whether durvalumab with or without olaparib would provide effective and safe maintenance therapy in patients with endometrial cancer.

Objectives and Endpoints

Primary objective	**Endpoint/variable**
To demonstrate the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy alone (Arm A) by assessment of progression-free survival (PFS), in patients with newly diagnosed advanced or recurrent endometrial cancer	PFS (per RECIST 1.1 as assessed by investigator), defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression). This will be assessed via determining the efficacy of: • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance in combination with olaparib versus standard of care (SoC) platinum-based chemotherapy. • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance versus SoC platinum-based chemotherapy.

Objectives and Endpoints

Secondary objectives	Endpoint/variable
To determine the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy alone (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients by assessment of: PFS2, OS, ORR, DoR, TFST, TSST, and TDT	PFS2: Second progression-free survival is defined as the time from randomisation to the earliest of progression event subsequent to first subsequent therapy (assessed by the investigator per local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression), or death due to any cause. OS: Overall survival is defined as the time from the date of randomisation until death due to any cause. ORR: Objective response rate is the proportion of patients with measurable disease at baseline who have complete response (CR) or partial response (PR), as determined by the investigator at local site. DoR: Duration of response is time from the date of first documented response until date of documented progression or death in the absence of disease progression. TFST: Time to first subsequent therapy or death is time from randomisation to the earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment or death due to any cause. TSST: Time to second subsequent therapy or death is time from randomisation to the earlier of start date of the second subsequent anti-cancer therapy after discontinuation of first subsequent treatment or death due to any cause. TDT: Time to study treatment discontinuation or death is time from randomisation to the earlier of the date of study treatment discontinuation or death.
To characterise the PK and immunogenicity of durvalumab and durvalumab in combination with olaparib	Serum concentrations of durvalumab Anti-drug antibodies (ADA) to durvalumab

Objectives and Endpoints

To determine effects on symptoms, functioning and overall health-related quality of life (HRQoL) of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy alone (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients	Change from baseline in: • Physical functioning score of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30) • Role functioning score of the EORTC QLQ-C30 • Global health status/quality of life (QoL) score of the EORTC QLQ-C30 • All other functioning and symptom subscale scores of the EORTC QLQ-C30 (excluding the financial subscale) Time to deterioration in: • Physical functioning score of the EORTC QLQ-C30 • Role functioning score of the EORTC QLQ-C30 • Back/pelvic pain of the EORTC QLQ-EN24 • Gastrointestinal (GI) symptoms of the EORTC QLQ-EN24 • Urological symptoms of the EORTC QLQ-EN24

Objectives and Endpoints

Safety objective	**Endpoint/variable**
To evaluate the safety and tolerability of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) compared to platinum-based chemotherapy alone (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients	Safety and tolerability will be evaluated in terms of AEs/serious AEs (SAEs), physical examination, vital signs including blood pressure, pulse, clinical laboratory including clinical chemistry/haematology parameters, and ECG Assessments related to AEs cover: • Occurrence/frequency • Relationship to investigational product (IP) as assessed by investigator • Common Terminology Criteria for Adverse Event (CTCAE) grade • Seriousness • Death • Discontinuation of IP • Dose modifications during the chemotherapy phase and the maintenance phase • AEs of special interest (AESIs) • Other significant AEs • Exposure • Immune-mediated adverse events (imAEs) – given the intended mechanisms of action of durvalumab, particular attention will be given to AEs that may follow enhanced T cell activation, or other imAE
Exploratory objectives	**Endpoint/variable**
To determine the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab in combination with olaparib (Arm C) when compared to durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) in patients with newly diagnosed advanced or recurrent endometrial cancer	Will include, but is not limited to: • PFS (per RECIST 1.1 as assessed by investigator) • OS

Objectives and Endpoints

To evaluate tumour predictive biomarkers of durvalumab and olaparib in advanced endometrial cancer patients	CCI
To evaluate additional tumour candidate predictive biomarkers of durvalumab and olaparib in advanced endometrial cancer patients	
To further assess the efficacy of treatment through longitudinal analysis of blood samples collected at regular intervals on study	
To explore whether resistance mechanisms to treatment can be identified through analysis of tumour and blood samples – archival tumour sample and blood samples at baseline and on progression (tumour sample optional on progression)	
Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored blood or archival tumour samples that were mandatory for entry onto the study or on optional blood or tumour biopsy samples collected during the course of the study.	Analysis and outcome variables yet to be defined.

Objectives and Endpoints

To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional) [a]	To identify pharmacogenetic correlates for the response to treatment through the retrospective analysis of DNA extracted from an optional blood sample.
To explore health status of patients with durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of health status by the assessment of • Health state utility derived from the EuroQoL five dimensions, five level health state utility index (EQ-5D-5L) • Quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) • Quality-adjusted PFS (QAPFS)
To explore patient-reported treatment tolerability with durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of selected symptoms from the patient-reported outcomes version of the CTCAE (PRO-CTCAE) and overall treatment tolerability using the patient global impression of treatment tolerability (PGI-TT).
To explore patient-reported severity of cancer symptoms, change in overall health condition, and overall benefit/risk evaluation for durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of patient global impression of severity of cancer symptoms (PGIS), patient global impression of change in health condition (PGIC), and overall perception of benefit/risk (PGI-BR).
To explore healthcare resource associated with durvalumab and olaparib in advanced endometrial cancer patients	Key healthcare resource use will be collected using HOSPAD

[a] These endpoints may be reported separately to the clinical study report.

Overall design

This is a prospective randomised, double-blind, placebo-controlled, multicentre Phase III study evaluating the efficacy, safety, and patient reported outcomes of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer compared to platinum-based chemotherapy (paclitaxel and carboplatin). Patients will receive a maximum of 6 cycles of chemotherapy in combination with durvalumab or durvalumab placebo during the chemotherapy phase. Durvalumab (or

placebo) and olaparib (or placebo) will be administered during the maintenance phase. The study will include 3 arms:

Treatment phase	Arm A	Arm B	Arm C
	Control	**Durvalumab+placebo**	**Durvalumab+olaparib**
Chemotherapy phase:	carboplatin/paclitaxel chemotherapy + durvalumab placebo	carboplatin/paclitaxel chemotherapy + durvalumab	carboplatin/paclitaxel chemotherapy + durvalumab
Maintenance phase:	durvalumab placebo + olaparib placebo	durvalumab + olaparib placebo	durvalumab + olaparib

Patients will be stratified according to MMR expression status (proficient versus deficient), disease status (recurrent versus newly diagnosed) and geographic region (Asia versus rest of the world [RoW]). Patients will provide a tumour sample at screening to determine MMR status for stratification.

Study Period

Estimated date of first patient enrolled Quarter 1, 2020
Estimated date of last patient completed Quarter 4, 2024

Number of patients

As part of the global recruitment, approximately 699 eligible patients with endometrial cancer will be recruited from approximately 210 sites and randomised in a 1:1:1 ratio to the study treatments (N=233 patients per arm). If necessary, enrolment in China will continue after global enrolment is closed (ie, last subject randomised from a non-China site) to allow inclusion of a China cohort consisting of approximately 129 patients randomised in a 1:1:1 ratio from sites in China. Any patient from China randomised before the global recruitment is closed will be included in the global population. Additional sites may be added depending on recruitment rates.

Treatments and treatment duration

- **Arm A (control)**: Patients will receive platinum-based chemotherapy (paclitaxel and carboplatin) every 3 weeks (Q3W) for a maximum of 6 cycles with durvalumab placebo (intravenous [IV]) Q3W during the chemotherapy phase. Following completion of the chemotherapy phase, patients without objective disease progression will receive durvalumab placebo (IV) every 4 weeks (Q4W) and olaparib placebo (tablets) twice daily (bd) in the maintenance phase until disease progression.
- **Arm B (durvalumab+placebo)**: Patients will receive platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of 6 cycles with 1120 mg durvalumab (IV) Q3W during the chemotherapy phase. Following completion of the chemotherapy phase, patients without objective disease progression will receive 1500 mg durvalumab (IV) Q4W and olaparib placebo (tablets) bd in the maintenance phase until disease progression.

- **Arm C (durvalumab+olaparib)**: Patients will receive platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of 6 cycles with 1120 mg durvalumab (IV) Q3W during the chemotherapy phase. Following completion of chemotherapy, patients without objective disease progression will receive 1500 mg durvalumab (IV) Q4W and 300 mg olaparib (tablets) bd orally in the maintenance phase until disease progression.

Patients should continue to receive study treatment until radiological disease progression per RECIST 1.1 as assessed by the investigator (refer to Appendix G), unless there is unacceptable toxicity, withdrawal of consent, or confirmed another discontinuation criterion is met.

Follow-up of patients after discontinuation of study drug

All patients will be followed for disease progression and survival until the final data cut-off (DCO). Patients who have discontinued treatment due to reasons other than radiological progression (such as toxicity or symptomatic deterioration, clinical progression, or starting subsequent anticancer therapy) will be followed up with tumour assessments until RECIST 1.1-defined PD or until death (whichever comes first) and followed for survival.

Survival

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

Independent Data Monitoring Committee

This study will use an external independent data monitoring committee (IDMC) comprised of independent therapeutic area experts and biostatisticians. The IDMC will assess ongoing safety analyses as well as the interim futility analysis. The IDMC will be convened after the first 30 patients complete 1 cycle of study treatment and meet approximately every 6 months thereafter until unblinding (unless there is a need for an ad hoc meeting or increased frequency). The IDMC will meet to review safety assessments and make recommendations to continue, amend or stop the study based on safety findings. In addition, the IDMC will meet for the futility analysis, which will occur approximately 2-months post last subject randomised (LSR), and when a minimum of 50% of the target number of PFS events for each comparison has occurred (approximately 25 months after the first patient has been randomised). See Section 9.5.2.

Full details of the IDMC procedures and communication process concerning all safety reviews and the interim analyses can be found in the IDMC Charter.

Statistical methods

The primary objective of the study is to determine the efficacy by PFS (per RECIST 1.1 as assessed by investigator) of durvalumab and durvalumab+olaparib. This will be assessed by determining the efficacy of:

- Arm C (durvalumab+olaparib) versus Arm A (control).
- Arm B (durvalumab+placebo) versus Arm A (control).

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

- H_{0CA}: Arm C = Arm A versus H_{1CA}: Arm C ≠ Arm A

and

- H_{0BA}: Arm B = Arm A versus H_{1BA}: Arm B ≠ Arm A

Where H_0 = the null hypothesis; H_1 = the alternate hypothesis.

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

OS will also be assessed for the durvalumab+placebo arm versus the control arm and for the durvalumab+olaparib arm versus the control arm.

The DCO for the primary analysis of PFS for the two comparisons of interest (Arm B versus Arm A and Arm C versus Arm A) will be undertaken at the same calendar time when approximately 299 PFS events have occurred (64% maturity) for the durvalumab+placebo arm versus the control arm and approximately 281 PFS events have occurred (60% maturity) for the durvalumab+olaparib arm versus the control arm (approximately 43 months after the first patient is randomised). A futility analysis of PFS for the comparison of the durvalumab+placebo arm versus control and the durvalumab+olaparib arm versus control will be performed before the primary analysis and will be conducted approximately 2-months post-LSR, and when a minimum of 50% of the target number of PFS events for each comparison has occurred (ie, 150 of 299 target events across the durvalumab+placebo and control arms, and 141 of 281 target events across the durvalumab+olaparib and control arms). The boundary for declaring futility and dropping an experimental arm will be observing a hazard ratio (HR) >1.15.

The first interim OS analysis will also be performed at the time of the primary PFS analysis, based on the same DCO date. For the comparison of the durvalumab+placebo arm versus the control arm, as well as durvalumab+olaparib versus control, it is anticipated that 74% of the target number of OS events will have occurred at this time (ie, approximately 208 of 280 OS events per comparison).

A second interim analysis of OS may be performed at the same calendar time when approximately 244 OS events (87% of the target number of OS events) have occurred for the comparison of the durvalumab+placebo arm versus the control arm, as well as the durvalumab+olaparib arm versus control (approximately 51 months after the first patient is randomised). A final analysis of OS may be performed at the same calendar time when approximately 280 OS events have occurred (60% maturity) for the comparison of the durvalumab+placebo arm versus the control arm, as well as the durvalumab+olaparib arm versus the control arm, approximately 63 months after the first patient is randomised.

For the OS comparisons, the alpha allocation for the secondary OS endpoints will be controlled at the interim and/or the final analysis timepoints separately for each treatment comparison using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates the O'Brien-Fleming approach, where the significance level applied at the interim analysis depends upon the proportion of information (ie, information fraction) available.

In order to characterise the benefits of the durvalumab+placebo arm versus control and the durvalumab+olaparib arm versus control, objective response rate (ORR), second progression-free survival (PFS2), time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST), time to study treatment discontinuation or death (TDT) and change from baseline in health-related quality of life (HRQoL) measures will be tested at a 2-sided significance level of 5%.

PFS, PFS2, OS, TFST, TSST and TDT will be analysed using a log-rank test stratified by MMR status (proficient versus deficient), disease status (recurrent versus newly diagnosed) and geographic region (Asia versus RoW). The hazard ratio and confidence interval (CI) will be estimated from a Cox Proportional Hazards model stratified by MMR status, disease status and geographic region.

ORR will be analysed using logistic regression adjusted by MMR status, disease status and geographic region.

Time to deterioration in EORTC QLQ-C30 and EORTC QLQ-EN24 endpoints will be examined comparing treatment versus control arm. Additional PRO data will be summarised descriptively.

Safety and tolerability data will be summarised using appropriate descriptive measures.

1.3 Schema

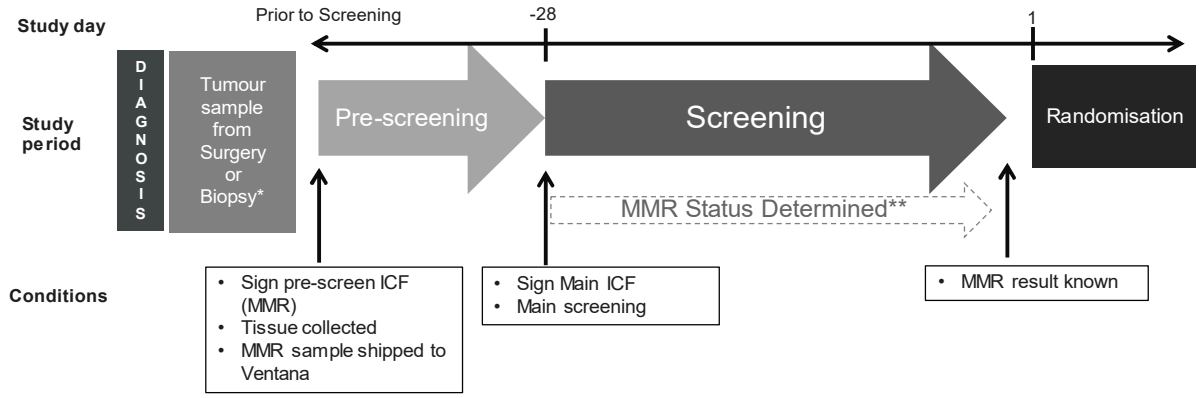
Pre-screening eligibility check

Prior to the main screening (time of diagnosis to start of main screening period), the pre-screen ICF should be signed so that the tumour biomarker sample can be obtained and MMR testing initiated. The purpose of the pre-screen period is to ensure that MMR status via central testing can be determined prior to randomisation. Inclusion and exclusion criteria to be checked at pre-screening are marked with an asterisk (*) in Sections 5.4 and 5.5.

Main screening

After tissue for MMR testing has been shipped for MMR status determination, the main ICF should be signed to proceed with the main screening period. An overview of the screening procedures is shown in Figure 1. Please see Table 1 for more information.

Figure 1 Screening process



Abbreviations: ICF = informed consent form; MMR = mismatch repair.
* Use of a freshly collected tumour sample is permitted provided the sample is taken as part of routine clinical practice
** Patients with unknown MMR status prior to randomisation will be considered screen failures and will not be eligible (see Section 5.4, inclusion criterion 6). If the original MMR testing cannot be completed by the end of the 28-day screening period due to technical failure, patients must be re-screened to ensure adequate time for MMR re-testing (see Sections 5.7.1 and 8.8.1). Sample must be shipped prior to signing the main informed consent and MMR results must be available prior to randomisation. Submission and testing of new samples can only be performed if the original testing failed due to technical failure. Please refer to the laboratory manual for further details regarding re-testing procedures.

Randomisation

Patients should be randomised and begin treatment on Day 1. Patients must not be randomised and treated unless all eligibility criteria have been met.

The randomisation scheme will be stratified according to:

- **Tumour tissue's mismatch repair (MMR) status**: patients with MMR deficient tumours versus those with proficient tumours. Tumour MMR status will be determined prior to randomisation based on evaluation of MMR status in tumour cells from a formalin-fixed, paraffin-embedded (FFPE) tumour tissue sample, using the Ventana immunohistochemistry (IHC) MMR panel.
- **Disease status**: patients with recurrent disease versus those newly diagnosed.
- **Geographic region**: Asia versus RoW.

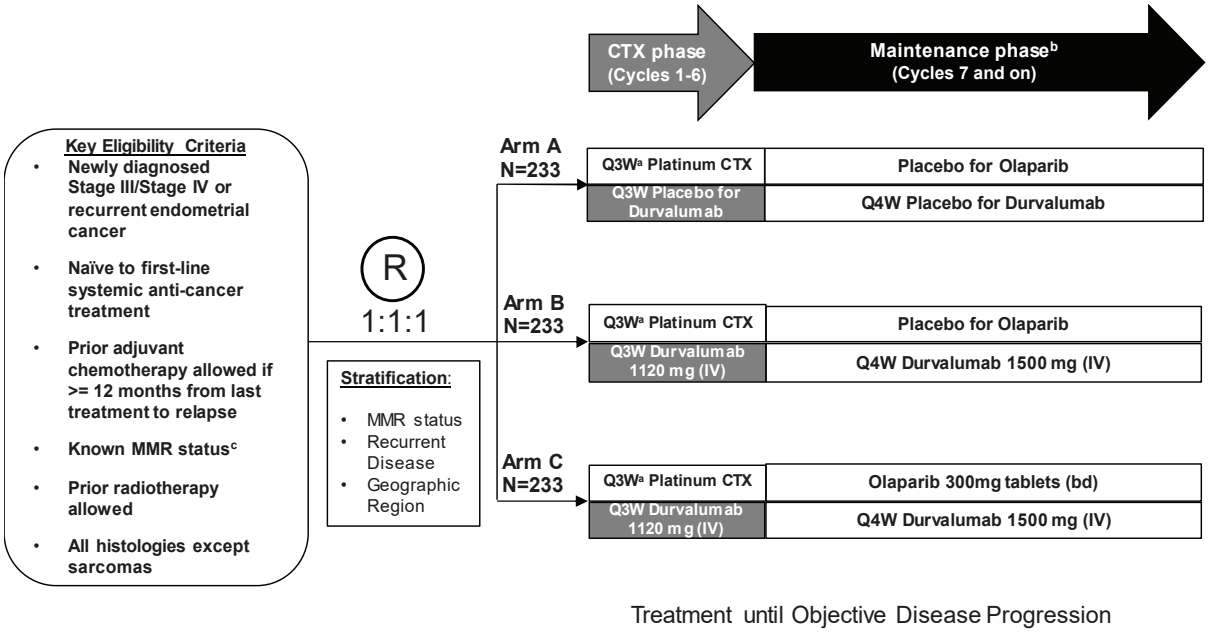
Study assessments

Patients in all treatment arms will have tumour assessments according to RECIST at baseline (no more than 28 days prior to randomisation), every 9 weeks (±1 week) after the date of randomisation for 18 weeks, and every 12 weeks (±1 week) thereafter, until objective radiological disease progression according to RECIST 1.1.

All patients will continue to be assessed for radiological tumour assessments according to the study schedule, until objective radiological disease progression, irrespective of any treatment

delays or discontinuation of study treatment. Once progression has occurred, the patient will be followed as per local clinical practice, but assessments should continue to be made every 12 weeks for second progression, and survival status assessed every 2 months, until the final analysis of the study. The general study design is summarised in Figure 2.

Figure 2 Study design



Abbreviations: bd = twice daily; CTX = chemotherapy; IV = intravenous; MMR = mismatch repair; PD = progressive disease; Q3W = every 3 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; R = randomisation.

[a] Chemotherapy should be administered for a maximum of 6 cycles.

[b] Maintenance treatment will continue until progression of disease or other discontinuation criteria are met.

[c] MMR status must be known prior to randomisation.

2 INTRODUCTION

2.1 Study rationale

Investigators should be familiar with the current durvalumab (MEDI4736) and olaparib (AZD2281) IBs.

2.1.1 Endometrial cancer

Endometrial cancer is one of the most common malignancies in the female genital tract with over 380,000 new cases worldwide in 2018 (Bray et al 2018), and an estimated 61,880 new cases diagnosed in the United States (US) in 2019 (Siegel et al 2019). There is an increasing prevalence in developed countries and the highest incidences have been observed in the US, Canada, and Northern and Western Europe (Bray et al 2018). From 2006 to 2015, the incidence rate increased by about 1% per year and from 2007 to 2016, the death rate increased by about 2% per year (American Cancer Society 2019). The main risk factor thought to be associated with the occurrence of endometrial cancer is exposure to excessive oestrogen levels associated with obesity, diabetes, use of tamoxifen, and reproductive factors (early menarche, late menopause, nulliparity) (Morice et al 2016). The growth of the aging population may also have a role in the increased incidence.

As the disease often displays symptoms of abnormal uterine bleeding, the majority (~75%) of patients are diagnosed at an early stage (Stage I or II), and these patients have a better prognosis with 5-year OS rate ranging from 74% to 91% (Creasman et al 2006, Siegel et al 2015). Standard therapy for these patients is surgery with or without radiotherapy. Systemic therapy is not frequently administered to these early stage patients. For patients diagnosed at a later stage or with advanced endometrial cancer, however, the prognosis is far worse.

2.1.2 Current standard of care for advanced endometrial cancer

Whilst there are a number of chemotherapy-based therapies recommended for first-line treatment of advanced endometrial cancer, physicians are now aligning on the use of a combination of carboplatin and paclitaxel as an increasingly preferred regimen for first-line treatment (Miller et al 2012, Bestvina and Fleming 2016, Colombo et al 2016, NCCN Uterine Neoplasms 2019).

2.1.3 Unmet medical need

Although endometrial cancer shows a strong initial sensitivity to platinum doublet chemotherapy compared to many other solid tumours with a response rate of approximately 51%, most patients diagnosed at an advanced stage will show progression of their disease with median PFS of approximately 12 months (Miller et al 2012, Aghajanian et al 2018). Five-year OS rates also remain poor for these patients with advanced disease (57% to 66% for Stage III and 20% to 26% for Stage IV disease (Creasman et al 2006, Siegel et al 2015).

A major limitation of the current standard chemotherapy treatment for advanced endometrial cancer is that most patients can only tolerate chemotherapy for a limited time due to associated toxicities and there are no approved maintenance treatment options available for these patients. This is compounded by the fact that there are currently no standard treatment options in the second-line setting or beyond, aside from salvage chemotherapy or participation in clinical trials. European Society for Medical Oncology (ESMO) guidelines state that, evidence supporting the use of second-line chemotherapy after platinum-containing therapy in patients with endometrial cancer is limited, especially in cases where the treatment-free interval following first-line chemotherapy is <6–12 months (Colombo et al 2016). Although various regimens have been evaluated in this setting, no randomised trials have been published. Therefore, no specific regimen can be recommended as standard of care (SoC) for second-line chemotherapy. Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommend best supportive care or enrolment in a clinical trial for patients with persistent progression of disseminated metastases (NCCN Uterine Neoplasms 2019).

Pembrolizumab has received Food and Drug Administration (FDA) approval for the treatment of solid tumours (including endometrial cancer) in patients that have progressed following prior treatment and who have no satisfactory alternative treatment options. In 2019, pembrolizumab also received FDA approval in combination with lenvatinib for patients with advanced endometrial carcinoma that is not high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR), who have disease progression following prior systemic therapy, and are not candidates for curative surgery or radiation. This indication was approved under an accelerated approval pathway based on tumour response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. However, the relative lack of development of new targeted therapies for endometrial cancer highlights the high unmet need for patients with advanced endometrial cancer. New treatment options, particularly in the maintenance setting, could build on the initial activity of carboplatin/paclitaxel, and provide the potential to prolong the progression-free interval and the interval between lines of chemotherapy.

This study will investigate the role of two therapeutic targets: a PD-L1 inhibitor (durvalumab) and a PARP inhibitor (olaparib) when used in combination with chemotherapy (paclitaxel and carboplatin) and/or as maintenance therapy.

2.2 Background and study rationale

2.2.1 Durvalumab background

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with programmed cell death protein-1 (PD-1) on T cells and CD80 (B7.1) on immune cells (IC).

Immune responses directed against tumours are one of the body's natural defences against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. PD-L1 is one such protein that is expressed in a broad range of cancers.

The proposed mechanism of action (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 tumour elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (IFN-γ) (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumour 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 antitumour immune response by binding to PD-L1 and shifting the balance toward an antitumour response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

Durvalumab was approved in the US in February 2018 for the treatment of patients with non-small cell lung cancer (NSCLC) who have not progressed following concurrent platinum-based chemotherapy and radiation therapy. In the European Union (EU), durvalumab was approved in September 2018 for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

Durvalumab has been approved to treat extensive-stage small cell lung cancer (administered in combination with chemotherapy). Refer to the package insert (or label) for your specific country, as applicable.

To date, durvalumab has been given to more than 6000 patients in studies, either as monotherapy or in combination with other anticancer agents, and is actively being developed in other indications. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

2.2.2 Rationale for durvalumab in endometrial cancer

Endometrial cancer is a heterogenous disease with various molecular patterns that are beginning to emerge that may provide a path for developing targeted treatment options. Approximately 20% of endometrial cancer patients have MSI-H or deficient mismatch repair (dMMR) tumours and, based on available data across studies, approximately 50% would be considered PD-L1 positive (Fleming et al 2017, Makker et al 2018, Ott et al 2017). Tumours that are hypermutated may carry more neoantigens and TILs, and PD-1/PD-L1 have been reported to be overexpressed in TILs of hypermutated endometrial cancer tumours

(Howitt et al 2015). Due to the prevalence of MSI-H/dMMR tumours found in endometrial cancer, there has been increased interest in testing immune checkpoint inhibitors. MMR deficient tumours have been reported to predict response to PD-1 blockade, which supports the hypothesis that these tumours may have a large proportion of mutant neo-antigens that sensitize tumours to immune checkpoint inhibitors (Le et al 2017). Of note, pembrolizumab (KEYTRUDA™) is approved in the US for the treatment of patients with solid tumours or colorectal cancer with MSI-H or dMMR, with a response rate of 36% observed in endometrial cancer patients (N=14).

Durvalumab has been tested in Phase II trials in both MSI-H/dMMR and microsatellite stable/proficient mismatch repair (MSS/pMMR) subtypes of recurrent endometrial cancer. Data is limited; based on the small numbers to date, a response rate of 40% (14/35 patients) was observed in dMMR patients in the PHAEDRA ACTRN12617000106336 study (Antill et al 2019). In this study, activity was lower in the pMMR cohort with just 1 response observed (ORR 3%, n=36). Whilst the majority of patients in the dMMR cohort were being treated in the first- or second-line setting, the pMMR cohort in this study had more heavily pre-treated patients (second-line or beyond). Another study (NCT03015129) showed an overall ORR of 14.8% (N=4/27) with durvalumab monotherapy (2 responses in MSI H/dMMR and 2 responses in MSS/pMMR patients) (Rubinstein et al 2019).

Whilst MSI-H/dMMR endometrial tumours are expected to be particularly sensitive to immune checkpoint blockade, the KEYNOTE28 study evaluating pembrolizumab (NCT02054806; Ott et al 2017), a study evaluating avelumab in endometrial cancer (Konstantinopoulos et al 2019), and recent data from the GARNET study (NCT02715284; Oaknin et al 2019) suggest that patients with MSS tumours may also derive some clinical benefit when treated with monotherapy PD-1/PD-L1 blockade.

The GARNET clinical trial (NCT02715284) is evaluating TSR-042 (dostarlimab), an anti-PD-1 monoclonal antibody, in second- and third-line patients with advanced endometrial cancer that have either MSI-H or MSS tumours. Preliminary results showed an overall ORR of 29.6% (n=125) for all patients. In the cohort of MSI-H patients the ORR was 48.8% (n=41), and in MSS patients the ORR was 20.3% (N=79) (Oaknin et al 2019). In both cohorts, over 80% of responders had an ongoing response, and the median duration of response was not yet reached (median follow-up was 10 months). Further there was a ≥50% reduction in total tumour burden in 85% of MSI-H and 69% of MSS responders. Whilst the ORR was higher for those patients with MSI-H tumours, this data indicates that there is clinical activity of immune checkpoint inhibitors in both MSI-H and MSS endometrial cancer patients and that both subgroups showed highly durable responses.

Given the preliminary activity of anti-PD-1 monotherapy demonstrated in the GARNET study, and the hypothesis that the antitumour effects of durvalumab are durable and sometimes occur long after the administration of the immunotherapy has already been stopped, it is considered desirable to also combine with agents that have activity upfront.

Therefore, the proposed study will test the efficacy of durvalumab in combination with chemotherapy with durvalumab maintenance (with or without olaparib maintenance therapy) in both dMMR and pMMR endometrial cancer patients.

2.2.3 Olaparib background

Olaparib (AZD2281, KU-0059436) is a potent polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents, including novel agents and immunotherapy.

PARP inhibition is an established approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks. Inhibiting PARPs leads to the trapping of PARP at sites of unrepaired single strand breaks, which then results in DNA double strand break formation during DNA replication. During the process of cell division, double strand breaks can be efficiently repaired in normal cells by HRR. Generally, tumours with homologous recombination deficiency (HRD), such as those harbouring breast cancer susceptibility gene *BRCA1/2* mutations, rely on error-prone DNA repair pathways which causes an accumulation of DNA damage and cell death. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

In some instances, where DNA repair defects may not result in the same level of sensitivity to single agent olaparib treatment, it may still be possible to induce and/or enhance tumour cell death through combinations with other anti-cancer treatments.

Olaparib received accelerated approval in December 2014 in the US under the tradename LYNPARZA for the treatment of advanced germline *BRCA* (g*BRCA*)-mutated ovarian cancer after 3 or more lines of chemotherapy. As of November 2020, olaparib has been approved by the FDA in the following indications:

- Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy
- Treatment of adult patients with g*BRCA*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy
- Treatment of patients with g*BRCA*-mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting
- Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy

- Maintenance treatment of adult patients with deleterious or suspected deleterious gBRCA-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.
- In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability.
- Treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior therapy with new hormonal agent.

Olaparib is approved in the EU for the following indications:

- Monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed (PSR) *BRCA* mutated germline and/or (dependent on country) somatic high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy
- 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
- Treatment of adult patients with g*BRCA*m, HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.
- Maintenance treatment of adult patients with advanced (Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) Stages III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- Maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability
- Maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

- Treatment of adult patients with metastatic castration resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

The ongoing Phase III program includes studies in ovarian, breast, prostate and pancreatic cancers. Olaparib is being evaluated in combination with other anti-cancer agents, including immuno-oncology agents.

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

2.2.4 Rationale for olaparib in endometrial cancer

2.2.4.1 Ongoing clinical studies with olaparib in endometrial cancer

There are several ongoing studies that are testing olaparib alone or in combination with other therapies in endometrial cancer. Much of the clinical development for olaparib has assessed the effect of olaparib (as single agent or in combination) in the treatment of patients with tumours enriched for HRD, including *BRCA*m cancers (germline and tumour). Based on the activity observed in breast and ovarian cancer patients with *BRCA* mutations, a study is underway to test this hypothesis in endometrial cancer. The TAPUR study (NCT 02693535) is assessing the activity of olaparib monotherapy in patients with solid tumours (including an endometrial cancer cohort) that have specific mutations, such as *BRCA*m. The endometrial cancer cohort in this study was recently expanded from 10 patients based on having a minimum 20% response rate (AstraZeneca internal data, unpublished). These are low numbers and have not yet been formally disclosed, but an initial response rate for olaparib in this population is anticipated soon. Although this is in *BRCA*m patients, there are other studies testing olaparib in combination with other drugs in an all-comer population.

The UTOLA study is underway to evaluate olaparib monotherapy as frontline maintenance in patients with platinum-sensitive advanced endometrial cancer (NCT03745950). In addition to olaparib, other PARP inhibitors are being evaluated in endometrial cancer. Single-agent niraparib is being tested as a second-line treatment in endometrial cancer in a single arm Phase II study, ROSCAN (NCT03016338). However, no results are available yet for either of these studies.

Olaparib in combination with other therapies, such as cediranib and vistusertib, has shown some activity in endometrial cancer, however, the specific activity of olaparib monotherapy is not yet understood. The OCTOPUS study demonstrated a 27% response rate in heavily pre-treated endometrial cancer patients receiving olaparib in combination with vistusertib (mTORC1/2 inhibitor). COPELIA is another study assessing olaparib in combination with cediranib in endometrial cancer patients, however, no results have been reported yet.

2.2.4.2 Platinum sensitivity predicts response to PARP inhibition

The rationale for the use of olaparib in endometrial cancer is derived from the scientific rationale that is supported by the successful use of olaparib in other cancers, particularly

ovarian cancer. High grade epithelial ovarian cancers have 2 principal phenotypic characteristics which may predict sensitivity to PARP inhibition. Firstly, epithelial ovarian cancers are highly responsive to platinum-based chemotherapy. Platinum agents induce DNA double strand breaks, which require HRR for effective and accurate repair. Secondly, in ovarian cancer, platinum sensitivity has been established as an effective biomarker for PARP inhibitor (PARPi) sensitivity.

Clinical trial data with 3 different PARP inhibitors used as maintenance therapy in the platinum-sensitive relapsed setting have demonstrated statistically significant and clinically relevant improvement in PFS versus placebo in patients who are in response to platinum-based chemotherapy. This beneficial effect is observed in both patients who harbour *BRCA* mutations and in patients without *BRCA* mutations (olaparib Study D0810C00019 [Study 19]; NOVA [Mirza et al 2016], and ARIEL3 [Coleman et al 2017]). Study 19 in ovarian cancer found a statistically significant increase in investigator-assessed PFS with the use of olaparib (versus placebo) maintenance therapy in unselected patients with advanced disease who were responsive to platinum therapy for recurrent disease (HR 0.35, 95% CI: 0.25 to 0.49; p<0.0001). The estimated median PFS was 8.4 months and 4.8 months in the olaparib and placebo arms, respectively (Ledermann et al 2012). Improvement in PFS was seen in subsets of patients whose tumours were g*BRCA* mutant (g*BRCA*m) and non-g*BRCA*m (Ledermann et al 2012, Ledermann et al 2014, Gelmon et al 2011). Based on these data, the FDA granted approval for olaparib in the PSR ovarian cancer population irrespective of *BRCA* status.

Looking at platinum sensitivity as a biomarker for PARPi beyond ovarian cancer, clinical data is limited to *BRCA*m populations, however Study D0810C00042 (Study 42) in late-line metastatic g*BRCA*-associated pancreatic cancer found 3/6 responses to olaparib in platinum-sensitive disease but no responses (0/8) in platinum-resistant disease (Kaufman et al 2015 and AstraZeneca data on file). Study D081FC00001 (POLO) evaluated olaparib as maintenance monotherapy in patients with metastatic g*BRCA*m-associated carcinoma of the pancreas whose disease had not progressed on first-line platinum-based chemotherapy. Recently reported data from this study indicated that maintenance olaparib provided a statistically significant and clinically meaningful improvement in PFS compared to placebo (HR:0.53; 95% CI 0.35, 0.82; p=0.004; median PFS 7.4 versus 3.8 months with olaparib and placebo, respectively, Golan et al 2019).

Endometrial cancers are also sensitive to first-line carboplatin/paclitaxel, with a response rate of approximately 51% (Aghajanian et al 2018, Miller et al 2020), and similarly to ovarian cancer, an increased platinum-free interval is associated with increased response to second-line platinum-based chemotherapy (Nagao et al 2013). If the concept of platinum sensitivity that has been seen in ovarian and pancreatic cancer translates to endometrial cancer, it may be hypothesised that olaparib will have high clinical activity in endometrial cancer patients who are sensitive to platinum. A case study has been reported of an endometrial cancer patient with brain metastases that exhibited disease highly sensitive to

platinum treatment. The patient did not have a germline *BRCA* mutation, and they received olaparib monotherapy on the bases of their prior platinum sensitivity, showing a significant reduction in the size of their brain metastases (Forster et al 2011).

2.2.4.3 Molecular features associated with PARP inhibitor (PARPi) sensitivity

In addition to high levels of platinum sensitivity, high grade epithelial ovarian cancer is associated with the near universal presence of mutations in *TP53* and a pattern of genomic instability that is attributed to the absence of fully functional repair of double-strand DNA breaks (Bowtell 2010, Bowtell et al 2015). Both the presence of loss of function mutations in HRR genes and high genome instability scores (eg, HRD) are associated with increased benefit from PARPi in ovarian cancer (Study 19, NOVA, ARIEL2, ARIEL3). The genomic profile of copy number high serous endometrial cancer closely resembles that of triple negative breast cancer and serous ovarian cancer (Morice et al 2016, Kandoth et al 2013), which suggests these tumours share similar biological phenotypes and may also benefit from PARPi therapy.

The Cancer Genome Atlas (TCGA) research network recently characterised 373 endometrial carcinomas and classified four new categories of tumour types: POLE ultra-mutated, microsatellite instability hypermutated, copy-number low, and copy-number high (Kandoth et al 2013). Based on AstraZeneca internal analysis of data from TCGA, as well as the MSK IMPAKT database (Soumerai et al 2018), approximately 5% HRRm and 10% HRD prevalence is predicted in patients with MSS endometrial tumours, whereas 30% HRRm and 2% HRD prevalence is predicted in patients with MSI-H tumours. Using a functional assay of HR-deficiency, an additional study has reported that approximately 46% of non-endometrioid endometrial cancers are HR-deficient (de Jonge et al 2019). MRE11 loss has also been demonstrated in approximately 30% of endometrial cancer, where it is associated with dMMR and preclinical sensitivity to PARPi (Koppensteiner et al 2014). The specific subgroups of endometrial cancer that are sensitive to PARP inhibition remain to be characterised, but preliminary studies to date suggest a rationale to test PARP inhibitors in endometrial cancer.

2.2.5 Rationale for combination treatment in endometrial cancer

2.2.5.1 Combination of immune checkpoint inhibitors with chemotherapy

Durvalumab in combination with chemotherapy is being evaluated in various solid tumours, including small cell lung cancer (CASPIAN NCT03043872), NSCLC (POSEIDON NCT03164616), triple negative breast cancer (BEGONIA NCT03742102), and ovarian cancer (N-DUR NCT02726997). The N-DUR study is still ongoing, but for the majority of patients, the side effects have been primarily due to the chemotherapy (neutropenia, anaemia). Another AstraZeneca trial evaluating durvalumab with bevacizumab in combination with platinum chemotherapy in ovarian cancer is also ongoing (DUO-O NCT03737643).

There are several studies of other PD-1 or PD-L1 inhibitors in combination with carboplatin and paclitaxel that are either published or currently recruiting:

- A Phase III trial of avelumab in combination with carboplatin and paclitaxel for the first-line treatment of ovarian cancer is ongoing (JAVELIN100; NCT02718417) and the Phase III trial of atezolizumab in combination with carboplatin, paclitaxel and bevacizumab is also open to recruitment (IMagyn050; NCT03038100).

- In a Phase Ib study in NSCLC, combination therapy with nivolumab 10 mg/kg, carboplatin AUC6, paclitaxel 200 mg/m^2 and bevacizumab 15 mg/m^2 Q3W has been demonstrated to be safe and tolerable with no dose-limiting toxicities observed (Kanda et al 2016; Japanese Pharmaceutical Information Centre Clinical Trials Information [JapicCTI]-132071).

- In addition, the Phase III study of atezolizumab in combination with carboplatin, paclitaxel and bevacizumab is reported to show improved PFS benefit over carboplatin, paclitaxel and bevacizumab alone as first-line treatment for NSCLC, with safety of the combination appearing consistent with the known safety profile of the individual medicines and no new safety signals identified (Reck et al 2017; NCT02366143).

- A Phase III trial of pembrolizumab in combination with platinum doublet chemotherapy in NSCLC patients reported that pembrolizumab combination treatment resulted in a significantly longer OS and PFS than chemotherapy alone without a major difference in toxicity (Gandhi et al 2018; KN-189 NCT02578680).

In endometrial cancer specifically, there are fewer studies evaluating PD-1/PD-L1 inhibitors in combination with chemotherapy, but there is a Phase II study evaluating pembrolizumab in combination with carboplatin/paclitaxel (NCT02549209), as well as a Phase III study evaluating atezolizumab in combination with paclitaxel and carboplatin in advanced endometrial cancer (AtTEND NCT03603184).

2.2.5.2 Combination of durvalumab and olaparib

The potential synergistic activity of combining a PARP inhibitor (PARPi) with a PD-L1 inhibitor is based on the hypothesis that pharmacological inhibition of PARP by olaparib will result in enhanced immunogenicity which can be further enhanced with an immune checkpoint inhibitor, such as durvalumab. This could occur through several mechanisms:

- Olaparib has been shown to activate the STING pathway in pre-clinical models, leading to increased production of cytokines and chemokines (such as CXCL10 and CCL5), which may have the potential to promote antitumour immunity (Shen et al 2019).

- Accumulating DNA damage induced through PARP inhibition has the potential to modify the immunogenicity of tumours through triggering several intracellular

signalling events that result in the activation of transcription factors, such as nuclear factor kappa B (NFκB), interferon (IFN) regulatory factor 3, and IRF7. 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, Reisländer et al 2019).

- PARP inhibitors can complement immune checkpoint blockade by increasing cell death, which may help to promote antigen release and subsequent immune priming (Kroemer et al 2013).

- Increased DNA damage can also lead to upregulation of surface receptors such as major histocompatibility complex (MHC) class I, ligands for natural-killer group 2, member D (NKG2D), and inducible T-cell costimulatory ligand (ICOSL), and could make tumor cells more visible and sensitive to killing by cytotoxic T-cells and NK cells (Tang et al 2014, Gasser et al 2005).

- PARP inhibition demonstrated increased activity in combination with anti-PD-L1 in preclinical models (Jiao et al 2017, Shen et al 2019).

Given the promising pre-clinical data which support the combination hypothesis, PARP inhibitors and immune-checkpoint inhibitors are now being studied in combination in the clinical setting. Safety and efficacy of the combination of olaparib and durvalumab is being assessed across multiple tumor types and settings in several ongoing studies:

- Ovarian Cancer (MEDI-O, Phase I National Cancer Institute Study ESR-14-10366 [Lee et al 2017] and DUO-O, Phase III; NCT03737643)

- Breast cancer, small cell lung cancer, ovarian cancer, and gastric cancer (MEDIOLA, Phase 1/II [NCT02734004; Bang et al 2019; Domchek et al 2019; Domchek et al 2018; Drew et al 2018; Krebs et al 2017]). Over 200 patients have been treated in this study with the combination of olaparib and durvalumab to date.

- Bladder cancer (BISCAY, Phase IB; NCT02546661)

- Urothelial cancer (BAYOU, Phase II; NCT03459846)

- Non-small cell lung cancer (ORION, Phase II; NCT03775486)

- Non-small cell lung cancer (HUDSON, Phase II; NCT03334617)

While assessment of the efficacy of the combination of olaparib and durvalumab is ongoing, there is sufficient safety data available to develop a safety and tolerability profile for the combination. Safety data from the ongoing MEDIOLA study (Bang et al 2019; Domchek et al 2019; Domchek et al 2018; Drew et al 2018; Krebs et al 2017) and completed

MEDI-O study (Lee et al 2017), both investigating the combination of durvalumab and olaparib, has been consistent across multiple tumor types. Observed safety and tolerability have been similar to that expected for either drug alone, with no unexpected safety signals identified to date.

In endometrial cancer, exploration of PARPi and immune checkpoint inhibitors has only recently begun. The UTOLA study (Phase IIb, NCT03745950) is evaluating olaparib monotherapy in the maintenance setting of first line endometrial cancer, and the DOMEC study (Phase II; NCT03951415) is testing the combination of olaparib with durvalumab in metastatic or recurrent endometrial cancer. There are also a number of ongoing studies evaluating the combination of other PARP inhibitors with immune checkpoint inhibitors, as well. These include:

- A phase II study of single agent niraparib (PARP inhibitor) versus niraparib with dostarlimab/TSR-042 (anti-PD-1) as a second-line treatment in endometrial (ROSCAN study; NCT03016338).
- A Phase Ib/IIa study of rucaparib (PARP inhibitor) combined with nivolumab (anti-PD 1) in advanced endometrial cancer patients (NCT03824704) (Alter et al 2019).
- A Phase II study of Avelumab (anti-PD-L1) in combination with talazoparib (PARP inhibitor) in patients with recurrent or persistent endometrial cancer (NCT02912572).
- A Phase Ib study, IOLite, investigating the dosing, safety, and efficacy of dostarlimab (anti-PD-1) in combination with niraparib (PARP inhibitor) with or without bevacizumab in advanced cancers, including endometrial tumors. Preliminary results show that dostarlimab is well tolerated in combination with niraparib with or without bevacizumab (NCT03307785) (Gabrail et al 2019).

2.3 Benefit/risk assessment

Based upon the available nonclinical, clinical efficacy and safety data, and the limited long-term efficacy provided by the currently available treatment options to patients, the investigation of the potential therapeutic efficacy of platinum-based chemotherapy (paclitaxel and carboplatin) in combination with durvalumab or in combination with durvalumab plus olaparib in patients with advanced or recurrent endometrial cancer is acceptable, and the overall benefit/risk assessment supports the proposed study design.

Both durvalumab and olaparib have regulatory approvals and well characterised safety profiles. Both agents have been extensively studied in multiple tumour types, and in combination regimens where this combination has been shown to be tolerable (Lee et al 2017, Krebs et al 2017, Domchek et al 2018, Domchek et al 2019, Bang et al 2019, Drew et al 2018). No major overlapping toxicities are expected from this regimen.

Encouraging clinical activity, combined with acceptable and manageable safety, has been seen to date with durvalumab in combination therapy studies. In a preliminary study of durvalumab in combination with weekly paclitaxel and carboplatin for the neoadjuvant treatment of ovarian cancer, no unexpected safety signals were observed (Westin, unpublished data). In general, the toxicity profiles of durvalumab and of olaparib are non-overlapping. Pneumonitis is considered to be the most important potential exception, which is considered to be a potential risk for olaparib and an identified risk for durvalumab. Presentations of pneumonitis can range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia (Teply and Lipson 2014). Early consideration of pneumonitis should be realised when patients present with new onset or worsening of respiratory symptoms such as dyspnoea or cough. Prompt treatment with steroids is important as per current established Toxicity Management Guidelines (see Section 8.2.6.2). Additional information about the frequency and risk of pneumonitis can be found in the current durvalumab and olaparib IBs. The management guidelines for pneumonitis (see Section 8.2.6.2) integrate the guidance provided for these two agents.

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 and current IBs. More detailed information about the known and expected benefits and risks of the chemotherapy agents (paclitaxel and carboplatin) can be found in the respective Package Inserts/Summaries of Product Characteristics.

See Section 9.5.2 and Appendix A for information regarding the Data Monitoring Committee.

2.3.1 Impact on Benefit/Risk from Study Disruptions due to Coronavirus Disease 2019

The emergence of the novel coronavirus disease 2019 (SARS CoV-2 / COVID-19) pandemic presents a potential safety risk for patients, and therefore several risk mitigation factors have been implemented in this study (see Section 4.5, Appendix J, and Appendix K).

3 OBJECTIVES AND ENDPOINTS

Objectives and associated endpoints are presented in Table 4.

Table 4 Study objectives and endpoints

Primary Objective	**Endpoint/Variable**
To demonstrate the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy (Arm A) by assessment of progression-free survival (PFS), in patients with newly diagnosed advanced or recurrent endometrial cancer	PFS (per RECIST 1.1 as assessed by investigator), defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression). This will be assessed via determining the efficacy of: • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance in combination with olaparib versus SoC platinum-based chemotherapy. • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance versus SoC platinum-based chemotherapy.
Secondary Objectives	**Endpoint/Variable**
To determine the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients by assessment of: PFS2, OS, ORR, DoR, TFST, TSST, and TDT	PFS2: Second progression-free survival is defined as the time from randomisation to the earliest of progression event subsequent to first subsequent therapy (assessed by the investigator per local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression), or death due to any cause. OS: Overall survival is defined as the time from the date of randomisation until death due to any cause. ORR: Objective response rate is the proportion of patients with measurable disease at baseline who have complete response (CR) or partial response (PR), as determined by the investigator at local site. DoR: Duration of response is time from the date of first documented response until date of documented progression or death in the absence of disease progression. TFST: Time to first subsequent therapy or death is time from randomisation to the earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment or death due to any cause. TSST: Time to second subsequent therapy or death is time from randomisation to the earlier of start date of the second subsequent anti-cancer therapy after discontinuation of first subsequent treatment or death due to any cause. TDT: Time to study treatment discontinuation or death is time from randomisation to the earlier of the date of study treatment discontinuation or death.
To characterise the PK and immunogenicity of durvalumab and durvalumab in combination with olaparib	Serum concentrations of durvalumab Anti-drug antibodies (ADA) to durvalumab

Table 4 Study objectives and endpoints

To determine effects on symptoms, functioning and overall health-related quality of life (HRQoL) of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy alone (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients	Change from baseline in: • Physical functioning score of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30) • Role functioning score of the EORTC QLQ-C30 • Global health status/quality of life (QoL) score of the EORTC QLQ-C30 • All other functioning and symptom subscale scores of the EORTC QLQ-C30 (excluding the financial subscale) Time to deterioration in: • Physical functioning score of the EORTC QLQ-C30 • Role functioning score of the EORTC QLQ-C30 • Back/pelvic pain of the EORTC QLQ-EN24 • Gastrointestinal (GI) symptoms of the EORTC QLQ-EN24 • Urological symptoms of the EORTC QLQ-EN24
Safety Objective	**Endpoint/Variable**
To evaluate the safety and tolerability of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) compared to platinum-based chemotherapy (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients	Safety and tolerability will be evaluated in terms of AEs/serious AEs (SAEs), physical examination, vital signs including blood pressure, pulse, clinical laboratory including clinical chemistry/haematology parameters, and ECG Assessments related to AEs cover: • Occurrence/frequency • Relationship to investigational product (IP) as assessed by investigator • Common Terminology Criteria for Adverse Event (CTCAE) grade • Seriousness • Death • Discontinuation of IP • Dose modifications during the chemotherapy phase and the maintenance phase • AEs of special interest (AESIs) • Other significant AEs • Exposure • Immune-mediated adverse events (imAEs) – given the intended mechanisms of action of durvalumab, particular attention will be given to AEs that may follow enhanced T cell activation, or other imAE

Table 4 Study objectives and endpoints

Exploratory Objectives	Endpoint/Variable
To determine the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab in combination with olaparib (Arm C) when compared to durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) in patients with newly diagnosed advanced or recurrent endometrial cancer	Will include, but is not limited to: • PFS (per RECIST 1.1 as assessed by investigator) • OS
To evaluate tumour predictive biomarkers of durvalumab and olaparib in advanced endometrial cancer patients	CCI
To evaluate additional tumour candidate predictive biomarkers of durvalumab and olaparib in advanced endometrial cancer patients	
To further assess the efficacy of treatment through longitudinal analysis of blood samples collected at regular intervals on study	
To explore whether resistance mechanisms to treatment can be identified through analysis of tumour and blood samples – archival tumour sample and blood samples at baseline and on progression (tumour sample optional on progression)	Analysis and outcome variables yet to be defined CCI CCI
Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored blood or archival tumour samples that were mandatory for entry onto the study or on optional blood or tumour biopsy samples collected during the course of the study.	Analysis and outcome variables yet to be defined.
To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional) [a]	To identify pharmacogenetic correlates for the response to treatment through the retrospective analysis of DNA extracted from an optional blood sample.

Table 4 Study objectives and endpoints

To explore health status of patients with durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of health status by the assessment of • Health state utility derived from the EuroQoL five dimensions, five level health state utility index (EQ-5D-5L) • Quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) • Quality-adjusted PFS (QAPFS)
To explore patient-reported treatment tolerability with durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of selected symptoms from the patient-reported outcomes version of the CTCAE (PRO-CTCAE) and overall treatment tolerability using the patient global impression of treatment tolerability (PGI-TT).
To explore patient-reported severity of cancer symptoms, change in overall health condition, and overall benefit/risk evaluation for durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of patient global impression of severity of cancer symptoms (PGIS), change in health condition (PGIC), and overall perception of benefit/risk (PGI-BR).
To explore healthcare resource associated with durvalumab and olaparib in advanced endometrial cancer patients	Key healthcare resource use will be collected using HOSPAD

[a] These endpoints may be reported separately to the clinical study report.

4 STUDY DESIGN

4.1 Overall design

This is a randomised, double-blind, placebo controlled, multicentre Phase III study to evaluate the efficacy, safety, and patient reported outcomes of durvalumab in combination with platinum-based chemotherapy (carboplatin and paclitaxel) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer compared to platinum-based chemotherapy. AstraZeneca considers that the endometrial cancer patient population involved in this study falls under the advanced cancer, limited life expectancy definition outlined in ICH S9 guideline "Non-clinical Evaluation For Anticancer Pharmaceuticals" and meets the requirements outlined in the guideline. The primary endpoint of this study will be progression-free survival (using investigator assessment of scans according to RECIST 1.1; see Appendix G for details). Secondary endpoints will include OS, PFS2, ORR, DoR, TFST, TSST, and TDT. For an overview of the study design see Figure 2, Section 1.3.

As part of the global recruitment, approximately 699 patients will be randomised in a 1:1:1 ratio to the study treatments specified below (N=233 patients per arm). If necessary, enrolment in China will continue after global enrolment is closed (ie, last subject randomised from a non-China site) to allow inclusion of a China cohort consisting of approximately 129 patients randomised in a 1:1:1 ratio from sites in China. Any patient from China randomised before the global recruitment is closed will be included in the global population.

- **Arm A (control):** Platinum-based chemotherapy (paclitaxel and carboplatin) with durvalumab placebo (IV) during the chemotherapy phase. Patients who achieve and maintain disease control (ie, complete response [CR], partial response [PR], or stable disease [SD]) during the chemotherapy phase will receive durvalumab placebo (IV) and olaparib placebo (tablets) in the maintenance phase.
- **Arm B (durvalumab+placebo):** Platinum-based chemotherapy (paclitaxel and carboplatin) with durvalumab (IV) during the chemotherapy phase. Patients who achieve and maintain disease control (ie, CR, PR, or SD) during the chemotherapy phase will receive durvalumab (IV) with olaparib placebo (tablets) in the maintenance phase.
- **Arm C (durvalumab+olaparib):** Platinum-based chemotherapy (paclitaxel and carboplatin) with durvalumab (IV) during the chemotherapy phase. Patients who achieve and maintain disease control (ie, CR, PR, or SD) during the chemotherapy phase will receive durvalumab (IV) with olaparib (tablets) in the maintenance phase.

For details on treatments given during the study, see Section 6.1.

Patients should be randomised and begin treatment on Day 1. The randomisation scheme will be stratified according to:

- **Tumour tissue's mismatch repair (MMR) status**: Patients with MMR deficient tumours versus those with proficient tumours. Tumour MMR status will be determined prior to randomisation based on evaluation of MMR status in tumour cells from a formalin-fixed, paraffin-embedded (FFPE) tumour tissue sample, using the Ventana immunohistochemistry (IHC) MMR panel.
- **Disease status**: Patients with recurrent disease versus those newly diagnosed.
- **Geographic region**: Asia versus rest of the world (RoW).

Patients will receive platinum-based chemotherapy and durvalumab/placebo for a maximum of 6 cycles. Patients who have no evidence of PD (per RECIST 1.1) will then receive durvalumab/placebo (same treatment as during chemotherapy phase) and olaparib/placebo during the maintenance phase.

Patients must meet the eligibility criteria for organ and bone marrow function and creatinine clearance after the last cycle of chemotherapy (see Section 5.3) to start maintenance treatment with olaparib/placebo. Maintenance treatment will start a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion and continue until objective disease progression (per RECIST 1.1).

Patients in all treatment arms will have tumour assessments according to RECIST at baseline (no more than 28 days prior to randomisation), every 9 weeks (±1 week) after the date of randomisation for 18 weeks, and every 12 weeks (±1 week) thereafter, until objective radiological disease progression according to RECIST 1.1.

All scans performed as disease assessment need to be made available to an AstraZeneca appointed clinical research organisation (CRO) for blinded independent central review (BICR) upon request. After the primary PFS analysis, central review of scans will no longer be required.

All patients will continue to be assessed for radiological tumour assessments according to the study schedule, until objective radiological disease progression, irrespective of any treatment delays or discontinuation of study treatment.

Once a patient has progressed the patient will be followed as per local clinical practice, but assessment should be made every 12 weeks for second progression, and survival status assessed every 2 months, until the final analysis of the study.

Patients will complete HRQoL and other PRO questionnaires at home, and sometimes at site, using an electronic device (ePRO). Patients will be issued with the ePRO device and given training on how to use it at the Cycle 1 Day 1 visit.

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

An IDMC will review unblinded safety data at regular intervals during the study (see Section 9.5.2).

4.2 Scientific rationale for study design

Treatment rationale

Poly (ADP-ribose) polymerase inhibitors (olaparib) and immune checkpoint inhibitors (durvalumab) are established cancer therapies and there is growing evidence that these therapies can be combined to gain synergistic antitumour effects while minimising the potential for significant side-effects. This study will assess the efficacy and safety of durvalumab and olaparib when added to platinum-based chemotherapy (paclitaxel and carboplatin) and/or as maintenance therapy in patients with newly diagnosed advanced or recurrent endometrial cancer.

Overall study design

The study is of a standard design for Phase III clinical trials, including double-blind randomisation and placebo control arms for both durvalumab and olaparib, so that the contribution of each agent can be assessed without bias.

The primary objectives of the study are to compare PFS (per RECIST 1.1 as assessed by investigator) in the durvalumab+placebo arm versus the control arm, and durvalumab+olaparib arm versus the control arm.

Study population

The eligibility criteria are designed to recruit a patient population that is representative of an advanced/recurrent endometrial cancer population, eligible for treatment with first-line platinum-based chemotherapy. Tumour markers will not be used for determining patient eligibility, but they will be used to allow for stratification by MMR status. Other CCI CCI CCI CCI markers CCI CCI will also be tested retrospectively to determine whether there is any differential clinical activity in patients with specific biomarkers. Evolving knowledge on the role of durvalumab or olaparib treatment in endometrial cancer from other ongoing clinical trials may also help to inform the study of additional biomarkers to evaluate in this study.

Stratification by MMR status

Defects in Mismatch Repair, known as MMR loss/deficiency is observed across various tumour types. In advanced endometrial cancer, approximately 15% of patients have an MMR-deficiency. Multiple institutions in the US have initiated testing all patients with a histologically-confirmed diagnosis of endometrial cancer (universal tumour testing) for MMR or MSI. MMR-deficiency can be detected by IHC staining, typically for the loss of expression of any of the 4 most common MMR proteins: MutL homologue 1 (MLH1), MutS protein homologue 2 (MSH2), MutS protein homologue 6 (MSH6), and PMS1 protein homologue 2 (PMS2). Loss of expression by IHC of any MMR protein suggests the possibility of a germline mutation in the corresponding MMR gene. Patients with such pathogenic germline MMR mutations suffer from Lynch Syndrome. The NCCN guidelines recommend screening for MMR-deficiency in all patients with endometrial cancers to identify individuals at risk for Lynch Syndrome. As highlighted in previous section, preliminary data suggest that agents targeting the PD-1 pathway leads to remarkable clinical responses in patients with endometrial cancers that are MMR-deficient tumours and, to a lesser extent, with MMR-proficient tumours, therefore providing the rationale to stratify based on MMR status.

Stratification by disease status

This study will enrol patients with newly diagnosed Stage III/ IV and recurrent endometrial cancer. Generally, recurrent disease shows a lower response rate to treatment and poorer prognosis compared to newly diagnosed cancer. Furthermore, patients with recurrent cancer may have unresolved toxicity from previous anti-cancer treatment and more comorbidities due to longer duration of disease which make them frailer than newly diagnosed patients.

Due to these differences, the randomisation will incorporate disease status as a stratification factor.

Stratification by geographic region

Patients with advanced disease (Stage III, IV, or recurrent) may receive a combination of surgery, radiotherapy, and systemic therapy depending on the extent of disease and geographic region. For example, in some Asian countries such as Japan, locally advanced disease is managed primarily by surgery with or without adjuvant chemotherapy. In contrast, in Western Europe and the United States, systemic therapy with or without radiation is a more common treatment option for these patients. In the metastatic setting, systemic chemotherapy alone is the most common treatment option for patients in all regions. However, Japanese physicians often utilize systemic therapy with surgery for Stage IV patients, while there is less emphasis on surgery for patients with metastatic disease in Western Europe and the United States (Kantar Health Report 2018).

The use of radiotherapy also appears to be different in Asia where radiotherapy is used less often. Recent data from the PORTEC I and II trials suggest that, while adjuvant radiotherapy has been shown to help provide locoregional control of endometrial cancer, it does not significantly improve long-term outcomes (Creutzberg et al 2000, Nout et al 2010). In spite of these relatively recent findings, many western physicians still use adjuvant radiotherapy to treat patients with advanced endometrial cancer.

The differences in the use of surgery and/or radiation in the treatment of advanced endometrial cancer reflect regional preferences in terms of optimal treatment for these patients. These differences have the potential to significantly impact both short-term and long-term outcomes. As this study is in intended to be a global trial, it is imperative to minimise these regional differences which could potentially imbalance the study. Thus, the randomisation scheme will incorporate geographic region as a stratification factor to account for possible differences in treatment paradigms for advanced endometrial cancer patients.

Choice of primary endpoint

Regulatory guidance indicates PFS can be considered an acceptable endpoint for demonstrating clinical benefit in settings such as first-line endometrial cancer, provided it is of sufficient magnitude. The size of PFS benefit that this study aims to detect (an improvement in median PFS of 5.1 months in the durvalumab arm over 12 months median PFS in the control arm (HR 0.70) and an improvement in median PFS of 9.8 months in the durvalumab+olaparib arm (HR 0.55) is considered of sufficient magnitude to support PFS as the primary endpoint. The FDA “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry” (FDA 2018) states PFS is an endpoint that can be used for regulatory approval, dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. The European Medicines Agency “Guideline on the evaluation of anticancer medicinal products in man” (CHMP 2017), proposes PFS is an acceptable primary endpoint for oncology clinical trials, since prolonged

PFS is considered to be of benefit to the patient. Similarly, the Society for Gynecologic Oncology consensus 2014 (Herzog et al 2014) also considered statistically significant PFS alone as acceptable when the clinical magnitude of effect is meaningful, especially for disease states with anticipated long post-progression survival times such as first-line patients, as is the case for this study (in which median PFS with platinum-based chemotherapy is expected to be approximately 12 months and median OS approximately 23 months). In addition to a statistically significant difference, other means of benefit would need to be demonstrated such as significant difference in time off therapy, or at least an OS trend. Additional supportive evidence that the clinical benefit indicated by PFS is maintained beyond first progression can be demonstrated by the intermediate endpoints of PFS2, TFST and TSST (Matulonis et al 2015).

In order to ensure the robustness and reliability of the PFS endpoint, centralised image interpretation of PFS is critical in settings where investigator assessment is subject to bias that may occur in an unblinded study. However, because this is a double-blind study with both durvalumab infusions and olaparib tablets blinded, investigator assessment can provide an unbiased determination of PFS. The centralised independent verification of PFS will be retained as a supportive analysis and will give confidence that bias in investigator assessment between treatment arms has not occurred.

In summary, PFS is considered an appropriate primary endpoint for this study in the first-line endometrial cancer setting, where there is a high unmet medical need, the anticipated PFS benefit is of sufficient magnitude, and long post-progression survival times are expected. BICR assessments are not expected to produce more robust results than investigator-assessed PFS. Therefore, the PFS primary endpoint of this study will be analysed using investigator assessment by RECIST, and performing a sensitivity analysis using BICR.

Patient reported outcomes

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 trials. PRO questionnaires will be used in this study that have been validated and are widely recognised.

Pharmacokinetics

Pharmacokinetics and anti-drug antibodies will be assessed for durvalumab since this is the first clinical trial of durvalumab in patients with endometrial cancer.

Olaparib PK will not be assessed in this trial since it is now well characterised and there are no data to suggest that patients exposed to olaparib in this trial would be different from the previous oncology studies (eg, no PK interaction between olaparib and durvalumab, no tumour type effect on olaparib PK). Furthermore, the benefit:risk ratio of olaparib 300 mg bd is well established across indications.

4.3 Justification for dose

4.3.1 Durvalumab

For ease of use and convenience to investigators and patients, durvalumab will be administered Q3W in the chemotherapy phase to align with the treatment interval of the platinum-based chemotherapy, and will use a fixed dose of 1120 mg (based on an average body weight of 75 kg, this is equivalent to a weight-based dose of 15 mg/kg Q3W).

A population PK analysis has indicated that body weight has a minor impact on the PK of durvalumab and subsequent modelling demonstrated that body-weight-based and fixed dosing regimens yield similar median steady-state PK concentrations. Based on a median body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is currently being administered in numerous clinical studies across multiple tumour types. Durvalumab 1500 mg Q4W dosing was convincingly supported by the National Cancer Institute (NCI) Study ESR-14-10366 (hereafter referred to as the "NCI study"; Lee et al 2017). This dosing regimen is equivalent to a fixed dose of 1120 mg Q3W and was chosen for the maintenance phase of this study, to align with other studies.

The 2 durvalumab dosing schedules used in this study (1120 mg Q3W in the chemotherapy phase and 1500 mg Q4W in the maintenance phase) are equivalent to administering 10 mg/kg Q2W as recommended in the label.

Please note, if a patient's weight falls to 30 kg or below (≤30 kg) during the maintenance phase, then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W.

4.3.2 Olaparib

Olaparib will be administered at the dose approved for use in ovarian and breast cancer, ie 300 mg bd. Dose reductions will be permitted, according to the Prescribing Information.

4.3.3 Durvalumab and olaparib combination

Durvalumab and olaparib have been administered in combination in a range of indications, including ovarian, breast, SCLC and gastric cancers (MEDIOLA; NCT02734004). The safety and tolerability of olaparib 300 mg bid in combination with durvalumab 1500 mg Q4W is convincingly supported by the NCI study (Lee et al 2017).

4.4 End of study definition

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

- European Union requirements define study completion as the last visit of the last patient for any protocol related activity.
- Food and Drug Administration requirements defines 2 completion dates:
  - Primary Completion Date – the date that the final patient is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.
  - Study Completion Date – is defined as the date the final patient is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last patient's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A patient is considered to have completed the study if she has completed all phases of the study including her last scheduled visit shown in the SoA (Section 1.1).

Patients may be withdrawn from the study if the study itself is stopped. The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely on the recommendation of the IDMC or if concerns for safety arise within this study or in any other study with durvalumab or olaparib.

See Section 6.7 for information regarding treatment with durvalumab and/or olaparib after the end of the study.

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

4.5 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis

The guidance given below supersedes instructions provided elsewhere in this clinical study protocol (CSP) and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home or Remote delivery of olaparib/placebo.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix J. For further guidance during the COVID-19 pandemic, refer to Appendix K.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. MMR re-testing may be permitted in the case of technical failure (see Section 8.8.1), however, all eligibility criteria must still be met within the required timeframes prior to randomisation.

5.1 Pre-screening eligibility check

Inclusion and exclusion criteria to be checked at pre-screening are marked with an asterisk (*) in Sections 5.4 and 5.5.

5.2 Eligibility for randomisation

Each patient should meet all of the inclusion criteria and none of the exclusion criteria in order to be randomised to study treatment. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; each patient

may be rescreened a single time if necessary, but only if the patient has not already been randomised to study treatment (see Section 5.7 for details).

In this protocol, enrolled patients are defined as those who sign the informed consent form. Randomised patients are defined as those who undergo randomisation and receive a randomisation number.

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

Patients are eligible to be included in the study only if all of the inclusion criteria (Section 5.4) and none of the exclusion criteria (Section 5.5) apply.

5.3 Eligibility for the maintenance phase

Patients should receive a maximum of 6 cycles of chemotherapy and must have a minimum of 4 cycles of platinum-based chemotherapy to continue into the maintenance phase.

Following completion of chemotherapy, durvalumab/placebo dosing schedule will change to 1500 mg Q4W (per Table 5). Patients will also receive olaparib/placebo treatment following completion of chemotherapy (treatment will commence a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion).

The patient MUST meet the following requirements within 3 days prior to dosing in order to receive olaparib/placebo:

- Adequate organ and bone marrow function, defined as:
  - Haemoglobin (Hb) ≥10.0 g/dL, with no blood transfusion in the past 28 days
  - Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
  - Platelet count ≥100 × 10^9/L
  - Total bilirubin ≤1.5 × institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed to participate in the study, in consultation with their physician.
  - Aspartate aminotransferase (AST) / Alanine aminotransferase (ALT) ≤2.5 × institutional ULN unless liver metastases are present in which case they must be ≤5 × institutional ULN.

- Creatinine clearance (CrCL) of ≥51 mL/minute, estimated using either the Cockcroft-Gault equation, a 24-hour urine test or another validated test as per local practice:

  $$\text{Estimated CrCL (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

- It must be confirmed that patients are not receiving any prohibited concomitant medications (see Section 6.5) in order to receive treatment with olaparib/placebo.

Note: If a patient cannot start olaparib/placebo maintenance within 9 weeks from the last day of chemotherapy infusion, the patient should continue durvalumab/placebo at 1500 mg Q4W (durvalumab/placebo should also continue during the 3 to 9 week window after the last day of chemotherapy infusion, if the olaparib/placebo start criteria have not yet been met).

5.4 Inclusion criteria

Age and gender

1. *Age ≥18 years at the time of screening and female.

Informed consent

2. *Capable of giving signed informed consent (as described in Appendix A 3) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Provision of signed and dated, written informed consent form prior to any mandatory study-specific procedures, sampling, and analyses is also required, in accordance with Appendix A 3. For patients aged <20 years and enrolling in Japan, a written informed consent should be obtained from the patient and her legally acceptable representative. All patients must sign both the pre-screen ICF and main ICF (however are not required to sign the optional Genomics Initiative ICF):

    a) The pre-screen ICF for the mandatory provision of tumour sample and biomarker testing, including central MMR testing.
    b) The main ICF for participation in the study. The main consent form also includes a separate consent question for the exploratory biomarker research component of the study (which includes an optional tumour biopsy). If a patient declines to participate in the optional exploratory biomarker research, there will be no penalty or loss of benefit to the patient and the patient will not be excluded from other aspects of the study.
    c) For inclusion in the optional Genomics Initiative, patients must provide informed consent for optional genetic research prior to collection of the blood sample. If a patient declines to participate in this research, there will be no penalty or loss of benefit to the patient, and the patient will not be excluded from other aspects of the study.

Disease characteristics

3. *Histologically confirmed diagnosis of epithelial endometrial carcinoma. All histologies, including carcinosarcomas, will be allowed. Sarcomas will not be allowed.

4. Patient must have endometrial cancer in one of the following categories:

    a) Newly diagnosed Stage III disease (measurable disease per RECIST 1.1 following surgery or diagnostic biopsy),

b) Newly diagnosed Stage IV disease (with or without disease following surgery or diagnostic biopsy)

c) Recurrence of disease (measurable or non-measurable disease per RECIST 1.1) where the potential for cure by surgery alone or in combination is poor.

5. *Naïve to first-line systemic anti-cancer treatment. For patients with recurrent disease only, prior systemic anti- cancer treatment is allowed only if it was administered in the adjuvant setting (as part of the upfront/adjuvant anti-cancer treatment, which may be concurrent or followed with chemoradiation) and there is at least 12 months from date of last dose of systemic anti- cancer treatment administered to date of subsequent relapse.

6. *An FFPE tumour sample from the locoregional or a metastatic site must be available and must be suitable for MMR status evaluation using the Ventana MMR IHC panel. In compliance with local regulations, all patients must provide consent for the tumour sample and for MMR testing. The sample must be shipped during the pre-screening period and valid MMR test results (proficient/deficient) MUST be available prior to randomisation at Cycle 1 Day 1 (see Section 8.8.1).

7. Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days of starting study treatment

8. Must have a life expectancy of at least 16 weeks.

Reproductive status

9. Postmenopausal or evidence of nonchildbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of Cycle 1 Day 1 and confirmed prior to treatment on Cycle 1 Day 1. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

   – Women <50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments, and if they have LH and FSH levels in the post-menopausal range for the institution.

   – Women ≥50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

   – Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Weight

10. Body weight >30 kg.

Organ function

11. Adequate organ and bone marrow function, defined as:

    - Haemoglobin ≥10.0 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). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN.

12. Measured creatinine clearance (CrCL) >51 mL/min or calculated creatinine clearance (CrCL) >51 mL/min as determined by Cockcroft-Gault (using actual body weight), a 24-hour urine test or another validated test as per local practice:
    Estimated CrCL (mL/min) = $\frac{(140\text{-age [years]}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$

5.5 Exclusion criteria

Medical history

1. *Any unresolved toxicity National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE version 5.0) Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria. Note:

    - Patients with Grade ≥2 neuropathy may be included only 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.

2. Major surgical procedure (as defined by the investigator) within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery. Note: Local surgery of isolated lesions for palliative intent is acceptable or diagnostic staging.

3. *History of allogenic organ transplantation.

4. *Previous allogenic bone marrow transplant or double umbilical cord blood transplantation.

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

   – Patients with vitiligo or alopecia

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

   – Any chronic skin condition that does not require systemic therapy

   – Patients without active disease in the last 5 years may be included but only after consultation with the study physician

   – Patients with coeliac disease controlled by diet alone.

6. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension (systolic blood pressure >160 mmHg; diastolic blood pressure >100 mmHg), unstable angina pectoris, cardiac arrhythmia, interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

7. *History of another primary malignancy except for:

   – Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence

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

   – Adequately treated carcinoma in situ without evidence of disease.

8. *History of leptomeningeal carcinomatosis.

9. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have a magnetic resonance imaging (MRI) (preferred) or computed tomography (CT) each preferably with IV contrast of the brain prior to study entry.

10. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg, unstable ischaemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation ≥500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.

11. *History of active primary immunodeficiency.

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

13. *Myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML.

Prior/concomitant therapy

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

15. *Prior treatment with PARP inhibitors.

16. * Any prior exposure to immune-mediated therapy, including (but not limited to) other anti CTLA-4, anti-PD-1, anti-PD-L1, or anti–programmed-cell-death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.

17. *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. Prior hormonal therapy for cancer treatment must be stopped at least 7 days prior to first dose of study treatment.

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

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

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

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

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

20. Concomitant use of known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks.

21. 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, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

Prior/concurrent clinical study experience

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

23. Previous IP assignment in the present study.

24. Participation in another clinical study with an investigational product administered in the last 12 months or concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

Other exclusions

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

26. *Unable to swallow orally administered medication.

27. *Any gastrointestinal disorder likely to interfere with absorption of the study medication.

28. Pregnant or breastfeeding.

29. Patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after last dose of study intervention or 6 months after the last dose of olaparib/placebo, whichever is later.

30. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

5.6 Lifestyle restrictions

5.6.1 Meals and dietary restrictions

The consumption of grapefruit juice is prohibited while on olaparib/placebo therapy, ie, from the start of the maintenance phase.

For information on concomitant medications, please refer to Section 6.5.

5.6.2 Contraception

Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a nonsterilised male partner must agree to the use of at least one highly effective form of contraception (as described in Appendix F), and their partners must use a male condom or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix F). This should be started from the signing of the main informed consent and continue throughout the period of taking study treatment and for at least 90 days after the last dose of study intervention or 6 months after the last dose of olaparib/placebo, whichever is later.

Please note that local guidelines and recommendations for administration of standard of care chemotherapy should always be followed, and may indicate continuation of contraception measures for a period longer than described above.

Non-sterilised male partners of a female patient of childbearing potential must use male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

For details of highly effective methods of contraception refer to Appendix F.

Please note, women 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 amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have LH and FSH levels in the post-menopausal range for the institution.
- Women ≥50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

5.6.3 Blood donation

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of study treatment(s).

5.6.4 Concomitant medications

Restrictions relating to concomitant medications are described in Section 6.5.

5.7 Screen failures

Screen failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised.

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

Rescreening will be allowed if the patient fails on any eligibility criteria, which subsequently resolves. If a patient who has failed screening is re-screened, a new E-code must not be assigned.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs). Data for screen-failed patients collected up to this time will be reported in the database.

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomised 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 randomised or started on treatment, and must be withdrawn from the study. These patients

should have the reason for study withdrawal recorded in the electronic case report form (eCRF).

5.7.1 Avoiding screen failures due to MMR testing

A pre-screening period is included in the study design to ensure that MMR status via central testing can be determined prior to randomisation.

A valid central MMR test result is required for stratification prior to randomisation (see inclusion criterion 6). If the central MMR testing cannot be completed due to technical failure, additional tumour samples may be sent to the laboratory for an MMR re-test. However, if the central MMR testing cannot be completed by the end of the 28-day screening period, patients must be re-screened to ensure adequate time for MMR re-testing and all other eligibility criteria; in particular, patients must still meet the criteria for organ and bone marrow function (inclusion criterion 11) and creatinine clearance (inclusion criterion 12) prior to starting study treatment. Patients requiring an MMR re-test must also have a baseline CT scan within 28 days prior to Cycle 1 Day 1.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) and non-investigational product(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 chemotherapy, durvalumab/placebo and olaparib/placebo. Study treatments are summarised in Table 5.

Patients should receive platinum-based chemotherapy and durvalumab/placebo for the first 6 cycles (minimum of 4 cycles). Patients without evidence of PD (per RECIST 1.1) will receive durvalumab/placebo and olaparib/placebo during the maintenance phase.

Table 5 Study treatments

	Arm A	Arm B	Arm C
Chemotherapy phase treatment	carboplatin/paclitaxel chemotherapy + durvalumab placebo Q3W	carboplatin/paclitaxel chemotherapy + durvalumab 1120 mg Q3W	carboplatin/paclitaxel chemotherapy + durvalumab 1120 mg Q3W
Maintenance phase treatment	durvalumab placebo Q4W + olaparib placebo tablets twice daily	durvalumab 1500 mg Q4W + olaparib placebo tablets twice daily	durvalumab 1500 mg Q4W + olaparib 300 mg tablets twice daily
Route of administration	IV durvalumab placebo / oral olaparib placebo	IV durvalumab / oral olaparib placebo	IV durvalumab / oral olaparib
Duration of study treatment	Until objective disease progression (PD)	Until objective disease progression (PD)	Until objective disease progression (PD)

Abbreviations: IV = intravenous; Q3W = every 3 weeks; Q4W = every 4 weeks.

During the chemotherapy phase, the intravenous study treatments should ideally be administered on the same day and in the following order:

1. **Durvalumab/placebo**

   Durvalumab dose of 1120 mg (Q3W) should be administered over 1 hour, however if there are interruptions during infusion, the total infusion time should not exceed 8 hours at room temperature.

2. **Paclitaxel**

   175 mg/m^2 by IV infusion over 3 hours.

3. **Carboplatin**

   AUC5 or AUC6 by IV infusion over 1 hour (or in accordance with local practice).

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca will supply durvalumab/placebo solutions, and olaparib/placebo tablets. Durvalumab placebo vials will be identical in appearance to durvalumab vials. Olaparib placebo tablets will be identical in appearance to olaparib tablets.

Refer to Table 6 for information on investigational study treatments.

Dose reductions for toxicity are only permitted for olaparib; the dose of durvalumab can be delayed for toxicities, but dose reductions are not allowed (see Section 6.6).

Table 6 Investigational study treatments

	Olaparib	Durvalumab
Study treatment name:	olaparib/placebo	durvalumab/placebo
Dosage formulation:	300 mg olaparib/placebo (2 × 150 mg olaparib/placebo tablets) bd 100 mg olaparib/placebo tablet available if dose reductions are required	1120 mg durvalumab/placebo Q3W for a maximum of 6 cycles, followed by 1500 mg durvalumab/placebo Q4W 500 mg vial containing a 50 mg/mL solution for IV infusion after dilution
Route of administration:	Oral	IV
Dosing instructions:	Two × 150 mg olaparib/placebo tablets should be taken twice daily at the same times each day, approximately 12 hours apart with one 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. If vomiting occurs shortly after the study treatment	Durvalumab/placebo should be administered prior to dosing with chemotherapy. The dose of durvalumab/placebo for administration must be prepared by the investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab/placebo vial to the start of administration should not exceed: • 24 hours at 2°C to 8°C (36°F to 46°F)

Table 6 Investigational study treatments

	Olaparib	Durvalumab
	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.	• 4 hours at room temperature A dose of 1120 mg/placebo (chemotherapy phase) or 1500 mg/placebo (maintenance phase) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 22.4 mL (chemotherapy phase) or 30.0 mL (maintenance phase) of durvalumab/placebo (ie, 1120 mg or 1500 mg of durvalumab, respectively) 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 a patient's weight falls to ≤ 30 kg during the maintenance phase, weight-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 concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Standard infusion time is 1 hour, however if 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. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab/placebo do not contain preservatives, and any unused portion must be discarded.

Table 6 Investigational study treatments

	Olaparib	Durvalumab
Packaging and labelling	Study treatment will be provided in HDPE bottles with child-resistant closures. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% w/v polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The placebo contains 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% w/v polysorbate 80; it has a pH of 6.0. The nominal fill volume for durvalumab and placebo is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.
Provider	AstraZeneca	AstraZeneca

Abbreviations: bd = twice daily; GMP = Good Manufacturing Practice; HDPE = high-density polyethylene; IP = investigational product; IV = intravenous; IWRS = interactive web response system; Q3W = every 3 weeks; Q4W = every 4 weeks; w/v = weight/volume.

6.1.2 Non-investigational products

The chemotherapy agents (paclitaxel and carboplatin) will either be locally sourced or, under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug, which will be labelled in the local language in accordance with regulatory guidelines. In the EU, carboplatin and paclitaxel are considered auxiliary medicinal products according to EU clinical trials guidance (EU Guidance 2017).

Chemotherapy is a "non-investigational drug" as it is a recommended SoC in international guidelines. Chemotherapy will be administered in accordance with the recommendation of this treatment combination in international guidelines (NCCN Uterine Neoplasms 2019).

Platinum-based chemotherapy should continue for a maximum of 6 cycles. If required due to toxicity, 4 cycles of platinum-based chemotherapy may be given as a minimum.
Chemotherapy dosing will be as follows:

- Carboplatin (AUC5 or AUC6) Q3W (Note: Dose reduction to AUC5 may be considered for patients who had prior pelvic radiotherapy)
- Paclitaxel 175 mg/m^2 Q3W.

Each chemotherapy agent will be administered in accordance with local guidelines and premedication may be provided.

For carboplatin dosing recommendations please refer to NCCN guidelines https://www.nccn.org/professionals/OrderTemplates/PDF/appendix_B.pdf. As per NCCN guidance, to avoid overestimation of CrCL and subsequent overestimation of carboplatin dose, in patients with low serum creatinine, the creatinine clearance should be estimated using a minimum value of 0.7 mg/dL (equivalent to 62 µmol/L). The Calvert Formula should be used to calculate the dose of carboplatin as shown:

Carboplatin dose (mg) = target AUC × (GFR + 25)

NOTE: It is recommended that the GFR used in the Calvert formula should not exceed 125 mL/min. For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance.

Maximum carboplatin dose (mg) = target AUC (mg/mL × min) × 150 mL/min

The maximum recommended doses of carboplatin are:

- AUC6 = 900 mg
- AUC5 = 750 mg

If chemotherapy is permanently discontinued early (prior to completing 4 cycles) as a result of toxicities or disease progression, all study treatments will be discontinued, and the patient will not enter the maintenance phase. A study treatment discontinuation visit will be conducted, and follow-up will continue unless the patient withdraws consent to continue in the study.

Patients who develop a hypersensitivity reaction to carboplatin should be managed according to standard clinical practice. Patients may be retreated as per local clinical guidance including increased hypersensitivity prophylaxis or using desensitising protocols. If hypersensitivity prevents further administration of carboplatin, substitution with cisplatin may be considered for patients, provided this aligns with standard clinical practice at the site and only where the chemotherapy is locally sourced. Substitution with cisplatin should be discussed with the AstraZeneca study physician before implementing.

Patients who develop a hypersensitivity reaction to paclitaxel should be managed according to standard clinical practice. Patients may be retreated as per local clinical guidance depending on the severity of the reaction. In cases of recurrent hypersensitivity reaction, despite adequate premedication, preventing further dosing of paclitaxel, the investigator may consider omitting paclitaxel from the chemotherapy regimen or substituting with another taxane (nab-paclitaxel or docetaxel) provided this aligns with standard clinical practise at the site and only where the chemotherapy is locally sourced.

Patients who develop chemotherapy induced peripheral neuropathy should be managed according to standard clinical practice. Dose of chemotherapy may be reduced as per local clinical guidance. If permanent discontinuation of paclitaxel is required due to persistent

significant peripheral neuropathy, substitution with docetaxel may be considered for patients, provided this aligns with standard clinical practice at the site, and only where the chemotherapy is locally sourced.

Any substitution of the protocolled chemotherapy should be discussed with the AstraZeneca study physician before implementing.

6.1.3 Duration of treatment and criteria for treatment after initial assessment of PD

Study treatment will start on Cycle 1 Day 1. Patients who do not have any evidence of radiological disease progression during the chemotherapy phase will continue to receive randomised durvalumab/placebo and olaparib/placebo during the maintenance phase. Patients will continue to receive study treatment until radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

In the rare instances when the RECIST 1.1-defined radiological findings are considered equivocal by the investigator or there is doubt whether or not there is evidence of objective progression (eg, technical issues including image artefacts), a follow-up scan should be performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD. If the repeat scan confirms progression, study treatment must be discontinued and the date of the initial scan should be declared as the date of PD. If the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST 1.1-defined PD.

Study treatment may be administered until radiological PD is confirmed by the subsequent scan, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, or spinal cord compression) will not be eligible to continue study treatment.

Post final data cut off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician considers they are gaining clinical benefit (see Section 6.7). For patients continuing to receive study treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and investigators monitor the patients' safety laboratory results prior to and periodically during treatment in order to manage AEs; this is in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving study 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.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may dispense study treatment. At site, all study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposal of unused study treatment are provided in the Laboratory Manual.

6.3 Measures to minimise bias: randomisation and blinding

6.3.1 Patient enrolment and randomisation

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

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

Prior to randomisation, the investigators or suitably trained delegate will:

- Obtain tumour sample and send for centralised MMR testing. Obtaining the tumour biopsy sample should be given the highest priority and, as such, the sample may be obtained and sent for MMR expression status evaluation prior to the 28-day screening window (after obtaining a separate, signed pre-screen ICF) in order to permit analysis prior to randomisation. Other screening activities may be conducted while MMR status is being assessed. MMR status must be available in the IVRS/IWRS in order for the patient to be randomised, as it is a stratification factor.
- Obtain a unique 7-digit enrolment number (E-code), through the IVRS/IWRS in the following format PPD PPD This number is the patient's unique identifier and is used to identify the patient on the eCRFs.

- Obtain signed informed consent before any further study specific procedures are performed. If laboratory or imaging procedures were performed for alternative 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 randomisation. For patients with a single target lesion, if a screening biopsy is collected prior to screening imaging for baseline tumour assessment, allow approximately 2 weeks before imaging scans are acquired.
- Determine patient eligibility (see Sections 5.4 and 5.5)
- Obtain signed informed consent for Genomics Initiative (optional)

At randomisation, once the patient is confirmed as eligible, the investigator or suitably trained delegate will:

- Obtain a unique randomisation number via the IVRS/IWRS. Numbers will start at 001 and will be assigned PPD by IVRS/IWRS as patients are eligible for entry into the study. The system will randomise the eligible patient to 1 of the 3 treatment groups. (MMR status results must be received from the laboratory prior to randomisation.)

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

Note: the randomisation scheme used for the China cohort will be the same as the randomisation scheme used for the Global Population.

Patients should begin treatment on Day 1. Patients must not be randomised and treated unless all eligibility criteria have been met. Patients should begin study treatment on the day of randomisation (in the event of logistical challenges, treatment should start no later than 3 calendar days following randomisation).

If a patient withdraws from participation in the study, then her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

6.3.2 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomised 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 randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised 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.

6.3.3 Methods for assigning treatment groups

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

Patients will be identified to the IVRS/IWRS per country regulations. Randomisation codes will be assigned PPD, within each stratum, as patients become eligible for randomisation. The IVRS/IWRS will provide the kit identification number to be allocated to the patient at the randomisation visit and subsequent treatment visits.

6.3.4 Methods for ensuring blinding

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

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

The randomisation code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. If unblinding has occurred, both IP treatments (durvalumab/placebo and olaparib/placebo) must be discontinued; however, the patient should continue to follow all other protocol procedures and assessments. 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 investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation 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 IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the patient's best interest for the investigator to know the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (eg, antidote available). In this case, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF (electronic or paper), as applicable. Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual patient have been made and documented.

Randomisation codes will not be broken for the planned analyses of data until database lock for the primary PFS analysis or interim analysis and all decisions on the evaluability of the data from each individual patient have been made and documented, and a decision is made to unblind the study at that timepoint.

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

6.4 Treatment compliance

Patient diaries will be administered to the patient to record treatment compliance for olaparib/placebo.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer olaparib/placebo. Study site staff will make tablet counts at regular intervals during treatment. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib/placebo at the appropriate scheduled visit, when new bottles will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Patients will also be trained on using patient diaries to record olaparib/placebo doses.

Study site staff will administer chemotherapy and durvalumab/placebo infusions.

Any change from the dosing schedule, dose interruptions, dose reductions (note: dose reductions are not allowed for durvalumab), and dose discontinuations should be recorded in the eCRF.

The Investigational Product Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The investigator(s) is responsible for ensuring that the patient has returned all unused olaparib/placebo tablets.

6.5 Concomitant therapy

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

The use of any natural/herbal products or other traditional remedies should be discouraged. Any medication or non-live, attenuated vaccine including over-the-counter or prescription

medicines, vitamins, and/or natural/herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

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

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

6.5.1 Anti-emetics/anti-diarrhoeals

From Cycle 1 Day 1 onwards, should a patient develop nausea, vomiting and/or diarrhoea, then these symptoms should be reported as AEs (see Section 8.3) and appropriate treatment of the event given.

6.5.2 Restricted and prohibited medications

Restricted, prohibited, and permitted concomitant medications for the investigational study medications (olaparib and durvalumab) are described in the Table 7 and Table 8. Refer also to the Dosing Modification and Toxicity Management Guidelines for durvalumab (see Section 8.4.5). For non-investigational agents, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

Other medication other than that described in Table 7 and Table 8, 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.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

Table 7 Prohibited medications

Prohibited medication/class of drug:	**Study treatments for which concomitant use is PROHIBITED:**	
Other anticancer therapy: • Any concurrent chemotherapy, , immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study • Radiotherapy (except palliative; see Table 8) • Biological therapy • mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study • Other novel agents	• Durvalumab/placebo • Olaparib/placebo	Not permitted while the patient is receiving study medication.
Live virus vaccines Live bacterial vaccines	• Durvalumab/placebo • Olaparib/placebo	Not permitted while the patient is receiving study medication and during the 30 day follow-up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with study medications are unknown.
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	• Durvalumab/placebo	Should not be given concomitantly, or used for premedication prior to the durvalumab/placebo infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study medication related AEs • Short-term premedication for patients receiving platinum-based chemotherapy where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions or for prophylaxis of chemotherapy-induced nausea and vomiting • Use in patients with contrast allergies. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).

Table 7 Prohibited medications

Prohibited medication/class of drug:	Study treatments for which concomitant use is PROHIBITED:	
Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)	• Durvalumab/placebo • Olaparib/placebo	Should not be given concomitantly. Should be used with caution in the 90 days after last dose of durvalumab. Increased incidences of pneumonitis (with 3rd generation EGFR-TKIs) and increased incidence of transaminase increases (with 1st generation EGFR-TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	• Durvalumab/placebo	Should not be given concomitantly unless agreed by the sponsor.

Abbreviations: AE = adverse event; bd = twice daily; CTLA-4 = cytotoxic T lymphocyte-associated-4; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitors; mAb = monoclonal antibody; PD-1 = programmed cell death protein-1; PD-L1 = programmed death-ligand 1.

[a] Hormone replacement therapy (HRT) is acceptable.

Table 8 Restricted concomitant medications

Medication/class of drug:	Study treatments for which concomitant use is RESTRICTED:	Usage (including limits for duration permitted and special situations in which it is allowed):
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir **Moderate CYP3A inhibitors:** ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	• Olaparib/placebo	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the eCRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. • Moderate CYP3A inhibitors – reduce the dose of olaparib to 150 mg bd 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 dose can be re-escalated to the dose the patient was receiving prior to the dose reduction.

Table 8 Restricted concomitant medications

Medication/class of drug:	Study treatments for which concomitant use is RESTRICTED:	Usage (including limits for duration permitted and special situations in which it is allowed):
Strong CYP3A inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort **Moderate CYP3A inducers:** bosentan, efavirenz and modafinil	• Olaparib/placebo	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer, then they must be monitored carefully for any change in efficacy of olaparib.
CYP3A4 substrates with narrow therapeutic margin: e.g. cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and warfarin. Sensitive CYP3A4 substrates: e.g. buspirone, felodipine, fluticasone, lovastatin, quetiapine, saquinavir, sildenafil and simvastatin. CYP2B6 substrates: e.g. bupropion and efavirenz. OATP1B1 substrates: e.g. bosentan, glibenclamide, repaglinide, statins and valsartan. OCT1, MATE1 and MATE2K substrates: e.g. metformin. OCT2 substrates: e.g. cimetidine and metformin. OAT3 substrates: e.g. furosemide and methotrexate. BCRP substrates: e.g. methotrexate and rosuvastatin. P-gp substrates: e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine.	• Olaparib/placebo	Effect of olaparib on other drugs: Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6 (and potentially substrates of CYP2C9, CYP2C19 and P-gp). The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Caution should be observed if statins or sensitive CYP3A4 substrates are co-administered. Appropriate clinical monitoring is recommended for patients receiving P-gp substrates or CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Table 8 Restricted concomitant medications

Medication/class of drug:	Study treatments for which concomitant use is RESTRICTED:	Usage (including limits for duration permitted and special situations in which it is allowed):
Anticoagulant therapy	• Olaparib/placebo	Patients who are taking warfarin may participate in this trial; however, it is recommended that INR be monitored carefully when given concomitantly with olaparib at least once per week for the first month, then monthly if the INR is stable. INR should be monitored in chemotherapy phase per local standard practice. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin, and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (eg, apixaban and rivaroxaban) if possible.
Palliative radiotherapy	• Durvalumab/placebo • Olaparib/placebo	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, 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 anti-cancer agents	• Durvalumab/placebo • Olaparib/placebo	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease provided these were started at least 4 weeks prior to beginning study treatment.

Abbreviations: bd = twice daily; CYP = cytochrome P450; eCRF = electronic case report form; INR = international normalised ratio; MATE = multidrug and toxin extrusion; NOACs = non-vitamin K antagonist oral anticoagulants; OAT = organic anion transporter; OATP1B1 = organic anion transporting polypeptide 1B1; OCT = organic cation transporter.

6.5.3 Subsequent therapies for cancer

The treating investigator is at liberty to define the most appropriate treatment should the cancer recur. Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of all study treatments (including access to other PARP inhibitors or immuno-oncology drugs), will be collected. Reasons for starting subsequent anti-cancer therapies (including access to other immuno-oncology drugs or investigational drugs) will be collected and included in the exploratory assessments of OS.

6.5.4 Rescue medication

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

6.5.5 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.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

6.5.6 Durvalumab drug-drug interactions

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

6.6 Dose modification

For guidance on dose modifications for management of AEs (including renal impairment) for olaparib and durvalumab, refer to Section 8.4.5.

6.6.1 Durvalumab

Dose delays are permitted for durvalumab therapy (as described in the Dosing Modification and Toxicity Management Guidelines [TMG]; see Annex to Protocol). However, **dose**

reductions are not permitted for durvalumab. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered. The durvalumab dose may be delayed for up to a maximum of 12 weeks. If the toxicity has not resolved by 12 weeks, durvalumab should be stopped permanently (as no dose adjustment is allowed).

Weight-based dosing at 20 mg/kg should be used for patients whose body weight falls to ≤30 kg during the maintenance phase of the study (Section 4.3.1 and Section 6.1.1).

Dosing intervals of cycles in the maintenance phase may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumour efficacy (RECIST) and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see the durvalumab IB).

6.6.2 Olaparib

In case a dose reduction is necessary, the olaparib (or olaparib placebo) treatment will be administered as follows:

Table 9 Dose reductions for olaparib/placebo to manage adverse events

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

Abbreviations: bd = twice daily.

Table 10 Dose reduction for olaparib/placebo if patient develops moderate renal impairment

Initial Dose	Moderate renal impairment (calculated creatinine clearance either by Cockcroft-Gault equation, a 24-hour urine test or another clinically validated test between 31 and 50 mL/minute)
300 mg bd	200 mg bd

Abbreviations: bd = twice daily.

Table 11 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 bd	100 mg bd	150 mg bd

Abbreviations: bd = twice daily; CYP = cytochrome P450.

For guidance on dose reductions for management of AEs (including renal impairment) refer to Section 8.4.5.2.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Section 6.5.2.

6.6.3 Chemotherapy

Investigators should follow local standard clinical practice regarding dose modifications for the chemotherapy treatments (paclitaxel and carboplatin, including any substituted agents used in the event of a hypersensitivity reaction requiring discontinuation of carboplatin or paclitaxel, as per Section 6.1.2).

In the event of a chemotherapy delay due to toxicity, and if further chemotherapy is planned, then durvalumab should be delayed as well.

For information regarding the use of granulocyte colony-stimulating factor (G-CSF), please see Section 8.4.5.3.

Chemotherapy should continue for a maximum of 6 cycles. To continue on maintenance treatment, a minimum of 4 cycles of chemotherapy is allowed for patients requiring it due to toxicity.

6.7 Treatment after the end of the study

Once patients have been discontinued from all study treatments, other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis.

At the completion of the study or at study termination, the clinical study database will be closed to new data with the exception of the China ITT cohort (see Section 9.4.8 for details). This will be considered the end of the study and after database lock, all patients will be unblinded. Patients who are receiving active treatment (durvalumab and/or olaparib) can either choose to discontinue treatment or, where the investigator believes patients are gaining clinical benefit and have not met any of the discontinuation criteria (see Section 7.1), patients may continue to receive the same active treatment they were receiving during the study.

AstraZeneca will continue to supply open-label drug to patients receiving durvalumab and/or olaparib, up to the time that they discontinue the treatment for whatever reason (See Section 7.1). All patients will receive follow-up care in accordance with standard local clinical practice. No further data collection is required, except for reporting of SAEs.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the patient(s) to alternative supply, where possible.

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. The roll-over or extension study would ensure treatment

continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable.

For patients who continue to receive treatment beyond the time of this data cut-off, investigators will continue to report all SAEs to AstraZeneca Patient Safety until the end of the follow-up period after treatment discontinuation, in accordance with Section 8.3.5. If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the one or more of the products used in this study, the investigator should notify AstraZeneca, Patient Safety. Additionally as stated in Section 8.3.5, any SAE or non-serious AE that is ongoing at the time of this data cut-off, must be followed up by the investigator for as long as medically indicated.

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

An individual patient will not receive any further study treatment if any of the following occur:

- Objective disease progression according to RECIST 1.1 criteria
- Clinical deterioration. NOTE: Clinical deterioration should only be used as a reason for discontinuation when objective disease progression has not yet been or cannot be determined. Patients with symptomatic or clinical deterioration requiring discontinuation of treatment without objective radiologic evidence of disease progression at that time should continue to undergo tumour assessments.
- Withdrawal of consent from further treatment with IP. The patient is free to discontinue treatment at any time, 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) or as defined in the local prescribing information for the chemotherapy agents (paclitaxel and carboplatin)
- 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)
- Bone marrow findings consistent with MDS/AML
- Initiation of alternative anticancer therapy including another investigational agent.

Any patient receiving treatment with investigational products (durvalumab/placebo or olaparib/placebo) who has an AE that contraindicates further dosing and is considered to be attributable to one of the study treatments but not the others, may continue on study and continue to receive the therapies that have not been considered to be the cause of the AE (a discontinuation of one drug should not affect the dosing schedule of the other drugs) and continue following the on-treatment SoA (see Section 6.1.2 for guidance on permitted drug substitutions in the event of a hypersensitivity reaction to carboplatin or paclitaxel leading to discontinuation). The only circumstance where only 1 chemotherapy agent and not the other may be discontinued is in the event of treatment-related toxicity.

Once patients have discontinued all study treatments, the treatment discontinuation visit will occur (see Table 3). Subsequent treatment options will be at the discretion of the investigator.

Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study. Patients can discontinue all study treatment but should be encouraged to remain in the study for post-treatment assessments and follow-up.

7.1.1 Procedures for discontinuation of study treatment

The investigator should instruct the patient to contact the site before or at the time if any study treatment is stopped. A patient that decides to discontinue any of the study treatments will always be asked about the reason(s) and the presence of any AEs. The date of last intake of each study treatment should be documented in the eCRF. All olaparib/placebo tablets should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing all study treatments should be given locally available SoC therapy, at the discretion of the investigator.

Any patient discontinuing all study treatments should be seen at the appropriate follow-up visits for the evaluations outlined in Table 3. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be determined by radiological assessment.

After discontinuation of all study medications, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow-up (see Section 7.2). All new AEs and SAEs occurring during the follow-up period after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 8.3.5) and followed to resolution as above. For guidance on reporting AEs after the follow-up period see Section 8.3.3.

Any patient who has not yet shown objective radiological disease progression at withdrawal from study treatment(s) should continue to be followed as per RECIST 1.1 as detailed in Section 8.1.1.

All patients must be followed for survival, up to the final analysis, provided they have not withdrawn consent to do so.

Discontinuation of study treatment, for any reason, does not impact on the patient's participation in the study. 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 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.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if she fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

7.3 Withdrawal from the study

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Incorrectly enrolled patients ie, the patient does not meet the required inclusion/exclusion criteria for the study (applicable to screening failures only; see Section 6.3.2 for procedures for handling incorrectly randomised patients).
- Patient lost to follow-up
- Death.

Note that patients who are withdrawn before randomisation will be considered as screen failures (see Section 5.7).

A patient may withdraw from the study (eg, withdraw consent), at any time (study treatments and assessments) at her own request, without prejudice to further treatment.

A patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, she may request destruction of any samples taken, and the investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The investigator will follow up patients as medically indicated. The patient will return ePRO devices.

AstraZeneca or its delegate will request investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study.

If a patient withdraws consent, she will be specifically asked if she is withdrawing consent to:

- Further participation in the study including any further follow-up (eg, survival calls)
- Disclosure of future information (the sponsor may retain and continue to use any data collected before such a withdrawal of consent)
- The use of any samples (see Section 8.8.2).

The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patient notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

See the SoA (Table 2 and Table 3), for data to be collected at the time of study treatment discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 1.1).

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

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

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

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

Procedures conducted as part of the patient's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy assessments

8.1.1 CT and MRI scans tumour assessments (RECIST 1.1)

Efficacy assessments will be derived (by AstraZeneca) using RECIST 1.1 assessments based on investigator evaluation. Details of RECIST 1.1 (Eisenhauer et al 2009) are provided in Appendix G. The preferred methods of assessment are CT or MRI scans of chest, abdomen and pelvis. The use of positron emission tomography (PET) scans is described in Appendix G. The same methods for assessment of tumour burden must be used at baseline and at each subsequent follow-up assessment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

Radiological examinations performed in the conduct of this study should be retained at sites as source data. Anonymised copies of the scans will be collected from all patients and will be sent to an AstraZeneca appointed CRO; scans will undergo BICR assessment.

All treatment decisions will be based on site assessment of scans. After the primary PFS analysis, central review of scans will no longer be required, and investigators will be notified when copies of the scans are no longer required to be shared with the CRO conducting the central review. However, sites should continue RECIST 1.1 tumour assessments until radiological progression and should record the RECIST assessments in the eCRF.

It is important to follow the assessment schedule as closely as possible; timing of scans is relative to the date of randomisation, irrespective of any dosing delays (Section 1.1). If scans are performed outside of the scheduled visit windows and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST 1.1, and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations have occurred, unless patients withdraw consent.

8.1.1.1 Tumour evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS times and ORR. The RECIST 1.1 guidelines that define measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix G. Categorisation of overall response will be based on the assessments of TLs, NTLs and new lesions.

For patients with TL at baseline, progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study, nadir). Tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before randomisation.

For patients with no evidence of disease (NED) at baseline (ie, TL and NTL are not applicable [NA]), following a complete resection after surgery, RECIST 1.1 outcomes at follow-up are NED or PD. Progression is defined by the detection of new lesions on follow-up radiological assessments (RECIST 1.1).

For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PD and Non-CR/Non-PD.

In the absence of clinical progression or if the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue randomised treatment and on-treatment assessments until the next scheduled scan, or sooner if clinically indicated, and reassess the patient's status with

a new scan. If the repeat scan confirms progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in NTLs such that, even in presence of SD or PR in TLs, the overall tumour 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.

8.1.1.2 Central reading of scans

An independent review will be conducted of all scans used in the assessment of tumours according to RECIST 1.1. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO for central analysis. Results of this independent review will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the investigator.

8.1.2 Survival status

All patients must be followed for survival, up to the final analysis, provided they have not withdrawn consent to do so.

Survival information may be obtained via telephone contact with the patient, patient's family, contact with the patient's current physician or by checking publicly available death registries where permitted by local laws. Survival data will be collected up to the data cut-off time of the final OS analysis. The status of all ongoing, withdrawn (from the study) and "lost to follow-up" patients should be obtained at the time of each OS analysis. In addition, attempts will be made to contact patients in the 7 days following the data cut-off for the primary PFS and for the survival analyses to provide complete survival data.

Following the data cut-off for the primary analysis of PFS, patients will continue to be followed up as detailed in the study schedule (Section 1.1) to the point of the final survival analysis. At this point, investigators will be notified that they can stop survival data collection. Monitoring and recording of SAEs will continue as per Section 8.3.2.

8.1.3 Patient reported outcome assessments

The following PROs will be completed electronically in the order presented below:

- European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (EORTC QLQ-C30; Section 8.1.3.1)
- EORTC Quality of Life Questionnaire – Endometrial Cancer Module (EORTC QLQ-EN24; Section 8.1.3.1)
- EuroQoL five dimensions, five level health state utility index (EQ-5D-5L; Section 8.1.3.2)

- Patient reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE; Section 8.1.3.3)
- Patient global impression of severity of cancer symptoms (PGIS; Section 8.1.3.4)
- Patient global impression of change (PGIC; Section 8.1.3.5)
- Patient global impression of treatment tolerability (PGI-TT; Section 8.1.3.6)
- Patient global impression of benefit/risk (PGI-BR; Section 8.1.3.7).

The PRO questionnaires (Appendix H) will be self-administered using ePRO. At baseline (Cycle 1 Day 1), the questionnaires will be completed at the site. At subsequent time points, the questionnaires will be completed at home or at the study site if the assessment time point coincides with a scheduled site visit. If a patient has missed a scheduled site visit that coincides with PRO data collection, PRO questionnaires should still be completed by the patient at home for that scheduled visit within the specified window.

Patients must be instructed to bring the handheld device to all study visits.

Each site must allocate the responsibility for the administration of the PRO questionnaires to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent.

Completion of questionnaires will take the patient approximately 25 minutes.

The following instructions should be followed for completion of PRO instruments:

- The research nurse or appointed site staff must explain to the patient the value and importance of completing PRO questionnaires, so they are motivated to comply with questionnaire completion. The patient should be informed that these questions are being asked to find out directly from them, how they feel, and the information they provide is critical to the success of the study.
- It is vital that the PRO reporting is initiated at the baseline visit (Cycle 1 Day 1), as specified in the study plan, to capture the effect of study treatment. The handheld device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.
- PRO questionnaires must be completed prior to treatment administration at the site and ideally before any discussions of health status, to avoid biasing the patient's response to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures such as collection of laboratory samples, to further minimise bias.
- PRO questionnaires should be completed by the patient in a quiet and private location. The patient should be given the time they need to complete the questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the patient has any medical problems, they should discuss them with the doctor or research nurse separately from the 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 by the ePRO vendor.
- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device if the patient is completing the PRO questionnaires at home.
- All PRO questionnaires are to be completed using an ePRO device. If technical or other device-related issues prohibit completion on the device, an appropriate back-up option may be considered with prior approval from AZ..
- The research nurse or appointed site staff must remind the patient that there are no right or wrong answers and avoid introducing bias by not clarifying questions for the patient. If the patient is uncertain about the meaning of a question, the site staff should ask the patient to answer based on what they think the item means.
- The patient should not receive help from relatives, friends, or clinic staff in deciding on the answers to the PRO questionnaires.
- If a patient uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when she attends the clinic, the patient will be exempted from completing the PRO questionnaires at that clinic visit, though they can complete them at home if within the allowable window.
- Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind, illiterate or does not speak the available language), the patient is exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and Review of PRO/Questionnaire/Diary (REVPRDI) eCRF.
- Site staff must administer questionnaires available in the language that the patient speaks and understands.
- Reminders should be sent to patient at home as needed to ensure compliance with the assessment schedules. Site staff must check compliance at each study visit and ideally more frequently to identify problems early, as minimising missing data is a key aspect of study success. If a patient's compliance drops to 85% or below, they will be flagged in the routine compliance report generated by the ePRO system. Ideally, the study site would have a check-in call to ask the patient if she has any difficulties. A solution to enhance/resolve compliance should be discussed with the patient. For missed questionnaires, the reason(s) for missing the assessment should be documented in the REVPRDI eCRF.

8.1.3.1 EORTC QLQ-C30 and EORTC QLQ-EN24

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993 to assess HRQoL, functioning, and symptoms in cancer clinical trials. It has undergone extensive testing and validation and has been translated and linguistically and culturally validated in numerous languages (Aaronson et al 1993). It is a 30-item self-administered questionnaire for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global health status/QoL scale, 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia,

constipation, and diarrhoea), and 1 item on the financial impact of the disease. All but 2 questions are rated on a 4-point verbal rating scale: "Not at all," "A little," "Quite a bit," and "Very much." The 2 questions concerning global health status and QoL have 7-point scales with ratings ranging from "Very poor" to "Excellent." For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate better functioning, better QoL, or worse symptoms (Aaronson et al 1993).

The EORTC QLQ endometrial cancer module EORTC QLQ-EN24, is a disease-specific supplement to the EORTC QLQ-C30 to capture endometrial cancer-specific symptoms and functioning (Golan et al 2019, Greimel and Nordin 2010, Greimel et al 2011). It is a validated instrument designed for patients with all stages of endometrial cancer treated with pelvic surgery, chemotherapy, radiotherapy, or concomitant radio/chemotherapy. The module consists of 24 questions grouped into the following scales: lymphoedema (2 items), urological symptoms (4 items), gastrointestinal symptoms (5 items), body image problems (2 items), sexual/vaginal problems (3 items), back/pelvic pain (1 item), tingling/numbness (1 item), muscular/joint pain (1 item), hair loss (1 item), taste change (1 item), sexual interest (1 item), sexual activity (1 item) and sexual enjoyment (1 item). All questions are rated on a 4-point verbal rating scale: "Not at all," "A little," "Quite a bit," and "Very much." Final scores are transformed such that they range from 0 to 100, where higher scores indicate better functioning or worse symptoms.

8.1.3.2 EQ-5D-5L

Patient-reported health state utility will be assessed using the EQ-5D-5L. The instrument asks patients to respond to 5 different dimensions covering mobility, self-care, usual activities, pain/discomfort, anxiety/depression, as well as rate how they feel on the day of assessment via a visual analogue scale.

8.1.3.3 PRO-CTCAE

The PRO-CTCAE will only be administered where a linguistically validated version exists for a country.

PRO-CTCAE, developed by the NCI, is an item library of symptomatic AEs experienced by patients while undergoing cancer treatment. It was developed in recognition that collecting treatment-related symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. To date, the library consists of 78 symptoms of the CTCAE that have been adapted for patient reporting and have undergone cognitive testing with patients. Symptomatic AEs relevant to the cancer treatments included in this study, and not already captured in other PRO instruments being used in this study, have been selected from the item library for inclusion. This includes 3 items capturing itching (1 item) and shivering/shaking chills (2 items).

8.1.3.4 PGIS

The PGIS is a single-item questionnaire assessing the patient's overall severity of cancer symptoms over the past week. The item is rated using a 6-point verbal rating scale from "No Symptoms" to "Very Severe".

8.1.3.5 PGIC

The PGIC is a single-item questionnaire assessing the patient's overall change in health condition since the start of study treatment(s). The item is rated using a 7-point Likert-type scale from "Much Better" to "Much Worse".

8.1.3.6 PGI-TT

The PGI-TT is a single-item questionnaire assessing the overall bother associated with symptomatic AEs. The item is rated using a 6-point verbal scale from "Not at All" to "Very Much".

8.1.3.7 PGI-BR

The PGI-BR will only be administered where a linguistically validated version exists for a country. The PGI-BR is a 5-item questionnaire assessing the patient's perception of the overall benefits and risks of treatment. The 5 items assess: overall trial experience, efficacy, side effects, convenience and overall assessment of the benefits and harms of treatment. Items are rated on 5- or 6-point verbal rating or Likert-type scales.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

8.2.1.1 Haematology, clinical chemistry and urinalysis

See Table 12, Table 13 and Table 14 for the list of clinical safety laboratory tests to be performed. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the SoA.

The investigator should assess the available results with regard to clinically relevant abnormalities. Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours), as per investigator's judgement. The laboratory results should be acknowledged or signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.9.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

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

Table 12 Clinical chemistry

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Event; TSH = thyroid-stimulating hormone.

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

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

[c] Bicarbonate (where available), chloride, gamma glutamyl transferase, magnesium, tests are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry assessments were performed within 3 days prior to starting study treatment and the investigator believes that results are unlikely to have changed significantly), and if clinically indicated.

[d] Creatinine clearance will be automatically calculated in the eCRF using Cockcroft-Gault (using actual body weight) when weight and creatinine are entered.

[e] If TSH is measured within 14 days prior to starting study treatment (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.

[g] These tests should be performed every 6 weeks, rather than every 3 weeks, during the chemotherapy phase, and every 4 weeks during the maintenance phase. Glucose can be tested in the fasting or fed state depending on local laboratory requirements.

[h] Lactate dehydrogenase (LDH) should be performed prior to any transfusion required for a CTCAE Grade ≥ 3 anaemia when the patient is receiving olaparib/placebo and durvalumab/placebo in combination (or is within 90 days of receiving the combination, if either drug has been discontinued), per Table 23.

Table 13 Haematology

Absolute neutrophil count[a]	Absolute lymphocyte count[a]
Haemoglobin	Platelet count
Total white cell count	Reticulocyte count [b]

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by Data Management if entered as percentage. Total white cell count therefore has to be provided.
[b] Reticulocyte count is required once prior to starting olaparib/placebo in the maintenance phase and as clinically indicated (eg, CTCAE Grade ≥ 3 anaemia) when the patient is receiving olaparib/placebo and durvalumab/placebo in combination (or is within 90 days of receiving the combination, if either drug has been discontinued) according to Table 23.

Table 14 Urinalysis

Bilirubin	Ketones
Blood	pH
Colour and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis should be done at baseline (screening) and then as clinically indicated.
Note: Microscopy is preferred to investigate white blood cells with use of high-power field for red and white blood cells; dipstick can also be used. As clinically indicated, white blood cells should be tested by either microscopy or dipstick (leukocyte esterase).

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

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 8.3.9.

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.

8.2.1.2 Coagulation

Activated partial thromboplastin time (APTT) and INR will be performed at screening and if clinically indicated.

International normalised ratio (INR) will be performed at screening and if clinically indicated. Patients 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.

Each coagulation test result will be recorded in eCRF.

8.2.1.3 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities.

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.

8.2.1.4 Disease specific tumour marker samples (CA125)

Cancer antigen 125 (CA125) assessment will be conducted as part of the routine safety blood samples. Every attempt should be made to assess CA125 at the scheduled time points. A rise in CA125 alone is not sufficient to declare progression and discontinue treatment.

Progression events should be determined by radiographic evidence of progression, based on RECIST 1.1; see Section 8.1.1.

Further assessment of CA125 after radiological progression will be at the discretion of the investigator according to local clinical practice.

8.2.2 Physical examination

A complete physical examination will be performed at screening and will include an assessment of the following: general appearance, respiratory, cardiovascular, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, pelvis, musculoskeletal (including spine and extremities) and neurological systems. Details will be recorded on an eCRF.

Following the screening assessment, targeted physical examinations are to be utilised by the investigator on the basis of clinical observations and symptomatology. It is not necessary to record the details on an eCRF. Any clinically significant changes should be recorded as AEs.

8.2.3 Vital signs

Vital signs will be evaluated at the timepoints specified in the SoAs (Section 1.1) and as clinically indicated at any other time.

Blood pressure (BP) and pulse rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size after 10 minutes rest. Body temperature will be measured in degrees Celsius according to local practice.

Height will be assessed at screening only. Weight will be assessed at screening and as clinically indicated at any other time.

The date of collection and measurement will be recorded on the appropriate eCRF. Any changes in vital signs should be recorded as an AE, if applicable. For information on how AEs based on changes in vital signs should be recorded and reported, see Section 8.3.9.

8.2.3.1 First infusion of durvalumab/placebo

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

BP and pulse will be collected from patients before, during, and after the 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 (±5 minutes after the end of the infusion)

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

8.2.3.2 Subsequent infusions

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 after infusion as per institution standard and as clinically indicated. The date of collection and measurement will be recorded on the appropriate eCRF. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF page.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.9. For any AEs of infusion reactions, the vital signs values should be entered into the CRF.

8.2.4 Electrocardiograms

ECGs are required at screening or within 7 days prior to starting study treatment, and when clinically indicated. Twelve-lead ECGs will be obtained after the patient has rested in a supine position for at least 5 minutes. ECGs will be recorded at 25 mm/sec.

The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. 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.

All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal/not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF.

The original ECG traces must be stored in the patient medical record as source data.

8.2.5 ECOG performance status

ECOG performance status will be assessed as follows:

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

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

8.2.6 Other safety assessments

8.2.6.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential (see Section 5.6.2) at the time points shown in the SoA (Section 1.1). Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

8.2.6.2 Pneumonitis/ILD investigation

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the (TMGs (see Section 8.4.5 and Appendix I) will be applied.

If pneumonitis/ILD is suspected, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately. For durvalumab, the guidance in the TMGs should be followed.

The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters, etc) will be captured in the

eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis/ILD should be considered and the TMGs should be followed.

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

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

8.3 Collection of adverse events

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

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

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised 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 8.3.5.

8.3.1 Regulatory reporting requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRB)/independent ethics committees (IEC), and investigators.

For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.2 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.

8.3.3 Time period and frequency for collecting AE and SAE information

SAEs will be collected from time of signature of the main ICF throughout the treatment period and including the follow-up periods. All other AEs will be collected from Cycle 1 Day 1 throughout the treatment period and including the follow-up periods.

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

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

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

8.3.4 Adverse events after the safety follow-up period

For pharmacovigilance purposes and characterisation, any SAE of MDS/AML or new primary malignancy occurring after the follow-up periods specified in Section 1.1 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 even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm.

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/she considers there is a reasonable possibility that the event is causally related to one or more of the investigational products in this study, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment after data cut-off 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 appropriate post-treatment follow-up period.

8.3.5 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 SAE and AEs of special interest (AESIs as defined in Section 8.3.15), will be followed until resolution, stabilisation, 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 will be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Any SAE or non-serious AE that is ongoing at the time of the 30-day follow-up (after last dose of olaparib) or 90-day follow-up (after last dose of durvalumab), whichever is later, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. 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.

8.3.6 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The dates when the AE started and stopped
- CTCAE grade and changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day); see Appendix B for CTCAE gradings
- Whether the AE is serious or not

- Investigator causality rating against the study treatments(s) (yes or no); if the causality rating is given as "yes", an assessment of which study treatment(s) the AE is considered causally related to should also be provided
- Action taken with regard to study treatment(s)
- Administration of treatment for the AE
- AE caused patient's withdrawal from study
- Outcome

In addition, the following variables will be collected for SAEs (see Appendix B):

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Reason for AE being identified as serious
- Date of hospitalisation
- Date of discharge
- Probable cause of death (if fatal)
- Date of death (if fatal)
- Autopsy performed (if fatal)
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of AE.

8.3.7 Causality collection

The investigator will assess causal relationship between study treatments 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 study treatments?'

For SAEs, causal relationship will also be assessed for other medications, including all study medications, as well as any 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.

8.3.8 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider 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.

8.3.9 Adverse events based on examinations and tests

The results from CSP mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). Deterioration as compared with baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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, anaemia versus low haemoglobin [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 assessment will be reported as an AE unless unequivocally related to the disease under study, see Section 8.3.11 and Section 8.3.12.

8.3.10 Hy's law

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

8.3.11 Disease progression

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

8.3.12 New cancers

The development of a new primary cancer should be reported as an AESI (see Section 8.3.15 and Appendix B 2) and would in most cases meet the criteria for an SAE. New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the 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.

8.3.13 Lack of efficacy

When there is patient deterioration in the condition for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

8.3.14 Deaths

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

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but 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 as a SAE within 24 hours (see Section 8.4.1 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

Deaths with an unknown cause should always be reported as a SAE. A post-mortem may be helpful in the assessment of the cause of death, and if performed a de-identified copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

8.3.15 Adverse events of special interest (AESIs)

An AESI is an AE of scientific and medical interest specific to understanding of the investigational product and may require close monitoring. An AESI may be serious or non--serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this investigational product.

8.3.15.1 Durvalumab AESIs

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. If the investigator has any questions in regard to an event being an imAE, the investigator should promptly contact the study physician.

AESI/imAEs observed with anti PD-L/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhoea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and type 1 diabetes mellitus), nephritis, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, pancreatitis, immune thrombocytopenia, 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 aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, haematological, 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 aetiology are also considered AESIs.

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

8.3.15.2 Olaparib AESIs

AESIs for olaparib comprise the important identified risk of MDS/AML, and the important potential risk of new primary malignancy (other than MDS/AML), and the potential risk of pneumonitis.

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

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

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

All SAEs that occur in patients still receiving durvalumab or olaparib treatment (or within the 90 days following the last dose of durvalumab treatment or within the 30 days following the last dose of olaparib treatment, whichever is the later) after the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

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

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study treatments, 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 one day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all 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 one calendar day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

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

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

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

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

The reference document for definition of expectedness is the Investigator's Brochure for the AstraZeneca drugs.

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, foetal 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, study treatment(s) should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatments 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 date of the first dose of study medication until 3 months after the last dose of study medication should be followed up and documented even if the patient was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

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

8.4.3 Overdose

There is currently no specific treatment in the event of overdose with olaparib or durvalumab and possible symptoms of overdose are not established.

Olaparib and durvalumab must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

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 or she becomes aware of it.

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.3. For other overdoses, reporting must occur within 30 days.

For the chemotherapy agents (paclitaxel and carboplatin), please refer to the local prescribing information for treatment of cases of overdose. If any overdose of the chemotherapy treatments is associated with an AE or SAE, the AE/SAE diagnosis or symptoms should be recorded in the relevant AE modules only of the eCRF.

8.4.4 Medication Error, Drug Abuse, and Drug Misuse

8.4.4.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but no later than 24 hours of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 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, drug abuse, or drug misuse (see Section 8.3.3) and **within 30 days** for all other events.

8.4.4.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an investigational product/study intervention or AstraZeneca

non-investigational product that either causes harm to the participant or has the potential to cause harm to the participant.

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

8.4.4.3 Drug Abuse

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

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.4.4 Drug Misuse

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

The full definition and examples of Drug Misuse can be found in Appendix B 4.

8.4.5 Toxicity management guidelines

8.4.5.1 Management of durvalumab-related toxicities

Comprehensive TMGs have been developed to assist investigators with the recognition and management of toxicities associated with the use of the durvalumab. These guidelines are applicable when durvalumab 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 current version of the TMGs is provided to the investigative site as an Annex document and is maintained within the Site Master File.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other aetiologic 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 aetiology, events should be considered potentially immune-mediated.

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 delays are permitted for durvalumab for up to a maximum of 12 weeks. If the toxicity has not resolved by 12 weeks, durvalumab should be stopped permanently (as no dose adjustment is allowed).

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 and the durvalumab TMGs).

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

All dose modifications will be recorded in the appropriate electronic system ie, eCRF.

Toxicity management and dose modifications for durvalumab

For AEs that are considered at least partly due to administration of durvalumab the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including withholding the agent[s] suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

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

8.4.5.2 Management of olaparib-related toxicities

Potential olaparib-related toxicities during the course of the study could be managed by interruption of the dose of olaparib/placebo treatment or dose reductions (see Appendix I). 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. Study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. If the reduced dose of 200 mg bd is not tolerable, no further dose reduction is allowed, and study treatment should be discontinued.

Once the dose has been reduced, dose escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 6.6.2).

8.4.5.3 Specific toxicity management and dose modification information – chemotherapy

Investigators should follow local standard clinical practice regarding dose modifications for chemotherapy treatments (paclitaxel and carboplatin, including any substituted agents used in the event of a hypersensitivity reaction requiring discontinuation of carboplatin or paclitaxel, as per Section 6.1.2). For specific information, please refer to the local prescribing information for the relevant agent.

In the event of a chemotherapy delay due to toxicity, and if further chemotherapy is planned, then durvalumab should be delayed as well.

It is recommended that investigators follow the American Society of Clinical Oncology (ASCO) guidelines regarding the use of G-CSF. Primary prophylaxis with G-CSF is not recommended, however, if a patient develops febrile neutropenia, appropriate management including G-CSF should be given according to local hospital guidelines.

Please note: It is recommended that G-CSF should only be administered at least 24 hours after the last dose of chemotherapy and should not be administered on the day before or on the day of chemotherapy. Therefore, G-CSF should not be used to enable chemotherapy dosing in the event of neutropenia and instead chemotherapy should be delayed until recovery of the neutrophil count. If a patient experiences an event of febrile neutropenia, then secondary prophylaxis using G-CSF should be considered and, if necessary, dose reduction of chemotherapy should be implemented for subsequent treatment based on the investigator's clinical judgement.

8.5 Pharmacokinetics (durvalumab only)

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

8.5.1 Collection of samples

Blood samples for determination of durvalumab concentration in serum will be obtained according to the SoAs (Section 1.1) and analysed by a designated third party on behalf of AstraZeneca.

Durvalumab/placebo PK pre-dose samples should be collected within 1 hour before the beginning of durvalumab infusion.

Samples will be collected, labelled, 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 ADAs

Blood samples for determination of durvalumab anti-drug antibodies (ADA) and ADA-neutralising antibodies in serum will be obtained according to the SoA and analysed 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 finalisation.

PK and ADA samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, 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 Biobank; see details in the Laboratory Manual).

8.6 Pharmacodynamics

Whole blood gene expression and whole blood soluble biomarkers are pharmacodynamic parameters in this study. See Section 8.8.2 for details.

8.7 Genetics

8.7.1 Mandatory genetic blood samples

A proportion of tumour mutations are reflective of pre-existing germline mutations. All patients are required to submit a blood sample for retrospective central germline mutation analysis of HRR genes (including *BRCA1* and *BRCA2*) and Lynch Syndrome related genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*).

In addition, this sample may be tested for germline MSI to enable assessment of tumour microsatellite instability using some methods. Mandatory germline mutation analysis will only be conducted if required for interpretation of a tumour test result, or if requested by the regulatory authorities. If this hereditary testing is done, the results will be shared with investigators in accordance with local requirements.

8.7.2 Optional exploratory genetic blood samples (Genomics Initiative)

If the patient agrees to participate in the optional genetic research study (Genomics Initiative), a blood sample will be collected. Participation is optional. Patients who do not wish to participate in this optional genetic research may still participate in the study. Genomic DNA will be extracted from whole blood obtained from patients. Genotyping of DNA may be performed to determine the association between genotype and clinical benefit and/or with likelihood of drug-related AEs. Genotyping data may also be used to subtract naturally occurring mutations and help to unambiguously identify true somatic mutations in tumour tissue. Genes associated with endometrial carcinoma development, progression, or likelihood of response to chemoradiation therapy may likewise be investigated. Genotyping will occur retrospectively; data will not be shared with patients, and results will not impact treatment decisions.

Genotypes may also be correlated with biomarker measures (eg, gene and/or protein expression) obtained from other sample types described in Section 8.8. A primary hypothesis is that different genotypes will be associated with different expression levels of factors within the PD-1 signalling and other immune-mediated pathways. Such variations in expression may affect the ability of an individual to mount an appropriate immune reaction to tumour and/or affect the likelihood of response to therapeutics targeting these pathways. Therefore, genotyping may provide easy to measure, baseline information regarding a patient's immune system, and a goal of this research is to understand how such genetic information may be used to predict pharmacodynamic responses to therapy.

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

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

8.7.3 Storage and destruction of genetic samples

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

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

8.8 Biomarkers

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

Pre-treatment tumour MMR expression will be evaluated in all patients. MMR results are required prior to randomisation. Baseline tumour requirements are briefly described in Section 8.8.1. Details of collection, volumes, storage and shipment of biological samples are presented in the Laboratory Manual.

Based on availability of tissue, additional exploratory biomarkers will be evaluated as described in Section 8.8.2. Exploratory, peripheral measures are also described in Section 8.8.2. Samples will be obtained according to the assessment schedules provided in the SoAs.

8.8.1 Tumour sample for MMR expression and additional exploratory biomarkers

All patients must sign a separate pre-screen consent form to provide a pre-treatment FFPE tumour sample that meets the tissue specifications for the determination of tumour MMR status using the Ventana MMR IHC panel. A tumour tissue sample should be identified for each patient by the participating site and shipped to the laboratory for MMR analysis and results should be reported prior to dosing. The tumour sample will also be used to test PD-L1 status and, if there is enough remaining tissue, for exploratory biomarker analyses. The patient's consent for the use of tumour sample for MMR and additional biomarker testing as described in this protocol and the ICF is mandatory. Patients should not be pre-screened based on prior or local MMR status results. Note that all patients, regardless of whether or not they already know their MMR status based on prior testing, MUST sign the pre-screen ICF and undergo central MMR testing. Please see below and consult the Study Pathology Manual for guidelines regarding sample preparation.

In compliance with local regulations, each patient should provide a FFPE tumour tissue sample from a tumour lesion that was not previously irradiated. The FFPE tumour tissue sample can be from either the locoregional or a metastatic site and be any of the following (additional details in the Study Pathology Manual):

- A tumour sample obtained from the cytoreductive surgery (in patients who have already undergone such surgery)
- A biopsy sample obtained at diagnosis (if a sample from cytoreductive surgery is not available)
- A newly collected tumour sample (if the sample is taken as part of routine clinical practice).

The FFPE tumour sample must be shipped to the laboratory and MMR results must be available prior to randomisation. A minimum of fifteen (15) unstained FFPE tissue sections freshly cut from the FFPE tissue block and not older than 4 weeks (determined from date of slide sectioning) must be submitted directly to the MMR test laboratory. Additionally, the remaining FFPE tissue block should be shipped to the central laboratory. If the FFPE tissue block is not available, a minimum of twenty five (25) FFPE tissue slides should be shipped to the central laboratory. Consult the study pathology manual and central laboratory manual for additional information.

For patients with unknown MMR status due to a technical test failure, the investigator may request sponsor approval to submit a new sample for re-testing; the results of the re-test must be available prior to randomisation. Re-testing of new samples is only permitted if the original testing could not be completed due to technical failure. Patients with unknown MMR status will be considered screen failures and will not be eligible for randomisation.
Please refer to the study pathology manual for further details regarding re-testing procedures, sample quality control and shipping.

For each patient that passes tissue sample quality control, the laboratory will generate a report following immunohistochemical assessment, specifying MMR proficient (ie, normal expression level of all 4 MMR proteins: MLH1, MSH2, MSH6 and PMS2) or MMR deficient (the absence of expression of at least one of the four assessed MMR proteins).

Residual tumour sample tissue after MMR testing may be used for exploratory biomarker testing or to develop and validate future companion diagnostic tests.

Baseline measures will be correlated with outcomes. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with durvalumab and olaparib therapy versus the control arm.

Results of the exploratory biomarker analysis may be reported separately to the CSR.

8.8.2 Additional samples for exploratory biomarker analysis

Blood and tumour samples for exploratory biomarker analyses will be obtained according to the schedules presented in the SoAs (Section 1.1). Details for collection, volumes, storage and shipment of biologic samples are presented in a separate Laboratory Manual.

Baseline measures will be correlated with outcomes. Note that samples will be obtained from patients randomised to each treatment arm. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with durvalumab+placebo versus control and durvalumab+olaparib combination therapy versus control, correlated with histologies.

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

The exploratory biomarker plan is described by sample type below.

Whole blood for cfDNA/HLA-LOH determination and T-cell receptor sequencing

Determining the molecular phenotype of a tumour from a peripheral blood sample has numerous advantages over relying on archival tumour samples or fresh biopsies, not least because these features may be tracked over time and genetic changes may inform tumour resistance mechanisms. CCI [redacted] Samples for cfDNA analysis will be obtained as described in Table 2. All cfDNA samples should be taken pre-dose. CCI [redacted]

Peripheral T-cell receptor diversity and tumour loss of heterozygosity of the HLA-locus have both been demonstrated to influence clinical response to immune checkpoint inhibitors (Chowell et al 2018). In addition to the extraction of cfDNA at indicated timepoints, the buffy coat will also be collected from the blood sample and stored. CCI [redacted]

Additional consent for future research will be requested, so that residual sample may be used to develop and validate future companion diagnostic tests and for additional exploratory work.

Whole blood gene expression (PaxGene-RNA)

A whole blood sample will be obtained pre-treatment from all patients. Total ribonucleic acid (RNA) will be prepared for quantification of RNA and/or miRNA expression using RT-QPCR, microarray, sequencing or similar technology.

CCI

Whole blood for soluble biomarkers (serum chemokines/cytokines)

Changes in the levels of chemokines and cytokines in the blood after treatment with anti-PD-L1 combinations have been shown to be associated with disease response (Socinski et al 2018). Pre-treatment serum samples will be obtained from all patients at timepoints described in the SoAs (Table 1). Please refer to the Laboratory Manual for specific instruction on sample collection. CCI

CCI

Optional tumour biopsy at disease progression

Provision of a tumour sample at disease progression is optional. Analyses for tumour specimens obtained on disease progression will focus on mechanisms of disease resistance to treatment CCI

CCI

Management of biomarker data

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

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

Reporting of exploratory biomarker data

Summaries and analyses for exploratory biomarkers may be documented in a separate analysis plan and may be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab or olaparib to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

8.8.3 Storage, re-use and destruction of biomarker samples

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities. To meet the requirement of FDA approval of a companion diagnostic, sections of the tumour will be retained for potential additional studies, as requested by the FDA, to support potential test approval. Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Samples may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy or PARP inhibitors as described in Sections 8.8.1 and 8.8.2.

8.8.4 Labelling and shipment of biological samples

The principal investigator will ensure that samples are labelled 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, Section C 3 "IATA 6.2 Guidance Document."

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labelling, 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 principal investigator at each centre will keep full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

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, and auditing of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca Biobank 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 analysed, 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 organisation(s) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site
- Ensure that the patient and AstraZeneca are informed about the sample disposal.

8.9 Medical resource use and health economics

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

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

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

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

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

9 STATISTICAL CONSIDERATIONS

The primary objectives of the study are to compare PFS (per RECIST 1.1 as assessed by investigator) in the durvalumab+placebo arm versus the control arm, and durvalumab+olaparib arm versus the control arm (see Table 4).

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

- H_{0CA}: Arm C = Arm A versus H_{1CA}: Arm C ≠ Arm A

and

- H_{0BA}: Arm B = Arm A versus H_{1BA}: Arm B ≠ Arm A

Where H_0 = the null hypothesis; H_1 = the alternate hypothesis.

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

OS will also be assessed for the durvalumab+placebo arm versus the control arm and for the durvalumab+olaparib arm versus the control arm.

As defined in the SAP, for the purposes of the statistical considerations section of this CSP, 'study treatment' refers to olaparib/placebo and durvalumab/placebo.

9.1 Sample size determination

Approximately 699 eligible endometrial cancer patients will be randomised globally at a 1:1:1 ratio to the study treatments. The randomisation will be stratified according to:

- Tumour tissue's MMR status
- Disease status
- Geographic region

The sample size was derived using the validated statistical software for the design, simulation and monitoring of clinical trials, EAST™ v6 and a validated non-proportional hazards-based AstraZeneca R-package. The sample size calculations were based on the following assumptions:

- The assumed median PFS of 12 months for the control arm is in line with data reported for carboplatin/paclitaxel in first-line endometrial cancer from the GOG-209 study (Miller et al 2012), as reported in the GOG-86P manuscript (Aghajanian et al 2018).
- The sample size has been derived on the assumption of a 3-month delay in separation of the PFS curves between Arm B versus Arm A and between Arm C versus Arm A. The assumed true average hazard ratio for the durvalumab+placebo arm is 0.70 (corresponding to an improvement in median PFS of 5.5 months over the assumed median PFS of 12 months in the control arm) and for the durvalumab+olaparib arm is 0.55 (corresponding to an improvement in median PFS of 11.2 months).

The DCO for the primary analysis of PFS for the two comparisons of interest (Arm B versus Arm A and Arm C versus Arm A) will be undertaken at the same calendar time when approximately 299 PFS events have occurred (64% maturity) for the comparison of the durvalumab+placebo arm versus the control arm and approximately 281 PFS events have occurred (60% maturity) for the comparison of the durvalumab+olaparib arm versus the control (approximately 43 months after the first patient is randomised).

If the average true PFS HR is 0.70 for the durvalumab+placebo arm versus the control arm, the study will provide 80% power to demonstrate a statistically significant difference for PFS with overall 2-sided significance level of 2.5%; this translates to a 5.5-month benefit in median PFS over 12 months on the control arm. The smallest treatment difference that would be statistically significant is an HR of 0.77.

If the average true PFS HR is 0.55 for durvalumab+olaparib versus control, this will provide >99% power to demonstrate a statistically significant difference for PFS with an overall 2-sided significance level of 2.5%; this translates to a 11.2-month benefit in median PFS over 12 months on the control arm. The smallest treatment difference that would be statistically significant is an HR of 0.76.

In addition, the sample size has been derived on the following assumptions:

- 27-month period of recruitment
- Approximately 10% uniform dropout rate over the study period.

The power calculations for OS were based on the following assumptions:

- Median OS of 22.7 months for the control arm
- The sample size has been derived on the assumption of a 3-month delay in separation of the OS curves between Arm B versus Arm A and between Arm C versus Arm A, hence the use of an average hazard ratio for OS. The assumed true average OS hazard ratio is 0.75 for the durvalumab+placebo arm versus control arm and durvalumab+olaparib arm versus control arm comparisons corresponding to an improvement in median OS of approximately 7.9 months over the assumed median OS of 22.7 months in the control arm.

The first interim analysis of OS will be performed at the time of the primary PFS analysis, based on the same DCO. For the comparison of the durvalumab+placebo arm versus the control arm, as well as durvalumab+olaparib versus control, it is anticipated that 74% of the target number of OS events will have occurred at this time (ie, approximately 208 of 280 OS events per comparison).

A further analysis of OS may be performed at when approximately 244 OS events (87% of the target number of OS events) have occurred for the comparison of durvalumab+placebo vs

the control arm, as well as durvalumab+olaparib vs the control arm, approximately 51 months after the first patient is randomised.

A final analysis of OS may be performed when approximately 280 OS events have occurred (60% maturity) for the comparison of the durvalumab+placebo arm versus the control arm, as well as the durvalumab+olaparib arm versus the control arm, approximately 63 months after the first patient is randomised. If the average true OS HR is 0.75 for the comparison of the experimental arm versus control, the study will provide 55% power to demonstrate a statistically significant difference for OS with overall 2-sided significance level of 2.5%; this translates to a 7.9-month benefit in median OS over 22.7 months on the control arm. The smallest treatment difference that would be statistically significant is an HR of 0.76. Note that these estimates are based on the assumption that no confounding will occur.

For the OS comparisons, the alpha allocation for the secondary OS endpoints will be controlled at the interim and/or the final analysis timepoints separately for each treatment comparison by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates the O'Brien-Fleming approach, where the significance level applied at the interim analysis depends upon the proportion of information (ie, information fraction) available.

9.2 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 15.

Note, Global recruitment to the study will close when approximately 699 patients are randomised. If necessary, enrolment in China will continue after global recruitment is closed (ie, last subject randomised from a non-Chinese site) to allow inclusion of a China cohort consisting of approximately 129 randomised patients. The China cohort will support standalone safety and efficacy analyses of the patients from sites in China (please see Section 9.4.8 for details).

All populations and planned analyses described, relate to the Global population unless otherwise stated. A patient randomised in China prior to global recruitment closure will be included in both the Global ITT population and the China cohort ITT population. A patient randomised in China after the global recruitment closure will be included only in the China cohort ITT population.

Table 15 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy Data	
PFS	Full Analysis Set (ITT population)
PFS2, OS, ORR [a], DoR [a], TFST, TSST, TDT, PROs, and symptom endpoints (including EORTC QLQ-C30 and EORTC QLQ-EN24, EQ-5D-5L, PGI-TT, PGIC, PGIS, PGI-BR and PRO-CTCAE)	Full Analysis Set (ITT population)

Outcome variable	Populations
Demographic data/baseline characteristics	
Demography	Full Analysis Set (ITT population)
Baseline and disease characteristics	Full Analysis Set (ITT population)
Protocol deviations (protocol deviations and important protocol deviations)	Full Analysis Set (ITT population)
Medical/surgical history	Full Analysis Set (ITT population)
Previous anti-cancer therapy	Full Analysis Set (ITT population)
Concomitant/previous medications/procedures	Full Analysis Set (ITT population)
Subsequent anti-cancer therapy	Full Analysis Set (ITT population)
Pharmacokinetic data (durvalumab only)	
Pharmacokinetic data	PK Analysis Set
Safety Data	
Exposure	Safety Analysis Set
Adverse events	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital signs	Safety Analysis Set
Electrocardiograms	Safety Analysis Set
Biomarker Data	
Biomarkers CCI CCI	Full Analysis Set (ITT population)

Abbreviations: CCI DNA; DoR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients 30; EORTC QLQ-EN24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer 24; EQ-5D-5L = EuroQoL five dimensions, five level health state utility index; FAS = full analysis set; CCI CCI CCI ITT = intent to treat; MMR = mismatch repair; CCI ORR = objective response rate; OS = overall survival; CCI PFS = progression free survival; PFS2 = time from randomisation to second progression or death; PGI-BR = patient global impression of benefit/risk; PGIC = patient global impression of change (in symptoms); PGIS = patient global impression of severity; PGI-TT = patient global impression of treatment tolerability; PK = pharmacokinetics; PRO = patient reported outcomes; PRO-CTCAE = Patient Reported Outcomes Common Terminology Criteria for Adverse Event; CCI ; TDT = time to discontinuation or death; TFST = Time to first subsequent therapy or death; CCI TSST = Time to second subsequent therapy or death.

[a] Patients who are evaluable for the analysis of ORR are those with measurable disease at baseline. Patients who are evaluable for the analysis of DoR are those who responded in the ORR analysis.

9.2.1 Full analysis set

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

9.2.2 PK analysis set

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

9.2.3 Safety analysis set

The safety analysis set will consist of all randomised patients who received any amount of study treatment (ie, durvalumab/placebo or olaparib/placebo). Safety data will not be formally analysed but summarised using the safety analysis set. Patients who initially received a dose of durvalumab/placebo will be summarised according to the arm to which they were randomised. This is in order to provide a summary of the underlying safety profile that patients should expect when initially prescribed treatment (ie, SoC, SoC + durvalumab, or SoC + durvalumab + olaparib).

9.3 Outcome measures for analyses

9.3.1 Calculation or derivation of efficacy variables

9.3.1.1 RECIST 1.1-based endpoints

The analysis of the primary endpoint, PFS, and the analyses of the secondary endpoints, ORR and DoR, will be based on the site investigator assessments using RECIST 1.1.

9.3.1.1.1 Investigator RECIST 1.1-based assessments

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

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD or not evaluable (NE) depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to randomisation. If a patient has had a tumour assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD).

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

9.3.1.1.2 Blinded Independent Central Review (BICR)

A BICR of radiological scans will be performed on all patients to confirm the robustness of the PFS endpoint.

All imaging assessments including unscheduled visit scans will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data

(CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a patient has had a tumour 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). Endpoints (of PFS) 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.

9.3.1.2 Primary endpoint: Progression-free survival (PFS)

PFS (per RECIST 1.1 as assessed by the site investigator) will be defined as the time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomisation + 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 consecutive missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have baseline data, 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 triggered progression.
- For BICR assessments, date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the reviewer selecting PD that the adjudicator agreed with, or of the reviewer who read the baseline scan first where both reviewers select PD as a timepoint response, and there is no adjudication for central review (BICR) data.
- For both BICR and investigator assessments, 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.

9.3.1.3 Overall survival (OS)

OS is defined as the time from the date of randomisation 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 data cut-off for the analysis (these contacts should generally occur within 7 days of the data cut-off). If patients are confirmed to

be alive or if the death date is after the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries, that is, the status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the OS analyses should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries where local laws allow.

In the event that the patient has actively withdrawn consent to the processing of their personal data, the death date of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

9.3.1.4 Objective response rate (ORR)

ORR is defined as the percentage of patients with a confirmed investigator-assessed response of CR or PR and will be based on a subset of all randomised patients with measurable disease at baseline per the site investigator. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders in the ORR.

9.3.1.5 Duration of response (DoR)

DoR (per RECIST 1.1 using investigator assessment) will be defined as the time from the date of first documented response (which is subsequently confirmed) until 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 PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR (which was subsequently confirmed). If a patient does not progress following a response, then their DoR will use the PFS censoring time. DoR will only be defined for patients who are responders in the ORR analysis.

9.3.1.6 Time from randomisation to second progression or death (PFS2)

Time from randomisation to second progression or death (PFS2) will be defined as the time from the date of randomisation to the earliest of the progression event subsequent to first subsequent therapy or death. The date of second progression will be recorded by the investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Second progression status will be reviewed following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for

whom a second disease progression has not been observed should be censored at date last known alive and without a second disease progression (ie, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death).

9.3.1.7 Time from randomisation to first subsequent therapy or death (TFST)

The TFST will be defined as the time from the date of randomisation to earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment or death due to any cause.

Any patient not known to have died at the time of the analysis and not known to have had a subsequent anti-cancer therapy will be censored at the last known time to have not received subsequent anti-cancer therapy, ie, the last of the follow-up visits where this was confirmed.

If a patient terminated the study for any reason other than death before first subsequent therapy, this patient will be censored for TFST evaluation at the earliest of their last known to be alive and termination dates.

Patients who did not receive any of the study treatments but remained in the study, the first alternative cancer therapy they receive will be the initial therapy. In this situation, TFST will be calculated as time from randomisation to the start of the initial alternative therapy or death.

9.3.1.8 Time from randomisation to second subsequent therapy or death (TSST)

The TSST will be defined as the time from randomisation to the earlier of start date of the second subsequent anti-cancer therapy after discontinuation of first subsequent treatment or death due to any cause. Any patient not known to have died at the time of the analysis and not known to have had a second subsequent anti-cancer therapy will be censored at the last known time to have not received second subsequent anti-cancer therapy, ie, the last of the follow-up visits where this was confirmed.

If a patient terminated the study for reason other than death before a second subsequent therapy, these patients will be censored for the TSST evaluation at the earliest of their last known to be alive and termination dates.

Patients who did not receive any of the study treatments, the first alternative cancer therapy they receive first subsequent anti-cancer therapy such that the second anti-cancer therapy would be the second subsequent anti-cancer therapy. TSST will then be calculated as time from date of randomisation to the start of the second alternative anti-cancer therapy or death.

9.3.1.9 Time from randomisation to study treatment discontinuation or death (TDT)

The TDT will be defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death due to any cause.

Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored at the last recorded date on which the patient was known to be alive.

9.3.2 Calculation or derivation of safety variables

The following adverse events are considered treatment emergent:

- Adverse events with an onset date on or after first dose of IP
- Worsening of pre-existing events on or after first dose of IP

and within 30 days following discontinuation of olaparib or 90 days following discontinuation of durvalumab, whichever is longer.

For other safety parameters, “on treatment” will be defined as assessments from the date of first dose of IP (Cycle 1 Day 1) and

- 30 days following last dose of olaparib
- 90 days following last dose of durvalumab.

9.3.2.1 Adverse events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AstraZeneca/designee.

For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that start after dosing or any AEs that start prior to dosing but which worsen following exposure to the treatment.

Adverse events observed in the on-treatment period or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only as a number of AEs following discontinuation of the study treatment are likely to be attributable to subsequent therapy. However, to assess the longer-term toxicity profile, AE summaries will also be produced containing AEs observed up until 30 days following discontinuation of olaparib or 90 days following discontinuation of durvalumab, whichever is longer (ie, without taking subsequent therapy into account). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

A separate data listing of AEs occurring more than 30 days after discontinuation of olaparib or 90 days after discontinuation of durvalumab (whichever is longer) will be produced. These events will not be included in AE summaries.

Adverse events of special interest

AESIs are events of scientific and medical interest specific to the further understanding of the safety profiles of olaparib and durvalumab and may require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI may be serious or non-serious.

Other significant adverse events

During the evaluation of the AE data, an AstraZeneca/MedImmune medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of study drug. Based on the expert's judgement, AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant AEs and reported in the CSR. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant AEs.

9.3.2.2 Other safety assessments

For vital signs, laboratory data, ECGs, and physical examinations, the baseline value will be the latest result obtained prior to the start of study treatment.

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

$$\text{Corrected calcium (mmol/L)} = \text{Total calcium (mmol/L)} + ([40 - \text{albumin (g/L)}] \times 0.02)$$

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.

Creatinine clearance

CrCL may be measured by 24-hour urine collection (or another clinically validated test) or calculated using the Cockcroft and Gault equation.

For creatinine values in mg/dL:

$$\text{Estimated CrCL (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For creatinine values in µmol/L:

$$\text{Estimated CrCL (mL/min)} = \frac{(140\text{-age [years]}) \times \text{weight (kg)} \times 1.04}{\text{serum creatinine (µmol/L)}}$$

9.3.3 Calculation or derivation of patient-reported outcome variables

All questionnaires will be scored according to published scoring guidelines or the developer's guidelines. All PRO analyses will be based on the FAS, unless otherwise stated.

9.3.3.1 EORTC QLQ-C30 and EN24

The EORTC QLQ-C30 and EN24 will be scored according to the EORTC Scoring Manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the scales. Higher scores indicate better functioning/HRQoL, but higher scores on symptom scales represent greater symptom burden. 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.

Change from baseline in all EORTC QLQ-C30 and EN24 subscale scores will be evaluated. For all scales, a clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 (Osoba et al 1998). At each post-baseline assessment, the change in scores from baseline will be categorised as improvement, no change, or deterioration as shown in Table 16.

Table 16 Clinically meaningful change and visit response – EORTC QLQ-C30 and EN24

Score	Change from baseline	Visit response
Health status/quality of life scale and functional scales	≥10-point increase from baseline	Improvement
	≥10-point decrease from baseline	Deterioration
	Otherwise	No change
Symptom scales	≥10-point increase from baseline	Deterioration
	≥10-point decrease from baseline	Improvement
	Otherwise	No change

Time to deterioration in functioning and disease symptoms

Patients whose functioning or symptom has not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last evaluable PRO assessment. Also, if functioning or symptom deteriorates or the patient dies after 2 or more missed PRO assessment visits, then the patient will be censored at the time of the last evaluable PRO assessment prior to the 2 missed visits.

Time to deterioration in the physical functioning and role functioning subscales of the EORTC QLQ-C30 and back/pelvic pain, urological symptom and GI symptom subscales of the EN24 will be calculated. Time to deterioration will be defined as the time from randomisation until the date of the first clinically meaningful deterioration that is confirmed at a subsequent visit (except if it was the patient's last available assessment) at least 14 days apart or death.

The population for the analysis of time to deterioration in functioning will include a subset of the FAS who have baseline scores of ≥10 and for symptom deterioration will include a subset of the FAS who have baseline scores of ≤90.

PRO compliance

Summary measures of overall compliance and visit compliance will be derived for each PRO questionnaire and presented in tables. These will be based upon the following definitions:

- Expected: Number of patients still under PRO follow-up expected to complete a questionnaire 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).
- Received: Number of patients from whom a completed questionnaire with at least 1 item completed was received
- Evaluable: Number of patients for whom at least 1 subscale can be determined
- Compliance rate (visit): Compliance will be calculated separately for each visit, including baseline, for each treatment arm as (Evaluable ÷ Expected) * 100.
- Completion rate (visit): Completion will be calculated separately for each visit, including baseline, for each treatment arm as (Evaluable ÷ randomised patients) * 100.
- Evaluable rate: Evaluability rate will be calculated separately for each visit, including baseline, for each treatment arm as (Evaluable ÷ Received) * 100.
- Overall compliance or completion rate: Patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least 1 Received/Evaluable postbaseline questionnaire. Patients are counted as Expected if they are expected to complete at least a baseline questionnaire. Rates are expressed in percentages.

9.3.4 Calculation or derivation of pharmacokinetic variables

9.3.4.1 Pharmacokinetic analysis

PK parameters will be determined from the raw data. The following PK parameters will be determined after the steady-state doses: peak and trough concentration (as data allow).

9.3.4.2 Immunogenicity analysis

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

9.3.5 Calculation or derivation of biomarker variables

Biomarker status, as defined in the exploratory objectives, will be assessed for evaluable patients in each cohort according to prespecified criteria that will be detailed in the statistical analysis plan (SAP).

9.3.6 Calculation or derivation of pharmacogenetic variables

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

9.4 Statistical analyses

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

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. More detail will be provided in the SAP.

9.4.1 Efficacy analyses

9.4.1.1 Timing of efficacy analyses

Futility and other interim analyses are described in Section 9.5.

The timing of efficacy analyses is summarised in Table 17 and is described below.

Table 17 Timing of efficacy analyses

Analysis	Timepoint
Primary PFS/ First interim OS analysis	The same calendar time when there are approx. 299 PFS events across durvalumab+placebo arm and control arm and approx. 281 events across durvalumab+olaparib arm and control arm
Second interim OS analysis	The same calendar time when there are approx. 244 deaths across durvalumab+placebo arm and control arm, and approx. 244 deaths across durvalumab+olaparib arm and control arm
Final OS analysis	The same calendar time when there are approx. 280 deaths across durvalumab+placebo arm and control arm, and approx. 280 deaths across durvalumab+olaparib arm and control arm

Abbreviations: Approx. = approximately.

9.4.1.2 Summary of planned efficacy analyses

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment group. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised 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, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomisation.

All data collected will be listed. Efficacy and PRO data will be summarised and analysed based on the FAS. PK data will be summarised and analysed based on the PK Analysis Set. Safety data will be summarised on the Safety Analysis Set.

All outputs will be summarised by treatment arm for all randomised patients (FAS).

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

Table 18 details which endpoints will be subject to formal statistical analysis, together with pre-planned secondary and supportive analyses, making it clear which analysis is regarded as primary for that endpoint. Note, all endpoints compare both the durvalumab+placebo arm versus control and the durvalumab+olaparib versus control in all randomised patients (FAS population), unless otherwise indicated.

In order to characterise the benefits of the durvalumab+placebo arm versus control and durvalumab+olaparib versus control, ORR, PFS2, TFST, TSST, TDT and change from

baseline in HRQoL measures will be tested at a 2-sided significance level of 5% alongside the primary PFS analysis.

An exploratory analysis comparing the durvalumab+olaparib and durvalumab+placebo arms will be undertaken. This will be further described in the SAP.

Table 18 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analysed	Notes
Progression-free survival	Stratified log-rank test Hazard ratio using a Cox proportional hazards model Plots and summaries of number (%) patients with progression or death events at landmark timepoints using Kaplan-Meier Supportive analyses: • Evaluation time bias; stratified log-rank test using investigator RECIST data • Attrition bias (using alternative censoring rules); stratified log-rank test using investigator RECIST data • Ascertainment bias; repeat of the primary PFS analysis using BICR data • Deviation bias (if meaningful to do); stratified log-rank test using investigator RECIST data
Objective response rate	Descriptive summary of the number and percentage of patients with a confirmed tumour response according to the investigator (CR/PR) based on the number of patients with measurable disease at baseline Adjusted logistic regression
Duration of response	Descriptive summary of the duration of response according to the investigator in responding patients, including the associated Kaplan-Meier curves (without any formal comparison or p-value attached)
PFS2, TFST, TSST, TDT	Stratified log-rank test Hazard ratio using a Cox proportional hazards model Plots and summaries of number (%) patients with events at landmark timepoints using Kaplan-Meier
Overall survival	Stratified log-rank test Hazard ratio using a Cox proportional hazards model Plots and summaries of number (%) of deaths at landmark timepoints using Kaplan-Meier
Change from baseline in EORTC QLQ-C30 and QLQ-EN24 scores	MMRM analysis of the change from baseline in EORTC QLQ-C30 and QLQ-EN24 scores
Time to deterioration (EORTC QLQ-C30 and QLQ-EN24 endpoints)	Stratified log-rank test Hazard ratio using a Cox proportional hazards model Plots and summaries of number (%) patients with deterioration events at landmark timepoints using Kaplan-Meier
EQ-5D-5L	Summary statistics on Health state utility Plots of summary information QAPFS using mixed effects models Duration of “good quality of life” using Q-TWiST analysis

Endpoints analysed	Notes
PK analysis (durvalumab only)	Descriptive statistics will be summarised for all individual concentration data per time points.

Abbreviations: BICR = blinded independent central review; CR = complete response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients 30; EORTC QLQ-EN24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer 24; EQ-5D-5L = EuroQoL five dimensions, five level health state utility index; FAS = full analysis set; MMRM = mixed model for repeated measures; PFS2 = time from randomisation to second progression or death; PK = pharmacokinetic; PR = partial response; QAPFS = quality-adjusted progression-free survival; Q-TWiST = quality-adjusted time without symptoms of disease or toxicity; RECIST = Response Evaluation Criteria in Solid Tumours; TDT = time to discontinuation or death; TFST = time to first subsequent therapy or death; TSST = time to second subsequent therapy or death

9.4.1.3 Primary endpoint: Progression-free survival

PFS will be analysed using a log-rank test stratified by MMR status (proficient versus deficient), disease status (recurrent disease versus newly diagnosed) and geographic region (Asia versus RoW). If the number of events is too small for a meaningful analysis (less than 5 events per stratum), a pre-specified strategy to account for such a situation will be applied. Further details will be documented in the SAP. The hazard ratio for each treatment comparison of interest together with its corresponding CI and p-value will be presented (a hazard ratio less than 1 will favour the experimental arm). The hazard ratio and confidence interval will be estimated from a stratified Cox Proportional Hazards model.

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

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

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

Subgroup analyses

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using investigator assessments) in the durvalumab+placebo arm versus control and in the durvalumab+olaparib arm versus control to assess consistency of treatment effect across potential or expected prognostic factors including the following subgroups of the FAS (but not limited to):

- MMR status (proficient versus deficient)
- Disease status (recurrent versus newly diagnosed)
- Region (Asia versus RoW).

Other baseline variables, including biomarkers, may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms.

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.

9.4.1.4 Overall survival

OS will be analysed using a stratified log-rank tests, using the same methodology as described for the primary PFS endpoint. The same stratification factors will be used as the primary PFS analysis. If the number of deaths is too small for a meaningful analysis (less than 5 deaths per stratum), a pre-specified strategy to account for such a situation will be applied. Further details will be documented in the SAP. The effect of durvalumab+placebo versus control will be estimated by the HR together with its corresponding CI and p-value. This will be repeated for the comparison of durvalumab+olaparib versus control.

A KM plot of OS will be presented by treatment arm for each comparison (durvalumab+placebo versus control and durvalumab+olaparib versus control).

Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS for each treatment.

9.4.2 Safety analyses

Safety data will be presented using descriptive statistics unless otherwise specified. Safety and tolerability data will be presented by treatment arm.

Data from all cycles of treatment will be combined in the presentation of safety data.

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

AEs will be presented for each treatment group by SOC, high level term and/or PT covering number and percentage of patients reporting at least one event and number of events where appropriate.

AEs occurring prior to start of IP, treatment emergent AEs and post-treatment AEs will be presented separately.

An overview of AEs will present for each treatment group the number and percentage of patients with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP, as well as AEs leading to IP dose interruptions/delays and AEs leading to IP dose reduction as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, Common Toxicity Criteria (CTC) grading, seriousness, death and events leading to discontinuation of IP as well as other action taken related to IP, events of special interest, other significant adverse events and timing of events.

Key patient information will be presented for patients with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

Other safety data will be assessed in terms of physical examination, clinical chemistry, haematology, vital signs, and ECGs. Full details of all safety analyses will be provided in the SAP.

9.4.3 Pharmacokinetic data (durvalumab only)

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

9.4.4 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 neutralising 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 neutralising properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the AstraZeneca Clinical Pharmacology group or designee.

9.4.5 Pharmacokinetic/pharmacodynamic relationships

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

9.4.6 Biomarker data

The relationship of MMR status to clinical outcomes of (including but not restricted to) PFS will be presented in the CSR. The relationship of exploratory biomarkers (CCI CCI to clinical outcomes may also be presented in the CSR, if applicable.

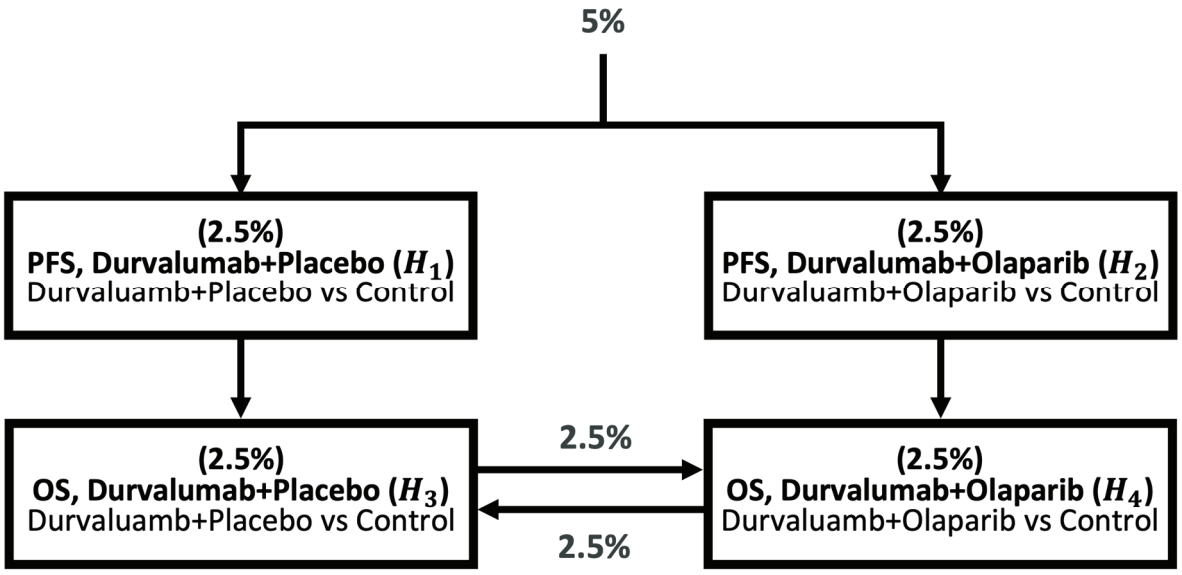
Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.4.7 Methods for multiplicity control

In order to strongly control the type I error at 5% (2-sided), a multiple testing procedure (MTP) with a gatekeeping strategy will be used across the key endpoints (PFS and OS) and treatment comparisons of interest (durvalumab+placebo arm versus control and

durvalumab+olaparib arm versus control). If the higher level null hypothesis in the MTP is rejected for superiority, the following hypothesis will then be tested as shown in Figure 3.

Figure 3 Illustration of multiplicity testing strategy



Alpha levels presented are 2-sided.

Hypotheses will be tested using a MTP with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, hypotheses will be tested in a pre-defined order as outlined in Figure 3. According to alpha (test mass) splitting and alpha recycling, the test mass that becomes available after each rejected null hypothesis is recycled to secondary hypotheses not yet rejected. Since OS is tested at multiple timepoints (ie, 2 interim analyses and final analysis), the OS tests that for the same comparison (ie, shown in one box in the MTP) will be considered as one test family. As long as one test in the family can be rejected, the family is rejected thus the assigned total alpha to the family can be recycled to the next MTP level. This testing procedure stops when the entire test mass is allocated to non-rejected null hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided), among all key hypotheses. Figure 3 shows the multiple testing framework.

The details on the alpha-exhaustive recycling procedure will be provided in the Statistical Analysis Plan.

Overall survival is tested at 2 interims and a final timepoint (see Section 9.5 for details). The alpha level allocated to OS will be controlled at the interim and primary time points by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien

Fleming approach, where the alpha level applied at the interim depends upon the proportion of information available. Note: If any interim analysis or primary analysis is statistically significant, the overall alpha (two-sided) will be allocated to the next level. If the interim results do not meet the criterion of stopping for superiority for a given hypothesis, then follow-up will continue until the final target number of OS events for that comparison has been observed, following which the hypothesis will be retested. If the null hypothesis is then rejected, subsequent testing will continue hierarchically. The above testing procedure will ensure strong control of the family-wise error rate (Glimm et al 2009).

Note, the interim/final OS analysis boundaries will ultimately be derived based on the actual number of events observed in the study; those referenced above and in Figure 3 are provided as examples only.

9.4.8 China cohort

The global recruitment into this study will close to all sites apart from China when approximately 699 patients have been randomised. Any patient from China, randomised before the global recruitment is closed (ie, last subject randomised from a non-Chinese site) will be included in both the global ITT population and the China cohort ITT population. A patient randomised in China after the global recruitment closure will be included only in the China cohort ITT population.

Approximately 129 patients from sites in China will be recruited and randomised in a 1:1:1 ratio to the study treatments and will follow the same study plan and procedures as patients recruited to the global study. The safety and efficacy data collected will be summarised and analysed separately to the global study safety and ITT analysis sets (as defined in Section 9.2).

The primary analysis of efficacy for the China cohort will be an assessment of programmatically derived PFS based on investigator assessments (RECIST 1.1) in the China cohort ITT population (China FAS). The China FAS comprises all patients from sites in China who are randomised regardless of whether they receive treatment or not. The data cut-off for the analysis of PFS in the China cohort will be undertaken at the same calendar time when approximately 55 PFS events have occurred (64% maturity) for the comparison of the durvalumab+placebo arm versus the control arm and approximately 52 PFS events have occurred (60% maturity) for the comparison of the durvalumab+olaparib arm versus the control arm.

Where data permit, summaries and analysis of secondary supportive efficacy endpoints (including at least but not limited to OS) will be performed for the China cohort. The detailed analysis plan will be documented in the China supplementary SAP.

When assessing safety and tolerability, summaries will be produced separately for the China cohort based on the China safety analysis set. The China safety analysis set includes all

subjects from sites in China who receive any amount of study treatment (ie, durvalumab/placebo or olaparib/placebo). The China safety data will be summarised descriptively and will not be formally analysed.

9.5 Interim analyses

9.5.1 Futility and interim analyses

A futility analysis of PFS for the comparison of the durvalumab+placebo arm versus control and the durvalumab+olaparib arm versus control will be performed approximately 2-months post-last subject randomised (LSR), and when a minimum of 50% of the target number of PFS events for each comparison has occurred (150 of 299 target events across the durvalumab+placebo and control arms, and 141 of 281 target events across the durvalumab+olaparib and control arms) (approximately 25 months after the first patient has been randomised). The boundary for declaring futility and dropping an experimental arm will be observing a HR>1.15. The futility analyses will be performed by an IDMC (see Section 9.5.2).

In addition to the futility analysis, 2 interim OS analyses are planned. The first interim OS analysis will be performed at the time of the primary analysis of PFS when approximately 74% of the target number of OS events would have occurred (ie, 208 of 280 OS events per comparison [durvalumab+placebo versus control and durvalumab+olaparib versus control]).

A second interim analysis of OS may be performed at the same calendar time when approximately 244 OS events (87% of the target number of OS events) have occurred for the comparison of the durvalumab+placebo arm versus the control arm, as well as the durvalumab+olaparib arm versus control (approximately 51 months after the first patient is randomised). Multiplicity adjustments for these interim analyses and the stopping rule are discussed in Section 9.4.7.

Note: If the OS interim results do not meet the criterion of stopping for superiority for a given hypothesis, then follow-up will continue until the final target number of OS events for that comparison has been observed, following which, the hypothesis will be re-tested.

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

9.5.2 Independent data monitoring committee (IDMC)

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.

In addition to the internal procedures for ensuring patient safety, this study will use an external IDMC comprised of independent therapeutic area experts and a biostatistician. The IDMC will assess ongoing safety analyses as well as the interim futility analysis.

The IDMC will be convened after the first 30 patients complete 1 cycle of study treatment and meet approximately every 6 months thereafter until unblinding (unless there is a need for an ad hoc meeting or increased frequency). The IDMC will meet to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. In addition, the IDMC will meet for the futility analysis, which will occur approximately 2-months post-LSR, and when a minimum of 50% of the target number of PFS events for each comparison has occurred (approximately 25 months after the first patient has been randomised).

For the interim analysis, the IDMC will review unblinded interim data and inform the sponsor whether the interim boundaries specified in Section 9.5.1 are met.

The study may also be stopped based on the findings of the interim safety analysis conducted by the IDMC. Otherwise, recommendations from the IDMC may include recommendations to continue or modify the study. The IDMC will not reveal the results of the analyses when they make recommendations. The final decision to modify or stop the study will however rest with AstraZeneca.

Full details of the IDMC procedures and communication process concerning all safety reviews and the interim analyses can be found in the IDMC Charter.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki, as amended at 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

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

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

The investigator will be responsible for the following:

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

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

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 Financial disclosure

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

A 3 Informed consent process

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

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign statements of informed consent at pre-screening and screening:

- The pre-screen informed consent is mandatory. It will be obtained prior to the screening informed consent, in order to acquire a tumour sample and perform MMR analysis prior to randomisation.
- The screening informed consent must be obtained prior to performing any screening/baseline procedures and evaluations. Informed consent for study procedures from screening onwards (main consent form) should be obtained after the MMR tumour sample has been shipped and within 28 days prior to Cycle 1 Day 1.

During the treatment period, patients who have an initial RECIST 1.1-defined progressive disease (PD) may continue to receive study treatment for the purpose of confirming disease

progression (see Section 6.1.3 for details). Patients or their legally authorised representative will be required to sign a statement of informed consent to continue study treatment until confirmation of disease progression.

The statements of consent will meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

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

Patients must be re-consented to the most current version of the ICFs during their participation in the study.

A copy of the ICFs must be provided to the patient or the patient's legally authorised representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and she will not be excluded from other aspects of the study.

Patients who are rescreened are required to sign a new main ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

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

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals

might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a patient's identity and might also have access to 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 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 her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

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

A 6 Dissemination of clinical study data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

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

A 7 Data quality assurance

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

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

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

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

The sponsor or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan(s).

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

The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

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

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

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study 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 multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence (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 unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above
- AEs for new primary malignant tumours reported during a study should generally be assessed as serious AEs. If no other seriousness criteria apply, the ‘important medical event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the primary malignant tumour event should be assessed and reported as a non-serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples include Stage I basal cell carcinoma and Stage IA1 cervical cancer removed via cone biopsy.
- Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter’s transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

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).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

CTCAE grade

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

For each episode of an AE, all changes to the CTCAE grade as well as the highest attained CTC grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A guide to interpreting the causality question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised 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 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an investigational product/study intervention or AstraZeneca non-investigational product 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 recognised 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, (eg, wrong route, wrong dose [error greater than ± 10%], or wrong site of administration)
- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (eg, kept in the refrigerator when it should be at room temperature)
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS – including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) (eg, forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of investigational product/study intervention or AstraZeneca non-investigational product for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of investigational product/study intervention or AstraZeneca non-investigational product for medicinal purposes outside of the authorised product information, or for unauthorised investigational products/study interventions or AstraZeneca non-investigational products, outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that they were feeling better when not taking the whole dose

- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

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

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

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

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, 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 organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 guidance document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories(https://www.iata.org/whatwedo/cargo/dgr/Pages/download.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, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650.

Exempt – all other materials with minimal risk of containing pathogens:

- Clinical 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/dangerous_goods/infectious_substances.htm)
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genomics Initiative

D 1 Use/analysis of DNA

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

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

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

Genetic research may consist of the analysis of the structure of the patient´s DNA, ie, the entire genome.

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

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

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

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

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

Exclusion criteria

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

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

Withdrawal of consent for genetic research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined Appendix C 2.

Collection of samples for genetic research

The blood sample for genetic research should be obtained from the patients during screening, if possible. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at screening, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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

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

Ethical and regulatory requirements

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

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the part of the consent form for the main study and the part for the genetic component of the study. A copy of the signed and dated consent form must be given to the patient and the original filed at the study centre. The principal investigator(s) is/are responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection

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

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

Data management

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

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

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

Statistical methods and determination of sample size

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

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE 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 IP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's law (PHL)

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

Hy's law (HL)

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section E 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's law criteria not met

If the patient does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's law criteria met

If the patient does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section E 6 within this Appendix)

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 PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For patients that met PHL criteria prior to starting IP, the investigator is not required to submit a PHL SAE unless there is a **significant change**# in the patient's condition.

- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study patient's follow-up (including any further laboratory testing) and the continuous review of data.

- Subsequent to this contact the investigator will:

    - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician. This includes deciding which tests available in the Hy's law lab kit should be used.
    - Complete the three liver eCRF modules as information becomes available.

    # A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

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 subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.

- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

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

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required when potential Hy's law criteria are met before and after starting study treatment

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

At the first on-study treatment occurrence of PHL criteria being met, the investigator will determine if there has been a **significant change**[#] in the patient's condition compared with the last visit where PHL criteria were met.

- If there is no significant change, no action is required.

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2.

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

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

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

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

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease), or did the patient meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix E 6?

If **No**: Follow the process described in Appendix E 4.1.

If **Yes**: Determine if there has been a significant change[#] in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Appendix E 4.

E 8 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory.

Hy's Law lab kit

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgM and IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive.
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China.

E 9 References

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury., Clinical Pharmacology and Therapeutics 2011;89(6):806-815.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation. July 2009. Available from: URL: https://www.fda.gov/downloads/guidances/UCM174090.pdf. Accessed 08 October 2019.

Appendix F Acceptable birth control methods

All treatments used in this study have a medium/high foetal risk.

Women of childbearing potential and who are sexually active, must agree to the use of at least one highly effective method of contraception (as listed below), and their partners must use a male condom, or they must totally/truly abstain from any form of sexual intercourse (see below). This should be started from the signing of the main informed consent and continue throughout the period of taking study treatment and for at least 90 days after the last dose of study intervention or 6 months after the last dose of olaparib/placebo, whichever is later.

Please note that local guidelines and recommendations for administration of standard of care chemotherapy should always be followed, and may indicate continuation of contraception measures for a period longer than that described above.

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 Sections F1 and F2 below. 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).

F 1 Non-hormonal highly effective methods of contraception (<1% failure rate)

- Total/true abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 90 days after the last dose of study intervention or 6 months after the last dose of olaparib/placebo, whichever is later. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine device PLUS male condom. Provided coils are copper-banded.

F 2 Hormonal highly effective methods of contraception (<1% failure rate)

- Normal and low dose combined oral pills PLUS male condom
- Cerazette® (desogestrel) PLUS male condom. Cerazette® is currently the only highly efficacious progesterone-based pill.

- Hormonal shot or injection (eg., Depo-Provera®) PLUS male condom
- Etonogestrel implants (eg, Implanon®, or Norplant®) PLUS male condom
- Norelgestromin/ethinyl oestradiol transdermal system PLUS male condom
- Intrauterine system (IUS) device (eg, levonorgestrel-releasing IUS Mirena®) PLUS male condom
- Intravaginal device (eg, ethinyl oestradiol / etonogestrel-releasing intravaginal devices such as NuvaRing®) PLUS male condom
- Patch PLUS male condom: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Xulane).

Appendix G Guidelines for evaluation of objective tumour response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

RECIST 1.1 with minor modifications is used in the study. The differences from the published RECIST guidelines include the removal of clinical examination and ultrasound as valid modalities to evaluate Target Lesions (TL), Non-Target Lesions (NTL) or new lesions; and the rule to identify new lesions on ^{18}FDG-PET scans.

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 guidelines (Eisenhauer et al 2009) with regard to investigator assessment of tumour 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 and abdominal masses/abdominal organomegaly identified by physical examination (manual palpation) that is not measurable by CT or MRI.
- Previously irradiated lesions[3]
- Skin lesions

[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 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.

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 TLs.

Target Lesions (TLs):

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at 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.

Tumour lesions selected for fresh screening biopsy should not be selected as TLs, 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 19.

Table 19 Summary of imaging modalities for tumour assessment

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

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

CT and MRI
CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible anatomical images for measurement of TL, assessment of NTL, and identification of any New Lesions.

It is recommended that IV contrast-enhanced CT examinations of the chest, abdomen and pelvis (including the entire liver and both adrenal glands) will be used to assess tumour burden at baseline and follow-up visits. Any other areas of disease involvement (eg, 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. Tumours 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 tumours as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumour size. Tumours 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 tumour assessments as they are not validated in the context of tumour assessment.

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

Histology and cytology
Histology on tumour biopsy samples will not be used as part of the tumour 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 tumour 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
^{18}F-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[4] not present on an FDG-PET scan from a previous visit or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no FDG-PET scan available from a previous visit, 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 confirm new lesions.

Tumour response evaluation

Schedule of evaluation

Baseline assessments 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 and should be performed within the 28 days prior to Day 1 of Cycle 1 of study treatment and ideally as close as possible to the start of

[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.

study treatment. Follow-up assessments will be performed at the times specified in the study plans (see Table 2 and Table 3).

If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled imaging visits.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be 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 2 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, embolisation, 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 tumour visit response for TL (see Table 20).

Table 20 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 21).

Table 21 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR = Complete response; PR = Partial response; PD = Progression of disease; NE = Not evaluable; NTL = Non-target lesion; TL = Target lesion.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumour 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 tumour. If a new lesion is equivocal, for example because of its small size, the treatment and tumour 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 tumour assessments where clinically feasible.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 22.

Table 22 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	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/non-PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NA	NA	No	NED

CR = Complete response; PR = Partial response; SD = Stable disease; PD = Progression of disease; NE = Not evaluable; NA = Not applicable (only relevant if there were no target and/or non-target lesions at baseline); NED = No evidence of disease.

Study treatment will be discontinued when disease progression per RECIST 1.1 is determined. In the rare instances when the RECIST 1.1-defined radiological findings are considered equivocal by the investigator or there is doubt whether or not there is evidence of objective progression (eg, technical issues including image artefacts), a follow-up scan will be performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD. If the repeat scan confirms progression, then study treatment must be discontinued, and the date of the initial scan should be declared as the date

of PD. If the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST 1.1-defined PD.

Study treatment may be administered until radiological PD is confirmed by the subsequent scan, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, or spinal cord compression) will not be eligible to continue study treatment.

Specifications for anatomical imaging

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

CT scan

CT scans of the chest, abdomen and pelvis should be contiguous throughout all the anatomic region of interest.

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

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours 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 tumour measurements but also identification of new disease.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the

prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed, CT without IV contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a maximum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

MRI scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies [eg, neck]) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

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

References

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

Appendix H Patient Reported Outcomes

H 1 EORTC QLQ-C30

Patient Reported Outcomes Questionnaire: EORTC QLQ-C30 was removed due to copyrights

Patient Reported Outcomes Questionnaire: EORTC QLQ-C30 was removed due to copyrights

H 2 EORTC QLQ-EN24

Patient Reported Outcomes Questionnaire: EORTC QLQ-EN24 was removed due to copyrights

Patient Reported Outcomes Questionnaire: EORTC QLQ-EN24 was removed due to copyrights

H 3 EQ-5D-5L

Patient Reported Outcomes Questionnaire: EQ-5D-5L was removed due to copyrights

Patient Reported Outcomes Questionnaire: EQ-5D-5L was removed due to copyrights

Patient Reported Outcomes Questionnaire: EQ-5D-5L was removed due to copyrights

H 4 PRO-CTCAE

Patient Reported Outcomes Questionnaire: PRO-CTCAE was removed due to copyrights

H 5 PGIS

Patient Reported Outcomes Questionnaire: PGIS was removed due to copyrights

H 6 PGIC

Patient Reported Outcomes Questionnaire: PGIC was removed due to copyrights

H 7 PGI-TT

Patient Reported Outcomes Questionnaire: PGI-TT was removed due to copyrights

H 8 PGI-BR

Patient Reported Outcomes Questionnaire: PGI-BR was removed due to copyrights

Patient Reported Outcomes Questionnaire: PGI-BR was removed due to copyrights

Appendix I Olaparib toxicity management instructions

Management of haematological toxicity

Management of anaemia

Table 23 Management of anaemia

Haemoglobin	Action to be taken
Hb <10 *but* ≥8 g/dL (CTCAE Grade 2)	First occurrence Give appropriate supportive treatment and investigate causality. Investigator judgement 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 >9g/dL. Subsequent occurrences: If repeat Hb <10 g/dL *but* ≥9 g/dL, investigator judgement to continue olaparib with supportive treatment (eg, transfusion) or dose interrupt (for a maximum of 4 weeks) and upon recovery dose reduction may be considered (to **250** mg bd as a first step and to **200** mg bd as a second step). If Hb <9 but ≥8 g/dL, dose interrupt (for a maximum of 4 weeks) until Hb ≥9 g/dL and upon recovery dose reduction may be considered (to **250** mg bd as a first step and to **200** mg bd 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 dose reduce to **250** mg bd as a first step and to **200** mg bd as a second step in the case of repeat Hb decrease. If transfusion is required when the patient is receiving olaparib/placebo and durvalumab/placebo in combination (or is within 90 days of receiving the combination, if either drug has been discontinued), the following should be performed prior to any transfusion • Direct Coombs test • Reticulocyte count • Haptoglobin • LDH

Abbreviations: bd = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; Hb = haemoglobin; LDH = lactate dehydrogenase.

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to guidance later in this section for the management of this.

Management of neutropenia, leukopenia and thrombocytopenia

Table 24 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE Grade 1 or better for a maximum of 4 weeks. If repeat CTCAE Grade 3-4 occurrence, dose reduce olaparib to 250 mg bd as a first step and 200 mg bd as a second step.

Abbreviations: bd = twice daily; CTCAE = Common Terminology Criteria for 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 CTCAE Grade 3 or worse neutropenia 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 24 hours of the last dose of study treatment unless absolutely necessary. Study treatment can be restarted at the same dose if the AE of neutropenia or leukopenia has recovered to CTCAE Grade ≤1 (ANC > 1.5×10^9/L). Growth factor support should be stopped at least 24 hours before restarting study drug (7 days for pegylated G-CSF).

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged haematological toxicity (≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse), refer to guidance later in this section for the management of this.

Management of prolonged haematological toxicities while on study treatment

If a patient develops prolonged haematological toxicity such as:

- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse neutropenia (ANC < 1×10^9/L)
- ≥2-week interruption/delay in study treatment due to Common Toxicity Criteria (CTC) Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50×10^9/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 haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC Grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE 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 AML is confirmed.

Management of non-haematological 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, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 adverse event occurs which 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, dyspnoea) 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 CT scan) should be performed to exclude pneumonitis. Please also refer to the durvalumab toxicity management guidelines in (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.

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) 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 [ESMO], National Comprehensive Cancer Network [NCCN]), generally a single agent antiemetic 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 eCRF.

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 25 Dose reductions for olaparib

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

Abbreviations: bd = twice daily

Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCL falls below the threshold for study inclusion (≥51 mL/minute), re-testing should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated CrCL either by Cockcroft-Gault equation, a 24-hour urine test or another clinically validated test) of between 31 and 50 mL/minute for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg bd (see Table 10).

Because the CrCL determination is only an estimate of renal function, in instances where the CrCL falls to between 31 and 50 mL/minute, 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 J Changes related to mitigation of study disruptions due to cases of civil crisis, natural disaster, or public health crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the Sponsor.

Study sites may continue to recruit new patients into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new patients effectively and in compliance with the protocol
- Data will continue to be entered into the eCRF and queries resolved in a timely manner

J 1 Reconsent of study patients during study interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in J2 to J5. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

J 2 Rescreening of patients to reconfirm study eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated AstraZeneca study physician. In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Table 1 the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Table 1. The procedures detailed in Section 5.2 must be undertaken to confirm eligibility using the same E-code as for the patient.

J 3 Home or remote visit to replace on-site visit (where applicable)

A qualified HCP from the study site or TPV service may visit the patient's home / or other remote location as per local Standard Operating Procedures (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

J 4 Telemedicine visit to replace on-site visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, and other relevant data to be collected according to study requirements to be reported and documented.

J 5 At-home or remote delivery of olaparib/placebo

Where a patient has discontinued/interrupted intravenous study treatments and is receiving olaparib/placebo study treatment only, alternative secure delivery methods for drug supply may be permitted if the patient is unable to attend the site, but only provided the critical safety assessments have been performed and the delivery methods are in line with local regulatory requirements.

J 6 Data capture during telemedicine or home / remote visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the patients themselves.

Appendix K Guidance during the COVID-19 Outbreak

K 1 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section K 4). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

Notably, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.5, Exclusion Criterion 6).

K 2 Potential Risks during COVID-19

Every effort should be made to follow the CSP. This appendix provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention durvalumab/placebo and olaparib/placebo.

The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

K 3 New Participant Enrolment

Study sites may continue to recruit new participants into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new participants effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criterion 6 (see CSP Section 5.5), participants with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such participants (including those who have confirmed COVID 19) should not be included for study participation.

Per exclusion criterion 30, patients who have circumstances that could limit compliance with study requirements should also be excluded. Please consider this criterion carefully considering evolving circumstances, travel restrictions and health care delivery in your local area that may impact the continued treatment in the study.

The Study Physician should be contacted if any additional guidance or clarification is needed via the local monitor or directly.

K 4 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed.

K 5 Vaccination against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of intravenous study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

K 6 Durvalumab/ Durvalumab Placebo: Product specific guidance in relation to the ongoing and emerging novel coronavirus (COVID-19) pandemic

K 6.1 Ongoing Participants receiving durvalumab/placebo

Participants receiving treatment with durvalumab/placebo should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, treatment with durvalumab/placebo should be interrupted until such assessments can be completed.

K 6.1.1 Participants with an event suspected to be COVID-19

Delay or omit treatment with durvalumab/placebo as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, treatment with durvalumab/placebo may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

K 6.1.2 Participants with confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have treatment with durvalumab/placebo withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

K 6.1.3 Restarting treatment with durvalumab/placebo

Treatment with durvalumab/placebo must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

K 7 Olaparib/Placebo: Product specific guidance in relation to the ongoing and emerging novel coronavirus (COVID-19) pandemic

For ongoing patients:

- Patients must continue to have safety blood tests as per protocol schedule. Alternative methods for safety assessments include using local laboratories and follow up by phone contact, virtual visits can be used (see Appendix J for mitigation procedures)
- If it becomes unfeasible to perform the required safety blood tests for a patient, then study treatment should be interrupted until this can resumed and the reason clearly documented, with reference to COVID-19.
- If a patient tests positive for the COVID-19 virus, interrupting olaparib/placebo treatment for 14 days or until symptoms resolve should be considered. Factors that should be taken into consideration might include:
  - Severity of COVID-19 symptoms
  - Status of safety blood results, particularly haemoglobin, neutrophils and lymphocytes
  - Benefit risk for the individual patients including curative vs palliative intent of treatment and response to olaparib/placebo
- If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib/placebo treatment should be interrupted, and prompt investigation initiated to determine whether symptoms are due to COVID-19 or potentially drug-induced pneumonitis.
- Olaparib is cleared by metabolism, predominantly by the CYP3A4/5 isozymes. Therefore, the use of olaparib/placebo with the concomitant use of strong inhibitors of these isoenzymes including some antibiotics and antivirals (eg telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir and telaprevir) is not recommended.

References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

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EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

Appendix L Abbreviations

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
Anti-HBc	Hepatitis B core antibody
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AZD2281	Olaparib
bd	Twice daily
BICR	Blinded independent central review
BP	Blood pressure
BRCA	Breast cancer susceptibility gene
*BRCA*m	*BRCA* mutated
CA125	Cancer antigen 125
CD	Cluster of differentiation
cfDNA	Cell-free DNA
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CrCL	Creatinine clearance
CR	Complete response
CRO	Contract research organisation
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CCI	
CTIS	Clinical Trial Information System (EU)

Abbreviation or special term	Explanation
CTLA	Cytotoxic T lymphocyte-associated
CYP	Cytochrome P450
CYP3	Cytochrome P450, family 3 gene locus
DCO	Data cut-off
DDR	DNA damage response
DILI	Drug-induced liver injury
dMMR	Deficient mismatch repair
DoR	Duration of response, defined as the time from date of first documented response until date of documented progression or death in the absence of disease progression
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
E-code	Enrolment code
ECOG	Eastern Cooperative Oncology Group: a performance status using scales and criteria to assess how a patient's disease is progressing
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitors
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients 30
EORTC QLQ-EN24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial Cancer 24
ePRO	Electronic patient-reported outcomes
EQ-5D-5L	EuroQoL five dimensions, five level health state utility index
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (US)
FFPE	Formalin-fixed, paraffin-embedded
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FSH	Follicle stimulating hormone
FWER	Family wise error rate
g*BRCA*	Germline *BRCA*
g*BRCA*m	Germline *BRCA*-mutated
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal

Abbreviation or special term	Explanation
GSHv	Group-sequential Holm variable
Hb	Haemoglobin
HbsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HL	Hy's Law
HIV	Human immunodeficiency virus
HLA-LOH	Human leukocyte antigen – loss of heterozygosity
HRCT	High resolution computed tomography
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRR	Homologous recombination repair
HRRm	Homologous recombination repair related gene mutation
HRQoL	Health-related quality of life
IB	Investigator brochure
IC	Immune cells
ICF	Informed consent form
IEC	Independent ethics committee
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.
IDMC	Independent data monitoring committee
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IHC	Immunohistochemistry
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
INR	International normalised ratio
IP	Investigational product
IRB	Institutional review board
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan-Meier
LDH	Lactate dehydrogenase

Abbreviation or special term	Explanation
LH	Luteinising hormone
LIMS	Laboratory Information Management System
LSR	Last subject randomised
mAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MEDI4736	Durvalumab
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	MicroRNA
MLH1	MutL homologue 1
MMR	Mismatch repair (tumour tissue)
MMRM	Mixed model repeated measures
MOA	Mechanism of action
MRI	Magnetic resonance imaging
MSH2	MutS protein homologue 2
MSH6	MutS protein homologue 6
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSS	Microsatellite stable
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate, defined as the proportion of patients with measurable disease who have complete response or partial response
OS	Overall survival, defined as the time from the date of randomisation until death due to any cause
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase
PARPi	PARP inhibitor
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PET	Positron emission tomography
PFS	Progression-free survival, defined as the time from randomisation until the date of objective disease progression (per RECIST 1.1) or death (by any cause in the absence of progression)

Abbreviation or special term	Explanation
PFS2	Second progression-free survival, defined as the time from randomisation to the earliest of progression event subsequent to first subsequent therapy (assessed by the investigator per local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression), or death due to any cause
PGI-BR	Patient global impression of benefit/risk
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PGI-TT	Patient global impression of treatment tolerability
PHL	Potential Hy's Law
PK	Pharmacokinetic
pMMR	Proficient mismatch repair
PMS2	PMS1 protein homologue 2
PR	Partial response
PRO	Patient-reported outcome(s)
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PSR	Platinum-sensitive relapsed
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QAPFS	Quality-adjusted progression-free survival
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
Q-TWiST	Quality-adjusted time without symptoms of disease or toxicity
RECIST	Response Evaluation Criteria in Solid Tumours. This study will use RECIST version 1.1.
REVPRDI	Review of PRO/Questionnaire/Diary
RNA	Ribonucleic acid
RoW	Rest of the world
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
s*BRCA*m	Somatic *BRCA*-mutated
SD	Stable disease
SoA	Schedule of activities
SoC	Standard of care
SpO_2	Saturation of peripheral oxygen
TCGA	The Cancer Genome Atlas

Abbreviation or special term	Explanation
CCI	
TDT	Time to discontinuation or death, defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death
TFST	Time to first subsequent therapy or death, defined as the time from randomisation to the earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment or death due to any cause
TIL	Tumour-infiltrating lymphocyte
TL	Target lesion
CCI	
TMG	Toxicity management guideline
TOI	Treatment outcome index
TP53	Tumour protein 53 (also known as p53)
TSST	Time to second subsequent therapy or death, defined as the time from randomisation to the earlier of start date of the second subsequent anti-cancer therapy after discontinuation of first subsequent treatment or death due to any cause
ULN	Upper limit of normal
US	United States of America
vs	Versus
WBDC	Web based data capture