Clinical Study Protocol	
Drug Substance	Durvalumab (MEDI4736), Olaparib
Study Code	D933IC00003
Version	4.0
Date	9 July 2021

A Phase II, Randomized, Multi-Center, Double-Blind, Comparative Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With Olaparib for First-Line Treatment in Platinum-Ineligible Patients With Unresectable Stage IV Urothelial Cancer

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden
EudraCT number: 2017-004556-27, NCT03459846

VERSION HISTORY

Version 1.0, 16 November 2017
Initial creation
Version 2.0, 20 July 2018
The language of pre-treatment and post-treatment was changed to pre-dose and post-dose, respectively, as applicable, for consistency throughout the protocol.
Section 1.1 (Schedule of Activities [text and Table 2 {timing for assessments of survival status, hematology, clinical chemistry, and TSH}]), Section 1.2 (Synopsis [Progression during treatment, Follow-up of patients post discontinuation of study drug, and Survival]), Section 2.3.2.2 (Risks), Section 4.3.1 (Durvalumab dose rationale), Section 6.7.1 (Durvalumab), Section 7.1.1 (Procedures for discontinuation of study treatment), Section 8.2.3 (Vital signs), and Section 8.3.2 (Time period and frequency for collecting AE and SAE information) were updated to align with the updated content and language in the durvalumab template Edition 1.0.
Table 1 was updated with the definition for End of Treatment as included in footnote "c," and all subsequent footnotes were updated accordingly from "d" to "u."
The language of PBMCs was updated to "Whole blood – exploratory analysis (mandatory)" in Tables 1 and 2, and the corresponding footnotes in Tables 1 and 2 were updated accordingly.
The timing of the PRO assessments in Table 2 was updated.
Section 1.2 (Synopsis) was updated with the correct estimated date for last patient completed.
Section 1.2 (Synopsis) was modified to reflect the changes in Section 3 (Objectives and Endpoints), Section 4.1 (Overall design), and Section 9.4 (Statistical Considerations).
Section 1.2 (Synopsis), Section 4.1 (Overall design), and Section 9.2 (Sample size determination) were updated to reflect the change in the number of patients randomized from approximately 256 to 150 patients and the change in the stratification factors to include the patient's homologous recombination repair (HRR) status (mutant versus wildtype).

Section 1.3 (Schema) was updated to reflect the change in the study design, specifically with regard to the number of patients screened and randomized and the stratification factors.
Section 2.1 (Study rationale) and Section 2.3.4 (Olaparib and durvalumab benefit/risk) were updated to reflect the change in the focus of the endpoints from the HRR mutant to the Full Analysis Set all-comers population.
Section 3 (Objectives and Endpoints) was updated to reflect the revised study objectives and endpoints in light of the change in the analysis plan to analyse the Full Analysis Set as the primary analysis population rather than the HRR mutant subgroup population.
Section 5.1 (Inclusion criteria [criterion number 6]) was updated to reflect the definition of platinum ineligibility.
Section 5.4 (Screen failures) was updated with the removal of the following text: “HRRwt patients excluded from study randomization as part of the biomarker enrichment procedure may not be rescreened” to reflect the revised randomization and stratification process for the study.
Section 6.4.1 (Procedures for randomization) and Section 6.4.2 (Patient enrollment and randomization) were updated to reflect the revised randomization and stratification process for the study.
Section 6.4.4 (Methods for ensuring blinding) and Section 6.4.5 (Methods for unblinding study) were updated with the removal of text concerning the patients, Investigators, and sites remaining blinded to HRR status.
Section 8.1.2 (Tumor biopsies) was updated to provide clarity concerning the genetic testing results.
Section 8.2.1 (Clinical safety laboratory assessments [Table 10]): Text was removed regarding the absolute percentage count.
Section 8.2.6 (Vulnerability Elders Survey-13) was added to include an additional assessment, and Table 1, Section 8.1.4, Section 8.1.4.4, and Section 9.4.2.1 were updated accordingly.
Section 8.5.3 (Storage and destruction of PK/ADA samples) was updated to include revised language concerning the destruction of durvalumab pharmacokinetic (PK) and anti-drug antibody samples and to include information regarding the handling of olaparib PK samples.

Section 8.7 (Genetics) was updated to include subsections 8.7.1 (Optional exploratory genetic sample) and 8.7.2 (Storage and destruction of genetic sample) that discuss the optional exploratory genetic sample and the storage and destruction of the genetic samples.
Section 8.8.1.3 (Collection of whole blood [mandatory]) was updated for clarity of the sample collection.
Section 9 (Statistical Considerations), Section 9.4.2 (Efficacy analyses), Section 9.4.3 (Safety analyses), and Section 9.4.9 (Exploratory analyses) were updated to reflect the changes made in Section 3 (Objectives and Endpoints).
Section 9.4.1.2 (Calculation or derivation of safety variables) was updated to reflect the changes made in Section 1.1 (Schedule of Activities [Table 2]) and in Section 8.3.2 (Time period and frequency for collecting AE and SAE information).
Section 9.4.1.4 (Calculation or derivation of biomarker variables) was updated to include the revised text concerning the determination of PD-L1 status for clarity.
Version 3.0, 15 November 2019
Appendix G was removed due to the TMG update. According to new template, the TMG will be submitted as standalone annex. Appendix G was removed as reference throughout the protocol.
Section 2.3.2.2 updates made per Durvalumab IB edition 15
Section 8.3.13 updates made per Durvalumab IB edtion 15 – AESI list and revised wording including changes in relation to removal of Appendix G
Section 8.4.5.1 updates made in language in relation to applying the TMG as separate clinical document
Appendix B2 added language on malignancies,
PFS will not be updated at the time of the final OS analysis for the HRRm subgroup. Change made throught the protocol.
Version 4.0, 9 July 2021
Section 2.2.1 Removal of reference to durvalumab being approved in second-line patients with locally advanced/metastatic urothelial cancer.

Section 2.2.2 Removal of reference to durvalumab being approved in US as a treatment for patients with urothelial carcinoma and replacement with text that durvalumab is licensed as a treatment for patients with certain types of lung cancer.
Section 2.2.3 Update on olaparib indications as per olaparib IB edition 20.
Section 2.3.2.1 Removal of reference to durvalumab being approved in US as a treatment for patients with urothelial carcinoma.
Section 4.3.1.3 Removal of reference to durvalumab being approved in US as a treatment for patients with urothelial carcinoma.
Section 4.4.1 Addition of alternative options of treatment supply to subjects in case olaparib or durvalumab are commercially available.
Section 5.3 Table 4 Update to the examples of brand names of contraceptive drugs, to be in line with olaparib IB Edition 20.
Section 8.3.13.2 Text on AESIs for olaparib updated to reflect that MDS/AML was changed to be an important identified risk to be in line with olaparib IB Edition 20.

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

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The procedures for the screening and treatment period in this study are presented in Table 1, and the procedures for the period following discontinuation of all study treatment are presented in Table 2. Patients who continue beyond Cycle 13 will continue with all Cycle 13 assessments until termination of treatment (see Table 1).

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

For both treatment arms

- Patient-reported outcome (PRO) assessments will be done at the beginning of the dosing cycle regardless of dosing delays. In case of dose delay, PRO assessments may also be assessed during all ad hoc unscheduled visits. Tumor efficacy (Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST 1.1]) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (not the date of therapy).
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc., required for dosing should be performed within 3 days prior to dosing.

For durvalumab treatment

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1) due to either an immune or a non-immune-related adverse event (AE).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible (see Section 8.4.5.1).
  - One cycle is equal to 28 days.
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST 1.1) and PRO assessments. Time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see the current Investigator's Brochure for durvalumab).

For olaparib/placebo treatment

- Patients may delay and subsequently resume dosing per standard clinical practice. Dose reductions may also occur if the study treatment dose is not tolerable (see Section 8.4.5.2).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.
  - One cycle is equal to 28 days (56 doses of olaparib/placebo administered twice daily [BID]).

Table 1 Schedule of assessments for patients who are receiving study treatment

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to PD [a, b]	EOT visit [c]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1**	**q28days ±3 days unless dosing needs to be held for toxicity reasons**					
Informed consent								
Informed consent: study procedures	X							5.1
Informed consent: genetic sample and analysis (optional)	X							5.1
Randomization [d]	X							4.1, 6.4
Study procedures								
Physical examination (full)	X							8.2.2
Targeted physical examination (based on symptoms)		X	X	X	X	X	X	8.2.2
Vital signs	X	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	8.2.3
Weight	X	X	X	X	X	X	X	8.2.3
ECG [f, g]	X	As clinically indicated						8.2.4
Concomitant medications	<----------						---------->	6.6
Demography, including baseline characteristics and tobacco use	X							5.1, 5.2
Eligibility criteria [h]	X							5.1, 5.2
TNM staging	X							5.1
Laboratory assessments								
HBsAg, HCV antibodies, and HIV antibodies	X							8.2.1
Clinical chemistry	X	X [i]	Prior to each durvalumab administration [j]				X	Table 9
Hematology	X	X [i]	Prior to each durvalumab administration [j]				X	Table 10
Coagulation parameters (aPTT and INR)	X	As clinically indicated						Table 10
TSH (reflex free T3 or free T4 [k])	X	X [i]	X	X	X	X	X	Table 9
Urinalysis [g, l]	X	As clinically indicated						Table 11
Pregnancy test [m]	X	As clinically indicated						5.1

Table 1 Schedule of assessments for patients who are receiving study treatment

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to PD [a, b]	EOT visit [c]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1**	**q28days ±3 days unless dosing needs to be held for toxicity reasons**					
Pharmacokinetics								
Durvalumab PK sample (serum)		X [n]	X [o]		X [o]			8.5.1.1
Olaparib PK sample (plasma)		X [o]	X [o]		X [o]			8.5.1.2
Monitoring								
WHO/ECOG performance status	X	X	X	X	X	X	X	8.2.5
AE/SAE assessment [p]	<----------						---------->	8.3
Drug accountability		X	All visits					6.3
IP administration								
Durvalumab [q]		X [r]	X [r]	X [r]	X [r]	X [r]		6.1.1.1
Olaparib/placebo [q]		X	X	X	X	X		6.1.1.2
Other assessments and assays								
Tumor biopsy (FFPE sample) [s]	X [s]					X [s]		8.1.2, 8.8.1.1
Genetic sample	X							8.7, Appendix D
Durvalumab immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)		X [o]	X [o]		X [o]			8.5.2
Whole blood for gene expression (PaxGene-RNA tubes)	X [o]	X [o]	X [o]			X [o]		8.8.1.2
Whole blood – exploratory analysis (mandatory) [t]	X	X	X	X	X	X	X	8.8.1.3
Urine (mutational analysis)	X	X	X	X	X	X	X	8.8.1.4
ctDNA (plasma)	X	X	X	X	X	X	X	8.8.1.5
EORTC QLQ-C30 and EQ-5D-5L [u]		X	q4w (±7 days relative to Cycle 1 Dose 1 date) until treatment discontinuation					8.1.4.1, 8.1.4.2

Table 1 Schedule of assessments for patients who are receiving study treatment

	Screening	C1 [a]	C2 [a]	C3 [a]	C4 [a]	C5 to PD [a, b]	EOT visit [c]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**					
Day	**-28 to -1**	**1**	**q28days ±3 days unless dosing needs to be held for toxicity reasons**					
PGIC [u]				X	q8w (±7 days relative to the date of Cycle 1 Dose 1 date) until treatment discontinuation			8.1.4.3
VES-13 [u]		X						8.2.6
Efficacy evaluations								
Tumor assessment (CT or MRI) (RECIST 1.1) [b]	X	q8w ±1 week beginning 8 weeks after randomization for the first 48 weeks, and then q12w ±1 week thereafter (relative to the date of randomization) until clinical progression with or without RECIST 1.1-defined radiological progression. An additional follow-up scan is requested, if clinically feasible. The schedule of q8w ±1 week for the first 48 weeks and then q12w ±1 week thereafter MUST be followed regardless of any delays in dosing.						8.1

[a] These cycles refer to the 28-day cycles of administration of durvalumab.

[b] Screening/Baseline scans and tumor assessments by RECIST 1.1 criteria should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to and prior to the date of randomization. Patients will have on-study scans done q8w ±1 week for the first 48 weeks relative to the date of randomization and then q12w ±1 week thereafter until clinical progression with or without RECIST 1.1-defined radiological progression. An additional follow-up scan is requested, if clinically feasible and if criteria for treatment beyond progression are met. Clinically stable patients with RECIST 1.1-defined radiological PD who continue to receive study treatment at the discretion of the Investigator and patient should receive a subsequent scan, preferably at the next regularly scheduled imaging visit but no earlier than 4 weeks later, and this subsequent scan is assessed using the Confirmation of Radiological Progression criteria described in Appendix F. RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen, and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessment at their next scheduled visit.

[c] EOT will occur when both IPs are discontinued.

[d] It is recommended that patients commence study treatment as soon as possible after randomization, and ideally within 3 days.

[e] On the first infusion day, patients in the durvalumab + olaparib and durvalumab + placebo groups will be monitored, and vital signs will be collected/recorded in the eCRF prior to, during, and after infusion of IP. BP and pulse will be collected from patients before, during, and after each infusion and 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 minute [ie, the beginning of the infusion]), approximately 30 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 60 minutes ±5 minutes). For subsequent infusions, BP, pulse, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of the infusion.

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

[g] Individual sites are required to indicate in the unscheduled visit eCRF if an ECG or a urinalysis was performed during study treatment.

[h] Eligibility should be confirmed prior to randomization.

[i] If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. Serum or plasma chemistry (serum sample is preferred), hematology, and/or LFT monitoring may be performed more frequently if clinically indicated.

[j] Chemistry/hematology parameters should be collected at any time during the cycle visit for subjects that have discontinued durvalumab due to toxicity.

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

[l] Site to specify type of test used and provide appropriate lab reference range. Preferred method is Urine Dipstick.

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

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

[o] Samples should be taken pre-dose for both olaparib and durvalumab.

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

[q] Treatment to be administered until confirmed PD.

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

[s] Archival tumor is mandatory for enrollment; biopsies at progression are optional, and the treating physician will judge the feasibility of such a procedure.

[t] Whole blood for exploratory analyses will be collected during screening, pre-dose on Day 1 of Cycles 1 to 4, every 12 weeks thereafter (ie, every 3 cycles), at discontinuation/progression, and at the 90-day follow-up visit (Table 2).

[u] PRO assessments will be done using a site-based electronic device at the beginning of the dosing cycle regardless of dosing delays. In case of dose delay, PROs may also be assessed during all ad hoc unscheduled visits. It is preferred that PRO questionnaires are completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid biasing the patient's responses to the questions.

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

ADA Antidrug antibody; AE Adverse event; aPTT Activated partial thromboplastin time; BP blood pressure; C Cycle; CR Complete response; CT Computerized tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EDTA Ethylenediaminetetraacetic acid; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EOT End of treatment; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; FFPE Formalin-fixed paraffin-embedded; HBV Hepatitis B virus; HCV Hepatitis C virus; HIV Human immunodeficiency virus; IM Intramuscular; IO Immuno-oncology; IP Investigational product; INR International normalized ratio; IV Intravenous; LFT Liver function test; MRI Magnetic resonance imaging; PD Progressive disease; PGIC Patient Global Impression of Change; PK Pharmacokinetic(s); PR Partial response; PRO Patient-reported outcome; q4w Every 4 weeks; q8w Every 8 weeks; q12w Every 12 weeks; q28days Every 28 days; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TNM Classification of Malignant Tumors (Tumor, Lymph Nodes, Metastasis); TSH Thyroid stimulating hormone; VES-13 Vulnerability Elders Survey-13; WHO World Health Organization.

Table 2 Schedule of assessments for patients who have discontinued all study treatment

	Time since last dose of IP								
Evaluation	**Day (±3)**	**Months (±1 week)**						**12 months and every 2 months thereafter (±2 weeks)**	**For details, see Section**
	30	**2**	**3**	**4**	**6**	**8**	**10**		
Physical examination (full)	X								8.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								8.2.3
Weight	X	X	X		X				8.2.3
Pregnancy test [a]	X	As clinically indicated							5.1
AE/SAE assessment	X	X	X						8.3
Concomitant medications	X	X	X						6.6
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy [b]								8.2.5
Subsequent anticancer therapy [c]	<----------							---------->	8.1
Survival status [d]		X	X	X	X	X	X	X (every 2 months)	8.1
Hematology	X	X	X						Table 10
Clinical chemistry	X	X	X						Table 9
Urinalysis [e]	As clinically indicated								Table 11
TSH (reflex free T3 or free T4) [f]	X	X	X						Table 9
Durvalumab PK sample (serum) [g]			X						8.5.1.1
Olaparib PK sample (plasma)	X								8.5.1.2
Immunogenicity assessment (ADA sampling) to identify ADA responses [g]			X		X				8.5.2
Whole blood – exploratory analysis (mandatory) [h]			X						8.8.1.3

Table 2 Schedule of assessments for patients who have discontinued all study treatment

	Time since last dose of IP								
Evaluation	**Day (±3)**	**Months (±1 week)**						**12 months and every 2 months thereafter (±2 weeks)**	**For details, see Section**
	30	**2**	**3**	**4**	**6**	**8**	**10**		
EORTC QLQ-C30 and EQ-5D-5L [i]	X	X	X	Patients who enter follow-up without PD and do not attain PD by follow-up Month 3 will continue with q8w (±7 days relative to follow-up Month 3 visit date) until PD and thereafter complete 1 more assessment. Patients who attain PD by follow-up Month 3 will complete only 1 additional q8w assessment.					8.1.4.1, 8.1.4.2
Tumor assessment (CT or MRI) (RECIST 1.1) [j]	q8w ±1 week beginning 8 weeks after randomization for the first 48 weeks, and then q12w ±1 week thereafter (relative to the date of randomization) until clinical progression with or without RECIST 1.1-defined radiological progression. An additional follow-up scan is requested, if clinically feasible. The schedule of q8w ±1 week for the first 48 weeks and then q12w ±1 week thereafter MUST be followed regardless of any delays in dosing.								8.1

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

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

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

[d] Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for UC after the last dose of the IP must be recorded in the eCRF.

[e] Individual sites are required to indicate in the eCRF if a urinalysis was performed during an unscheduled visit.

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

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

[h] Whole blood for exploratory analyses will be collected during screening, pre-dose on Day 1 of Cycles 1 to 4, every 12 weeks thereafter (ie, every 3 cycles), at discontinuation/progression (Table 1), and at the 90-day follow-up visit.

[i] PRO assessments will be done using a site-based electronic device. It is preferred that PRO questionnaires are completed prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

[j] Patients will have on-study scans done q8w ±1 week for the first 48 weeks relative to the date of randomization and then q12w ±1 week thereafter until clinical progression with or without RECIST 1.1-defined radiological progression. An additional follow-up scan is requested, if clinically feasible. Clinically stable patients with RECIST 1.1-defined radiological PD who continue to receive study treatment at the discretion of the Investigator and patient (following consultation with AstraZeneca) should receive a subsequent scan, preferably at the next regularly scheduled imaging visit but no earlier than 4 weeks later, and this subsequent scan is assessed using the Confirmation of Radiological Progression criteria described in Appendix F. RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen, and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessment at their next scheduled visit.

ADA Antidrug antibody; AE Adverse event; CT Computerized tomography; ctDNA circulating tumor deoxyribonucleic acid; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; IP Investigational product; IV Intravenous; MRI Magnetic resonance imaging; PD Progressive disease; PK Pharmacokinetics; PRO Patient-reported outcome; q4w Every 4 weeks; q8w Every 8 weeks; q12w Every 12 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone; UC Urothelial cancer; WHO World Health Organization.

1.2 Synopsis

International co-ordinating investigator

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Protocol title: A Phase II, Randomized, Multi-Center, Double-Blind, Comparative Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With Olaparib for First-Line Treatment in Platinum-Ineligible Patients With Unresectable Stage IV Urothelial Cancer

Rationale:

Treatment options for platinum-ineligible patients with urothelial cancer (UC) remain limited with relatively low objective response rate (ORR) with monotherapy programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) therapy. Olaparib will be combined with the PD-L1 inhibitor durvalumab to broaden the therapeutic effect of durvalumab monotherapy, based in part on the separate non-overlapping mechanisms of action of the component agents and on the potential for mechanistic synergy. Based on this biology, the hypothesis to be tested in this study is that increased DNA damage triggered through poly (ADP ribose) polymerization (PARP) inhibition will result in enhanced antitumor immunity that can be further enhanced through combination with an immune checkpoint inhibitor in UC. It is also anticipated that the combination of olaparib and durvalumab will be of particular benefit to patients with metastatic UC with DNA repair-deficient cancers (as assessed by presence of inactivating mutations in homologous recombination repair [HRR] genes). However, this mechanism of enhanced PARP inhibitor-induced immune activation may be operative in all patients, and therefore, the study design will be employed to evaluate the safety and efficacy of olaparib and durvalumab in both HRR mutated (HRRm) and HRR wild-type (HRRwt) patients.

Objectives and endpoints

Primary objective:	**Endpoint/Variable:**
To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in terms of PFS	PFS as determined by Investigator assessment according to RECIST 1.1
Secondary objectives:	**Endpoint/Variable:**
Key secondary objective:	
To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo	OS
Additional secondary objectives:	
To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo	DoR, ORR, and PFS6 according to RECIST 1.1 using Investigator assessment OS18
To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in the subset of patients with HRRm	PFS, DoR, ORR, and PFS6 according to RECIST 1.1 using Investigator assessment
To assess the PK of durvalumab and olaparib in both treatment arms	Concentration of durvalumab and olaparib
To investigate the immunogenicity of durvalumab in both treatment arms	Presence of ADAs for durvalumab
To assess disease-related symptoms and HRQoL in patients with UC treated with durvalumab + olaparib combination therapy compared with durvalumab + placebo	EORTC QLQ-C30: Global health status/QoL, functioning (physical), and multi-term symptoms (fatigue and pain)
Safety objective:	**Endpoint/Variable:**
To assess the safety and tolerability profile of durvalumab + olaparib combination therapy compared with durvalumab + placebo	AEs/SAEs, physical examinations, laboratory findings (including clinical chemistry, hematology and urinalysis), WHO/ECOG performance status, and vital signs
Exploratory objectives	**Endpoint/Variable:**
To assess overall change in health status since the start of study treatment in UC patients treated with durvalumab + olaparib combination therapy compared with durvalumab + placebo	PGIC
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L during assigned treatment	EQ-5D-5L will be used to derive health state utility based on patient-reported data
To collect blood, urine, and tissue samples for defining biological responses to durvalumab + olaparib and for identifying candidate markers that may correlate with likelihood of clinical benefit	Biomarkers (eg, DNA or ctDNA alterations, protein expression detected by IHC, change in ctDNA levels, and mRNA expression) correlating with clinical response

ADA Anti-drug antibody; AE Adverse event; CR Complete response; ctDNA Circulating tumor deoxyribonucleic acid; DNA Deoxyribonucleic acid; DoR Duration of response; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EQ-5D-5L EuroQoL 5 dimension, 5-level health state utility index; HRQoL Health-related quality of life; HRRm homologous recombination repair mutated; IHC Immunohistochemistry; mRNA Messenger ribonucleic acid; ORR Objective response rate; OS Overall survival; OS18 Patients alive at 18 months; PD-L1 Programmed death ligand 1; PFS Progression-free survival; PFS6 Progression-free survival at 6 months; PGIC Patient Global Impression of Change; PK Pharmacokinetic(s); PRO Patient-reported outcome; QoL Quality of Life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; UC Urothelial cancer; WHO World Health Organization.

Overall design:

This is a Phase II, randomized, double-blind, placebo-controlled, multi-center, comparative global study to determine the efficacy and safety of durvalumab + olaparib combination therapy versus durvalumab + placebo (durvalumab monotherapy) as first-line treatment in patients ineligible for platinum-based therapy with unresectable Stage IV UC.

Study period:

Estimated date of first patient enrolled: Q1 2018

Estimated date of last patient completed: Q2 2021

Number of patients:

Approximately 150 patients globally will be randomized in a 1:1 ratio to either the durvalumab + olaparib treatment group or the durvalumab + placebo treatment group (75 patients per arm). The randomization will be stratified based on HRR status (mutant versus wild type) and Bajorin risk index (a composite stratum for lymph node only metastasis versus metastasis to any other organ system and Eastern Cooperative Oncology Group [ECOG] performance status [0, 1 versus 2]).

Treatments and treatment duration:

Durvalumab and olaparib/placebo will be administered beginning on Day 1 until confirmed progressive disease (PD) as per RECIST 1.1 as assessed by the Investigator unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Progression during treatment

During the treatment period, patients receiving durvalumab + olaparib or durvalumab + placebo who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is to be collected after the initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD, and this scan is evaluated using the Confirmation of Radiological Progression criteria, which are outlined in Appendix F. If the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST 1.1-defined PD, which in turn will require a subsequent scan evaluated using the Confirmation of Radiological

Progression criteria outlined in Appendix F. However, patients in the immunotherapy arm(s) will not be permitted to continue immunotherapy if progression occurs after confirmed response (complete response or partial response as defined by RECIST 1.1) to immunotherapy treatment in the target lesions (regardless of the appearance of new lesions) (ie, the response and progression events both occurred in the target lesions while receiving immunotherapy during the same treatment period).

Follow-up of patients post discontinuation of study drug

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

Survival

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

Independent data monitoring committee:

An independent data monitoring committee (IDMC) composed of independent experts will be established to perform an interim assessment of the safety of durvalumab + olaparib combination therapy in this population. The first safety review will take place approximately 6 months after the study has started. Safety reviews will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment.

The IDMC will meet approximately every 6 months, unless otherwise requested by the IDMC. IDMC members will be consulted to ensure appropriate frequency.

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

Statistical methods:

The primary objective is to assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in terms of progression-free survival (PFS) as determined by the Investigator according to RECIST 1.1 in the Full Analysis Set (FAS). The secondary objective is to assess overall survival (OS) in the FAS. Other secondary efficacy variables include ORR, duration of response (DoR), the proportion of patients who are progression-free at 6 months and the proportion of patients alive at 18 months (OS18).

The primary analysis of PFS will be performed at 1 timepoint only, when approximately 118 events have occurred (79% maturity). Assuming a median PFS of 3 months for durvalumab monotherapy (durvalumab + placebo arm) and recruitment of 150 patients in

6 months, it is estimated that this data cutoff (DCO) will occur 7 months following recruitment of the last patient.

There will be up to 2 analysis timepoints for OS. The first OS analysis will occur at the same time as the primary PFS analysis and will be based on an estimated 44 OS events across therapies (29% maturity), and the second OS analysis will occur when approximately 100 OS events have occurred (67% maturity). With an approximate 6-month recruitment period and an assumed median OS of 16 months in the durvalumab + placebo arm, it is anticipated that the final analysis will be performed at approximately 27 months after the last patient has been recruited.

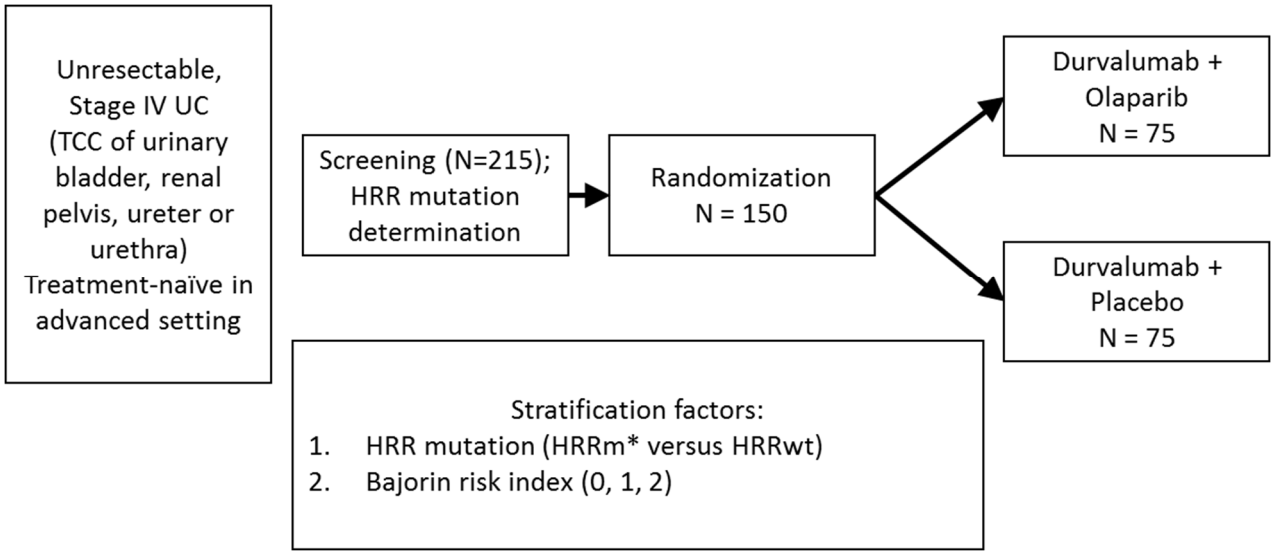
PFS will be based on the RECIST 1.1 using the Investigator tumor assessments. The analysis will be performed for patients in the FAS population, using a stratified log-rank test with covariates for HRR status (HRR mutant versus wildtype), PD-L1 tumor status (defined in Section 9.4.1.4) and Bajorin risk index (0 versus 1 versus 2). The effect of treatment will be estimated by the hazard ratio (HR) together with the corresponding 95% confidence interval from a stratified Cox model (an HR less than 1 will favor durvalumab in combination with olaparib).

Safety data will be summarized descriptively.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



*The expected prevalence of HRRm is approximately 14%.

HRR Homologous recombination repair; HRRm Homologous recombination repair mutation; HRRwt Homologous recombination repair wild-type; TCC Transitional cell carcinoma; UC Urothelial carcinoma.

2. INTRODUCTION

Bladder cancer is the most common tumor of the urinary tract and is the ninth most common cancer diagnosis worldwide, with more than 330,000 new cases each year and more than 130,000 deaths per year, with an estimated male:female ratio of 3.8:1.0. At any point in time, 2.7 million people have a history of urinary bladder cancer (Ploeg et al 2009, Babjuk et al 2014). Almost 90% of carcinomas of the urinary bladder are transitional cell carcinomas (TCCs) (National Comprehensive Cancer Network 2016). TCCs may be found along the entire length of the urinary tract, including the renal pelvis, ureter, urethra, or urinary bladder; collectively termed urothelial cancer (UC).

At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive bladder cancer (MIBC) (Babjuk et al 2014). Nevertheless, approximately 40% of the patients with NMIBC will progress to muscle-invasive disease in 5 years depending on tumor pathological features (Sylvester 2006).

Muscle-invasive tumors are usually treated by radical cystectomy and chemotherapy. Cisplatin-containing combination chemotherapy with gemcitabine/cisplatin or methotrexate, vinblastine, adriamycin, and cisplatin is standard in advanced surgically unresectable and metastatic patients who are fit enough to tolerate cisplatin.

In the advanced disease setting, first-line cisplatin/gemcitabine-based chemotherapy showed an objective response rate (ORR) of approximately 49% with a median duration of response (DoR) of 9.6 months. ORR is represented by PR of approximately 37% and CR of approximately 12%. Approximately 33% of patients achieved stable disease (SD). The median time to progressive disease (PD) was 7.4 months (95% confidence interval [CI], 6.6 to 8.1 months) with a median survival of 13.8 months (95% CI, 12.3 to 15.8 months) (Von der Maase et al 2000).

Despite the high rate of disease control (above 80%) with cisplatin-based chemotherapy in the first-line setting, disease progression invariably occurs after completing or discontinuing chemotherapy, even in patients who initially respond to chemotherapy. Furthermore, at least 40% of patients are unfit for cisplatin-containing chemotherapy due to a poor performance status, impaired renal function, or comorbidity (de Wit 2003). Some patients unfit for cisplatin-based chemotherapy may be offered a carboplatin-based regimen, but many of the patients who are ineligible for cisplatin-based chemotherapy are also ineligible for a carboplatin-based doublet. Historically, these patients were treated with single-agent taxane or gemcitabine (Bellmunt et al 2014).

Carboplatin-containing chemotherapy is less effective than cisplatin-based chemotherapy in terms of CR and survival and should not be considered interchangeable. Several randomized Phase II studies of carboplatin versus cisplatin combination chemotherapy have demonstrated lower CR rates and shorter overall survival (OS) for the carboplatin arms. In patients who are not eligible for cisplatin-based chemotherapy, ORR values are approximately 30% to 40% and median progression-free survival (PFS) was 5.8 months, with median OS rarely exceeding 10 months (Criteria Committee NYHA 1964, De Santis et al 2012). The overall poor prognosis for cis-ineligible patients provides sufficient rational to seek alternative treatments. Given the broad success of immunotherapies in treating malignant disease, therapies that modulate the immune system have also been evaluated in UC.

2.1 Study rationale

Treatment options for platinum-ineligible patients with UC remain limited with relatively low ORR with monotherapy programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) therapy. Olaparib, an approved cancer therapy that targets DNA damage repair mechanisms, will be combined with durvalumab, a PD-L1 inhibitor, to broaden the therapeutic effect of durvalumab monotherapy. The rationale for this combination is based in part on the separate non-overlapping mechanisms of action of the component agents and on the potential for mechanistic synergy detailed below. Inhibition of poly (ADP ribose) polymerization (PARP) in sensitive tumor cells, for example, in those carrying mutations in the breast cancer susceptibility (*BRCA)1* or *BRCA2* genes, results in accumulating levels of DNA damage and genomic instability, ultimately resulting in cell death (Farmer et al 2005). Accumulating DNA damage has the potential to modify the immunogenicity of tumors through a number of key mechanisms:

- Triggering of intracellular signaling events that result in the activation of nuclear factor kappa B (NFκB) and interferon (IFN) regulatory factor 7. These transcriptional regulators result in the increased production of cytokines and chemokines that have the potential to promote antitumor immunity, such as type I IFNs (Chatzinikolaou et al 2014).
- Upregulation of surface receptors such as major histocompatibility complex, ligands for natural-killer group 2, member D, and inducible T lymphocyte (T-cell) costimulatory ligand, which render tumor cells more visible to detection by cytotoxic T cells (Tang et al 2014).
- Increasing the number of cluster of differentiation (CD) 8(+) T and natural killer (NK) cells, boosting production of interferon gamma (IFNγ) and tumor necrosis factor alpha (TNF-α), and prolonging survival of patients bearing the BRCA1-deficient cancer types (Huang et al 2015).
- Death of tumor cells and release of antigen, which may help to promote antigen presentation and immune priming (Kroemer et al 2013).

These effects would be expected to help promote a more robust antitumor immune response than that obtained with monotherapy PD-1 or PD-L1 inhibition. In keeping with this hypothesis, several tumor types with genetic defects expected to lead to increased DNA damage show evidence of enhanced immune recognition. For example, BRCA-mutated (BRCAm) tumor cells are associated with higher levels of tumor-infiltrating lymphocytes and secreting lymphocyte attractants (eg, C-X-C motif ligand 10) and immune-suppressive ligands such as PD-L1 (Mulligan et al 2014). Currently, only *BRCA1/2* mutation status has been shown to be a biomarker for PARP inhibitor sensitivity in the pivotal clinical studies. However, mutation status in other HRR genes may also render tumors sensitive to PARP inhibition (Mateo et al 2015, Talens et al 2017).

There is also nonclinical evidence to support olaparib as an effective option for platinum-sensitive tumors, such as non-small cell lung cancer (NSCLC), ovarian, and bladder cancer through an analysis that demonstrated the correlation of olaparib response with several standard-of-care therapies in a panel of cancer cell lines. Analysis of the in vitro data demonstrated a strong correlation between olaparib and both cisplatin (0.908, p=0.00028) and carboplatin (0.958, p=0.00001). Consistent with the broad cell-line data, the strong correlation between platinum response and olaparib response was also observed in vivo (AstraZeneca internal data, see olaparib Investigator's Brochure [IB]). This correlation between olaparib and platinum sensitivity is theorized to be due the underlying mechanisms surrounding platinum agents, PARP inhibition, and their correlation with tumor cells exhibiting DNA-repair gene mutations, which lack effective and accurate mechanisms for DNA repair.

Based on this biology, the hypothesis to be tested in this study is that increased DNA damage triggered through PARP inhibition will result in enhanced antitumor immunity that can be further enhanced through combination with an immune checkpoint inhibitor in UC. This hypothesis is supported by published studies in mouse models of cancer, demonstrating that administration of a PARP inhibitor to sensitive tumor types results in increased T-cell infiltration and activation within tumors (Higuchi et al 2015, Huang et al 2015). In order to test this hypothesis clinically, this study will test olaparib in combination with durvalumab treatment in a platinum-sensitive disease such as bladder cancer. It is anticipated that this combination will be of particular benefit to patients with metastatic UC with DNA repair-deficient cancers (as assessed by the presence of inactivating mutations in homologous recombination repair [HRR] genes). However, this mechanism of enhanced PARP inhibitor-induced immune activation may be operative in all patients, and therefore, the study design will be employed to evaluate the safety and efficacy of olaparib and durvalumab in both HRR mutated (HRRm) and HRR wildtype (HRRwt) patients.

2.2 Background

2.2.1 Immunotherapies

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

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

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

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

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of nonclinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005; Iwai et al 2002; Okudaira et al 2009; Topalian et al 2012; Zhang et al 2008) with responses

that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition, high mutational burden, for example, in bladder carcinoma (Alexandrov et al 2013), may contribute to the responses seen with immune therapy.

Immunotherapy with PD-1 (ie, PDCD1) or PD-L1 (ie, CD274) inhibitors have shown significant activity in advanced UC. Atezolizumab, a PD-L1 inhibitor, showed an ORR of 23% and median OS of 15.9 months (95% CI 10.4 to not estimable). Treatment was generally well tolerated with only 8% of patients discontinuing therapy due to an adverse event (AE) (Balar et al 2017). Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti PD-L1 agent, have been granted approval by agencies such as the United States of America (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of a number of malignancies, including metastatic melanoma, squamous and non-squamous NSCLC, squamous cell carcinoma of the head and neck, and urothelial carcinoma. Pembrolizumab showed a similar ORR of 29% as initial treatment of advanced UC in a study of 370 cisplatin-ineligible patients, including patients with Eastern Cooperative Oncology Group (ECOG) performance score of 2 (O'Donnell et al 2017). Given the observed efficacy and favorable safety profile, patients with UC ineligible for platinum-based chemotherapy have derived particular benefit from immunotherapy. Durvalumab monotherapy studies in cis-ineligible patients are ongoing.

Besides response to chemotherapy, other prognostic factors are the Karnofsky performance status of <80% and presence of visceral metastases, ie, any organ system other than lymph nodes. These so-called Bajorin prognostic factors have also been validated for newer combination chemotherapy regimens and carboplatin combinations (Bajorin et al 1999). These risk factors are used for enrollment stratification in this clinical study, with the modification of using ECOG rather than Karnofsky performance status.

Immunotherapy with PD-1 or PD-L1 has proven to be an important advance for patients with metastatic UC; however, the ORR is relatively low and PFS is generally short (approximately 2 to 3 months). There remains only a limited number of treatment options for patients ineligible for cisplatin-containing chemotherapy after early progression with immunotherapy. There exists a significant unmet medical need in UC to extend the benefit of immunotherapy to a larger proportion of the total patient population.

Comprehensive genomic analysis of urothelial bladder cancers have provided an understanding of the molecular mutations underlying the disease. The most frequent recurrent mutations occur in genes controlling cell cycle and chromatin or receptor kinase signaling (Cancer Genome Atlas Research Network 2014). For UC patients treated with radical cystectomy, *PIK3CA* mutations correlate with a

better prognosis than *TP53* and *CDKN2A* alterations (Kim et al 2015). Deleterious mutations in DNA damage response and repair (DDR) genes, such as *NBN* and *ERCC2*, have also been implicated in the progression and/or prognosis of bladder cancer (Bellmunt et al 2007, Mullane et al 2016).

Genomic predictors have also been used retrospectively to analyze patient outcome data. An extensive panel of DDR genes (MSK-IMPACT) has been interrogated in UC patients to determine whether DDR pathway alterations are predictive of response to standard of care (Teo et al 2017). The presence of DDR alterations is associated with increased response to neoadjuvant chemotherapy, improved outcome following platinum-based chemotherapy, and trends toward improved outcome to chemoradiation (Desai et al 2016, Iyer et al 2016, Teo et al 2017). Of note, analysis of the DDR gene panels in bladder tumors has been used to impute the overall tumor mutational burden (TMB) and has demonstrated an association between the prevalence of DDR aberrations and TMB (Teo et al 2017). The estimates for TMB have also been generated using the HRR status testing laboratory and are reported to align with the distribution of TMB in TCGA bladder tumors and the MSK-IMPACT panel (Rosenberg et al 2016). Emerging clinical data supports this hypothesis; a clinical trial testing of atezolizumab in locally advanced and metastatic UC patients, who have progressed following platinum-based chemotherapy, demonstrate an association with high TMB and response to PD-L1 blockade. TCGA bladder tumor subtype and PD-L1 expression were also identified as independent prognostic factors showing an association with atezolizumab clinical response (Rosenberg et al 2016). Together, recent reports provide a correlation between accrual of DDR mutations and overall TMB, and response to immunotherapies.

PARP inhibition as a therapeutic strategy target for HRRm tumors

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by HRR. Tumors with homologous recombination deficiencies, such as ovarian or breast cancers in patients with germline *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens. *BRCA1*- and *BRCA2*-defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fong et al 2009). The MOA for olaparib results from the trapping of inactive PARP onto the SSBs preventing their repair (Helleday 2011, Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HRR.

Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knockout models, either as a stand-alone treatment or in combination with established chemotherapies (data on file at AstraZeneca). Olaparib is a potent PARP inhibitor (PARP-1, -2, and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anticancer agents.

2.2.2 Durvalumab

Durvalumab (MEDI4736, Imfinzi™) is a human mAb of the immunoglobulin (Ig) G1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand 2 [PD-L2]) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed MOA for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in the restored proliferation of IFNγ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 2.3.2 and Section 8.3.13.1. Refer to the current durvalumab IB for a complete summary of nonclinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

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

2.2.3 Olaparib

Olaparib (AZD2281, KU-0059436, Lynparza™) is a potent inhibitor of PARP developed as a monotherapy as well as for combination with chemotherapy, ionising radiation and other anti-cancer agents including novel agents and immunotherapy. The olaparib capsule formulation was registered for use in the EU and US in December 2014 for ovarian cancer. The olaparib tablet formulation is registered for use in the US, EU and several other countries for first-line maintenance treatment of *BRCAm* advanced ovarian cancer, first-line maintenance treatment of advanced ovarian cancer in combination with bevacizumab, second- and later-line maintenance treatment of advanced ovarian cancer, first- and later-line treatment of *gBRCAm* HER2-negative metastatic breast cancer, first-line maintenance treatment of *gBRCAm* metastatic pancreatic cancer, and treatment of HRRm metastatic castration-resistant prostate cancer. These indications are being rolled out globally.

Refer to the current olaparib IB for a complete description of the nonclinical and clinical experience.

2.3 Benefit/risk assessment

2.3.1 Unmet medical need in urothelial cancer

There exists a significant unmet medical need in UC to extend the benefit of immunotherapy to a larger proportion of the total patient population. Combination treatment approaches, such as durvalumab and olaparib, may address this unmet medical need.

2.3.2 Durvalumab

2.3.2.1 Benefits

A total of 23 sponsored clinical studies have been or are being conducted with durvalumab as a single agent or in combination with other agents. As of 12 July 2016, a total of 5225 patients had received at least 1 dose of durvalumab across a number of tumor types (refer to the current durvalumab IB).

The potential benefit of durvalumab in bladder cancer was demonstrated in a cohort of 182 patients with locally advanced or metastatic UC who had progressed while on or after a platinum-based chemotherapy. The overall ORR based on blinded independent central review (BICR) was 17%. In patients who had received only 1 neoadjuvant or adjuvant prior therapy, the ORR was 24%. With

a median follow-up time of 5.6 months, among the responding patients, 45% had ongoing responses of 6 months or longer and 16% had ongoing responses of 12 months or longer (median DoR: not reached [range: 0.9+ months to 19.9+ months]) (Massard et al 2016).

2.3.2.2 Risks

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

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

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, , rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g. Guillain Barre syndrome, myasthenia gravis).

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

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

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and, in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.5.1).

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

2.3.3 Olaparib

2.3.3.1 Benefits

As of 15 December 2016, approximately 6558 patients are estimated to have received olaparib in the clinical program. An estimated 4475 patients with ovarian, breast, pancreatic, gastric, and a variety of other solid tumors are estimated to have received treatment with olaparib. Since 2012/2013, most new clinical studies have utilized the tablet formulation, which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. In the AstraZeneca-sponsored, interventional studies, olaparib was given either as monotherapy (2618 patients) or in combination with chemotherapy or other anticancer agents, including studies where patients received monotherapy and combination therapy sequentially (n=1181).

Data from the available nonclinical studies and subsequent clinical development program demonstrate that olaparib appears to be active and generally well tolerated in patients with solid tumors including those with BRCAm cancers. In ovarian cancer, responses have been seen in all patient groups, including platinum-resistant and refractory cancer.

2.3.3.2 Risks

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

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

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

Please see the current edition of the IB for the most recent summary of the risks of olaparib.

2.3.4 Olaparib and durvalumab benefit/risk

As noted in Section 2.1, the hypothesis to be tested in this study is that increased DNA damage triggered through PARP inhibition will result in enhanced antitumor immunity that can be further enhanced through combination with an immune checkpoint inhibitor in UC. Additionally, there is a strong correlation between olaparib and platinum sensitivity due to the underlying mechanisms surrounding platinum agents (cisplatin and carboplatin), PARP inhibition, and their correlation with tumor cells exhibiting DNA-repair gene mutations that lack effective and accurate mechanisms for DNA repair. While patients in this study are medically unfit for platinum therapies, the sensitivity of their tumors to PARP inhibition will be tested.

Encouraging clinical activity, combined with acceptable and manageable safety, has been seen to date with durvalumab in combination therapy studies. In general, the toxicity profiles of durvalumab and olaparib are non-overlapping. Pneumonitis is considered to be the most important potential exception. See Section 8.3.13.3 for the management guidelines for pneumonitis integrate the guidance provided for these 2 agents.

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

Clinical data on the tolerability and safety of durvalumab plus olaparib are emerging. A Phase I, dose escalation study reported that there were no dose-limiting toxicities for durvalumab plus olaparib in 12 female subjects with cancer. The most frequent treatment-emergent AEs were hematologic toxicities, including lymphopenia and anemia (Lee et al 2017). The combination of durvalumab plus olaparib is also being evaluated in several tumor types (MEDIOLA; NCT02734004) with reported safety data in small cell lung cancer. The most frequent Grade 3 and higher AEs in this study were anemia (39.5%) and lymphopenia (13.2%). The majority of other AEs could be attributed to underlying disease (Krebs et al 2017). Thus far, treatment-related AEs for durvalumab

plus olaparib have been consistent across studies and indications, with no evidence of an increase in frequency or severity of immune-mediated adverse events (imAEs).

2.3.5 Summary benefit/risk statement

Treatment options for platinum-ineligible patients with UC remain limited with relatively low ORR with PD-1 or PD-L1 monotherapy. The molecular targeting of olaparib to specific subsets of tumors may provide an opportunity for more effective and potentially less toxic cancer treatment for some patients compared with currently available regimens. In this study, olaparib will be combined with the PD-L1 inhibitor durvalumab to broaden the therapeutic effect of durvalumab monotherapy.

Based upon the available nonclinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with olaparib in patients with unresectable Stage IV UC not eligible for platinum-based therapy is planned. Therefore, the benefit-risk profile in the proposed study is considered acceptable.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/Variable:**
To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in terms of PFS	PFS as determined by Investigator assessment according to RECIST 1.1
Secondary objectives:	**Endpoint/Variable:**
Key secondary objective:	
To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo	OS
Additional secondary objectives:	
To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo	DoR, ORR, and PFS6 according to RECIST 1.1 using Investigator assessment OS18

To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in the subset of patients with HRRm	PFS, DoR, ORR, and PFS6 according to RECIST 1.1 using Investigator assessment
To assess the PK of durvalumab and olaparib in both treatment arms	Concentration of durvalumab and olaparib
To investigate the immunogenicity of durvalumab in both treatment arms	Presence of ADAs for durvalumab
To assess disease-related symptoms and HRQoL in patients with UC treated with durvalumab + olaparib combination therapy compared with durvalumab + placebo	EORTC QLQ-C30: Global health status/QoL, functioning (physical), and multi-term symptoms (fatigue and pain)
Safety objective:	**Endpoint/Variable:**
To assess the safety and tolerability profile of durvalumab + olaparib combination therapy compared with durvalumab + placebo	AEs/SAEs, physical examinations, laboratory findings (including clinical chemistry, hematology and urinalysis), WHO/ECOG performance status, and vital signs
Exploratory objectives	**Endpoint/Variable:**
To assess overall change in health status since the start of study treatment in UC patients treated with durvalumab + olaparib combination therapy compared with durvalumab + placebo	PGIC
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L during assigned treatment	EQ-5D-5L index will be used to derive health state utility based on patient-reported data
To collect blood, urine, and tissue samples for defining biological responses to durvalumab + olaparib and for identifying candidate markers that may correlate with likelihood of clinical benefit	Biomarkers (eg, DNA or ctDNA alterations, protein expression detected by IHC, change in ctDNA levels, and mRNA expression) correlating with clinical response

ADA Anti-drug antibody; AE Adverse event; CR Complete response; ctDNA Circulating tumor deoxyribonucleic acid; DNA Deoxyribonucleic acid; DoR Duration of response; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EQ-5D-5L EuroQoL 5 dimension, 5-level health state utility index; HRQoL Health-related quality of life; HRRm homologous recombination repair mutated; IHC Immunohistochemistry; mRNA Messenger ribonucleic acid; ORR Objective response rate; OS Overall survival; OS18 Patients alive at 18 months; PD-L1 Programmed death ligand 1; PFS Progression-free survival; PFS6 Progression-free at 6 months; PGIC Patient Global Impression of Change; PK Pharmacokinetic(s); PRO Patient-reported outcome; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; UC Urothelial cancer; WHO World Health Organization.

4. STUDY DESIGN

4.1 Overall design

This is a Phase II, randomized, double-blind, placebo controlled, multi-center, comparative global study to determine the efficacy and safety of durvalumab + olaparib combination therapy versus durvalumab + placebo (durvalumab monotherapy) as first-line treatment in patients ineligible for platinum-based therapy with unresectable Stage IV UC. Approximately 150 patients will be recruited and randomized in each stratum in a 1:1 ratio to either durvalumab + olaparib or durvalumab + placebo. The randomization will be stratified based on the patient's HRR status (mutant versus wildtype) and Bajorin risk index (a composite stratification for visceral metastases [lymph-node-only metastasis versus metastasis to any other organ system] and ECOG performance status [0, 1, versus 2]) (see Section 6.4.1 for further details).

For an overview of the study design, see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1.

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

4.2 Scientific rationale for study design

4.2.1 Rationale for efficacy study endpoints

The primary objective of this study is to determine the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in terms of Investigator-assessed PFS.

This Phase II study will be sized to detect evidence of improved efficacy. Conventionally, ORR, PFS, and OS are used as validated measures of clinical benefit. Based on available datasets regarding response characteristics in other HRRm solid tumors with PARP inhibition, it is hypothesized that ORR will be improved by the addition of olaparib to durvalumab. However, ORR does not incorporate survival measures as in OS and PFS. OS is generally regarded as the most reliable cancer endpoint and preferred for studies that can be conducted to adequately assess survival. However, PFS may serve as a surrogate endpoint for OS when differences between treatment arms are of sufficient magnitude and clinically important (FDA Guidance 2011, Pazdur 2008). ORR improvement in study subjects may result in PFS benefits, and therefore, the study will be designed to detect significant improvement in PFS in subjects treated with olaparib + durvalumab versus durvalumab monotherapy. A PFS primary endpoint also affords an earlier

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

OS will be analyzed as a key secondary endpoint.

Other secondary endpoints, including ORR, DoR, and the proportion of patients who are progression-free at 6 months (PFS6) and patients alive at 18 months (OS18), will be examined to further evaluate the antitumor effect of durvalumab + olaparib versus durvalumab + placebo.

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

4.2.2 Rationale for other study endpoints

Biological samples will be used to explore potential biomarkers in tumor, plasma, and/or serum, which may influence the progression of cancer (and associated clinical characteristics) and/or response.

Blood samples will be taken to allow for research into PK of durvalumab and olaparib, immunogenicity of durvalumab, and the relationship between durvalumab PK exposure and clinical outcomes, efficacy, AEs, and/or safety parameters.

4.2.3 Rationale for treatment duration

Treatment in this study will continue until RECIST 1.1-defined PD and Investigator determination that the patient is no longer benefiting from treatment with the investigational product (IP) or until another discontinuation criterion is met (see Section 7.1).

4.3 Justification for dose

This study will utilize a fixed dose for durvalumab treatment (1500 mg every 4 weeks [q4w] intravenously [IV]) + olaparib/placebo. Based on an average body weight of 75 kg, a fixed dose of 1500 mg of durvalumab q4w is equivalent to 20 mg/kg q4w.

Olaparib will be dosed orally at 300 mg BID to patients with creatinine clearance (CrCl) ≥51 mL/min and 200 mg BID to patients with CrCl ≥31 mL/min but <51 mL/min.

4.3.1 Durvalumab dose rationale

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

4.3.1.1 Pharmacokinetic/Pharmacodynamic data

Based on available PK/pharmacodynamic data from the ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg every 2 weeks (q2w) or 15 mg/kg every 3 weeks (q3w), durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near-complete target saturation (membrane-bound and soluble programmed cell death ligand 1 [sPD-L1]), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, see the current IB.)

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by the area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks). Median maximum drug concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg q4w (~1.5-fold), and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (~1.25-fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w, with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in the majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of anti-drug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

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

4.3.1.2 Clinical data

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

4.3.1.3 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from Study CDON-MEDI4736-1108 (ie, Study 1108). Population PK analysis indicated only a minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weightbased (10 mg/kg q2w or 20 mg/kg q4w) and fixed dosing (750 mg q2w or 1500 mg q4w) of durvalumab was evaluated by comparing predicted steady-state PK exposure ($AUC_{ss,0\text{-}28days}$, $C_{max,ss}$, and $C_{min,ss}$) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg, and a fixed dose of 1500 mg q4w was selected to approximate 20 mg/kg q4w (based on an average body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 110 kg. Simulation results demonstrate that body weight-based (10 mg/kg q2w) and fixed (750 mg q2w) regimens yield similar median steady-state PK exposures and associated variability, supporting the potential switch of durvalumab from weight-based to fixed dose. Similar considerations hold for the q4w dosing regimens (20 mg/kg q4w versus 1500 mg q4w).

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters (Zhang et al 2012).

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

4.3.2 Olaparib dose rationale

For combination dosing with durvalumab, olaparib dose selection is based on the results from the National Cancer Institute (NCI) Study ESR-14-10366 and AstraZeneca Study D081KC00001, a Phase I/II study of durvalumab in combination with olaparib in patients with advanced solid tumors. In Study ESR-14-10366, olaparib was administered according to the dosing schedule used in monotherapy, and durvalumab was studied at a fixed dose of 10 mg/kg q2w for the first 2 cohorts. Later in the study, the durvalumab dosing schedule was changed to a dose schedule of q4w. Administration of the durvalumab/olaparib combination was well tolerated, with the majority of events observed being Grade 1 and only occasional instances of Grade 2 severity. AEs observed more than twice in this study included fatigue (6 events), absolute lymphocyte count low (4 events), headache (3 events), and nausea (3 events). No instances of Grades 3 to 4 toxicity and no instances of dose-limiting toxicity were observed. Data from this study formed the basis for the dose selection in Study D081KC00001. On the basis of these data, the dose of olaparib to be used in this study will be the recommended monotherapy dose of 300 mg BID administered to patients with CrCl ≥51 mL/min or 200 mg BID administered to patients with CrCl ≥31 mL/min but <51 mL/min.

Dose reductions may be required in patients experiencing toxicities related to olaparib treatment (Section 6.7.2).

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

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

See Appendix A 6 for guidelines for the dissemination of clinical study data.

4.4.1 Treatment after final overall survival data cutoff

At the time of the final data cutoff (DCO) for the final OS analysis, all patients remaining in the study will be considered to have completed the analysis portion of the study. At this time, the clinical study database will be closed to new data.

Patients who are receiving treatment at the time of the final DCO may continue receiving durvalumab or durvalumab and olaparib if the Investigator judges that they are gaining clinical benefit.

All patients will receive scans and follow-up care in accordance with standard local clinical practice. All data will be recorded on patient charts but will not otherwise be reported for the purposes of this study.

For patients who do continue to receive treatment beyond the time of the final DCO, Investigators will report SAEs to AstraZeneca Patient Safety via electronic case report forms (eCRFs) until 90 days after the last dose of study treatment, in accordance with Section 8.4.1. Any non-serious AE that is ongoing at the time of this DCO will be followed up at the discretion of the Investigator and per local practice and in alignment with the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5). Data will not be captured for the purposes of this study outside of being recorded in the patients' source documents.

Following the final DCO, SAE reporting applies only to patients who are active on durvalumab or olaparib and within 90 days after the last dose; in all other cases, only a statement of death notification is to be sent to AstraZeneca. No data will be recorded in the study database after final DCO for the study.

AstraZeneca will continue to supply durvalumab and olaparib in the continued access phase while, in the opinion of the Investigator, the patient is benefiting but if the product development reaches a point where other options of supply become available these will be discussed with the Investigator. If an alternative supply route is determined to be the better option, AstraZeneca will work with the Investigator to transition patients to an alternative supply, where possible.

5. STUDY POPULATION

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

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

In this protocol, "enrolled" patients are defined as those who sign an informed consent. "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

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

5.1 Inclusion criteria

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

Informed consent

1 Capable of giving a signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US and EU Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

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

3 Provision of signed and dated, written genetic informed consent (optional) prior to collection of sample for genetic analysis.

The ICF process is described in Appendix A 3.

Age

4 18 years or older, at the time of signing the ICF. For subjects aged <20 years and enrolled in Japan, a written ICF should be obtained from the subject and his or her legally acceptable representative.

Type of patient and disease characteristics

5 Histologically or cytologically documented TCC/UC (transitional cell and mixed transitional/non-transitional cell histologies; pure variant histologies are not eligible) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra) at screening also meeting the following:

- Unresectable, Stage IV disease (ie, T4b, any N; or any T, N2-N3 [Note: The Investigators will use their discretion to confirm the cause of N2 disease (reactive or inflammatory)]; or M1)
- No prior systemic therapy for unresectable, Stage IV disease. Patients who have received a prior platinum-based regimen as definitive chemoradiation or adjuvant or neoadjuvant treatment administered with curative intent are eligible, provided that disease relapse has occurred >12 months from completion of last therapy (for chemoradiation and adjuvant treatment) or >12 months from last oncologic surgery (for neoadjuvant treatment).

6 Ineligible for platinum-based chemotherapy defined as (i) in the opinion of the Investigator, unfit for carboplatin-based chemotherapy and (ii) meeting one of the following criteria:

- CrCl <60 mL/min calculated by Cockcroft-Gault equation (using actual body weight) or by measured 24-hour urine collection. (In cases where both are performed, measured 24-hour urine collection will be used to determine eligibility.)
- Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 audiometric hearing loss (25 dB in 2 consecutive wave ranges)
- CTCAE Grade ≥2 peripheral neuropathy
- New York Heart Association Class III heart failure (Criteria Committee NYHA 1964)
- ECOG 2 (Oken et al 1982)

7 Known tumor HRR mutation status prior to randomization. Either de novo biopsies collected as part of routine clinical practice or archival tumor samples (taken ≤3 years prior to screening) are acceptable. Formalin-fixed, paraffin-embedded (FFPE) tumor sample from the primary cancer **must** be available for central testing and should be of sufficient quantity to allow HRR mutation status, PD-L1 status, and other exploratory biomarker analyses.

8 World Health Organization (WHO)/ECOG performance status of 0, 1, or 2 at enrollment and randomization.

9 Patients with at least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion at baseline. Tumor assessment by computed tomography (CT) scan or magnetic resonance imaging (MRI) must be performed within 28 days prior to randomization.

10 Life expectancy ≥12 weeks at randomization.

11 Adequate organ and marrow function as defined below:

- Hemoglobin ≥10.0 g/dL
- Absolute neutrophil count $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Total bilirubin (TBL) ≤1.5× the upper limit of normal (ULN), unless due to Gilbert's syndrome, who will be allowed in consultation with their physician and AstraZeneca.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5× ULN; for patients with hepatic metastases, ALT and AST ≤5× ULN
- Measured CrCl ≥31 mL/min by 24-hour urine collection or CrCl ≥31 mL/min calculated by Cockcroft-Gault equation (using actual body weight)

Males:

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

Females:

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

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

Weight

13 Body weight >30 kg at enrollment and randomization.

Sex

14 Male or female.

Reproduction

15 Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

5.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

Medical conditions

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

- Patients with vitiligo or alopecia.
- 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 3 years may be included but only after consultation with AstraZeneca.
- Patients with celiac disease controlled by diet alone may be included but only after consultation with AstraZeneca.

2 Other invasive malignancy within 5 years before the first dose of the IP, except for the following pending a discussion with AstraZeneca:

- Patients with a history of prostate cancer (tumor/node/metastasis stage) of Stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention
- Patients who have been adequately treated for a malignancy with a low potential risk for recurrence (eg, cervical carcinoma in situ, non-melanomatous carcinoma of the skin, or ductal carcinoma in situ of the breast that has been surgically cured).

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

4 Brain metastases or spinal cord compression unless the patient's condition is stable (asymptomatic; no evidence of new or emerging brain metastases) and off steroid for at least 14 days prior to the start of the IP. Following radiotherapy and/or surgery, patients with brain metastases must wait 4 weeks after the intervention and must confirm stable condition using imaging before randomization.

5 History of active primary immunodeficiency.

6 Active infection including **tuberculosis (TB)** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB 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.

7 History of allogenic organ transplantation.

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

Prior/concomitant therapy

9 Prior exposure to a PARP inhibitor or immune-mediated therapy (with exclusion of Bacillus Calmette Guerin [BCG]), including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines. Prior local intravesical chemotherapy or BCG is allowed if completed at least 28 days prior to the initiation of study treatment.

10 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.

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

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

12 Concomitant use of known strong cytochrome P450 (CYP) 3A (CYP3A) inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, and telaprevir) or moderate CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, and verapamil). The required washout period prior to starting study treatment is 2 weeks.

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

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

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

Prior/concurrent clinical study experience

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

17 Previous IP assignment in the present study or previous exclusion at randomization.

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

19 Patients with a known hypersensitivity to durvalumab, olaparib, or any of the excipients of the products.

Other exclusions

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

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

5.3 Lifestyle restrictions

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

1 Female patient of childbearing potential

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception, defined as one that results in a low failure rate (ie, less than 1% per year; Table 4) from the

time of screening and must agree to continue using such precautions for 90 days after the last dose of the IP. Non-sterilized male partners of a female patient must use male condom plus spermicide (except in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, 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.

2 Male patients with a female partner of childbearing potential

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide (except in countries where spermicides are not approved) from screening through 90 days after receipt of the last dose of the IP. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, rhythm method, and withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 4).

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

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

Highly effective methods of contraception, when used consistently and correctly, are described in Table 4. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; 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).

In addition to the guidelines described above, local prescribing information relating to contraception and the time limits for such precautions must be followed.

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

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

[a] This is also considered a hormonal method.

[b] This hormonal method is not approved in Japan.

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

Restrictions relating to concomitant medications are described in Section 6.6.

5.4 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients can be rescreened a single time, but they cannot be re-randomized.

6. STUDY TREATMENTS

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

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca/MedImmune will supply all IPs; see Table 5 for further details on the IPs.

Table 5 Study treatments

	Durvalumab	**Olaparib**	**Placebo**
Study treatment name	Durvalumab (MEDI4736)	Olaparib	Placebo
Dosage formulation [a]	500-mg vial solution for infusion after dilution	100 and 150 mg tablets	Matching tablet
	50 mg/mL solution		
Route of administration	IV	Oral	Oral

Table 5 Study treatments

	Durvalumab	Olaparib	Placebo
Dosing instructions [b]	1500 mg IV q4w[c]	300 mg BID administered to patients with CrCl ≥51 mL/min; 200 mg BID will be administered to patients with CrCl ≥31 mL/min but <51mL/min	Matching placebo for oral tablet BID
Packaging and labeling	Provided in 500-mg vials, labeled in accordance with GMP Annex 13 and per country regulatory requirements [d]	Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language.	Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language.
Provider	AstraZeneca	AstraZeneca	AstraZeneca

[a] Refer to Section 6.3 for detailed formulation and preparation instructions for IPs.

[b] Detailed instructions for IP administration are provided below. Refer to Section 6.2 for details on duration of treatment and criteria for treatment through progression (Appendix F).

[c] If a patient's weight falls to ≤30 kg or below, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q4w until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w.

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

BID Twice a day; CrCl Creatinine clearance; GMP Good Manufacturing Practice; IV Intravenous; q4w Every 4 weeks.

6.1.1.1 Durvalumab

Durvalumab (MEDI4736), administered as 1500 mg q4w via IV infusion, will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL.

Additional details for dosing delays can be found in Section 8.4.5.1.

6.1.1.2 Olaparib and placebo

Olaparib/placebo tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib/placebo will be dispensed to patients on Day 1 and then at each visit per Table 1 until the patient completes the study, the patient withdraws from the study, or closure of the study.

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

Patients will be administered olaparib/placebo orally at 200 or 300 mg BID continually based on the patient's CrCl level. Patients initiating olaparib at 200 mg BID due to reduced CrCl may escalate the dose to 300 mg BID at the beginning of the next treatment cycle if the CrCl increases to ≥51 mL/min. Olaparib/placebo tablets should be taken at the same time each day, approximately 12 hours apart with 1 glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. IP tablets can be taken with or without food.

See Sections 6.7.2 and 8.4.5.2 for dose modification and dose reduction, respectively.

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

6.2 Duration of treatment and criteria for treatment through progression

Durvalumab and olaparib/placebo will be administered beginning on Day 1 until confirmed PD as per RECIST 1.1 as assessed by the Investigator unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, and spinal cord compression) will not be eligible for continuing durvalumab or olaparib/placebo. For all patients who are treated through progression, the Investigator should ensure that patients do

not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment would not further benefit the patient.

Post final 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 feel that they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and the investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Toxicity Management Guidelines (see Section 8.4.5.1).

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

6.3 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 authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized 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). Site personnel must also confirm that appropriate temperature conditions have been maintained during storage at the site(s) for all study treatment received and that any discrepancies are reported and resolved before use of the study treatment.

6.3.1 Preparation

6.3.1.1 Durvalumab

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

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

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

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. A total of 30.0 mL of durvalumab (MEDI4736) (ie, 1500 mg of durvalumab [MEDI4736]) will be added to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. The IV bag should be mixed by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's weight falls to ≤30 kg, weight-based dosing equivalent to 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration. Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

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

Co-administration of other drugs through the same infusion line is not permitted. 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 infusion should

be completed according to institutional policy to ensure the full dose is administered. If the line is not flushed, it should be documented.

6.3.2 Storage

6.3.2.1 Durvalumab

The Investigator, or an approved representative (eg, pharmacist), will ensure that all IPs are stored in a secured area, in refrigerated temperatures (2°C to 8°C [36°F to 46°F]) and in accordance with applicable regulatory requirements, and must not be frozen. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the Monitor upon detection and must be resolved before use of the study treatment. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

6.3.2.2 Olaparib and placebo

Olaparib and placebo IPs should be kept in a secure place under appropriate storage conditions. The IP labels specifies the appropriate storage.

6.4 Measures to minimize bias: randomization and blinding

This study is a double-blinded study with both the patient and the treating Investigator blinded to the treatment assignment.

All patients will be centrally/regionally/locally assigned to randomized study treatment using an interactive voice/web response system (IVRS/IWRS), per the randomization scheme generated by the Biostatistics Group, AstraZeneca, or delegate. 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.

The IVRS/IWRS will also be used to track drug supply.

6.4.1 Procedures for randomization

Patients must not be randomized unless all eligibility criteria have been met.

Randomization into the study will be stratified based on the patient's HRR status (mutant or wildtype) and Bajorin risk index (a composite stratification for visceral metastases [lymph-node-only metastasis versus metastasis to any other organ system] and ECOG performance status [0, 1 versus 2]) (Bajorin et al 1999). Thus, the study will randomize patients in an approximate 1:1 ratio to either receive durvalumab + olaparib or durvalumab + placebo into 1 of the following 6 strata:

- HRRm and Bajorin risk index 0
- HRRm and Bajorin risk index 1
- HRRm and Bajorin risk index 2
- HRRwt and Bajorin risk index 0
- HRRwt and Bajorin risk index 1
- HRRwt and Bajorin risk index 2

The Bajorin risk index will be defined as follows:

- 0 – no risk factors: lymph-node-only metastasis and ECOG performance status of 0 or 1
- 1 – 1 risk factor: either lymph-node-only metastasis and ECOG performance status of 2 or metastatic disease to any other organ system and ECOG performance status of 0 or 1
- 2 – 2 risk factors: metastatic disease to any other organ system and ECOG performance status of 2

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

Patients will be identified to the IVRS/IWRS per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. It is recommended that patients commence study treatment as soon as possible after randomization, and ideally within 3 days. The IVRS/IWRS Centralized Randomization Center will inform the

investigator of the kit ID number to be allocated to the patient at the randomization visit. The Investigator (or delegate) will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new kit ID number. The kit ID number dispensed at each visit will correspond to the treatment to which the patient was originally randomized.

6.4.2 Patient enrollment and randomization

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

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will perform the following:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization. For patients with a single target lesion (TL), if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.
- Obtain a unique 7-digit enrollment number (E-code), through the IVRS/ IWRS in the following format (ECCNNXXX: CC being the country code, NN being the site number, and XXX being the patient enrollment code at the site). This number is the patient's unique identifier and is used to identify the patient on the eCRFs.
- Obtain a tumor sample. Either de novo biopsies (preferred) or archival tumor samples (taken ≤3 years prior to screening) are acceptable. FFPE tumor sample from the primary cancer **must** be available for central testing and should be of sufficient quantity to allow HRR mutation status, PD-L1 status, and other exploratory biomarker analyses. If there is no written confirmation of the availability of an archived tumor sample prior to enrollment, the patient is **not** eligible for the study. Tumor lesions used for newly acquired biopsies should not be RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy. Fine-needle aspirate specimens are not acceptable. Please refer to the laboratory manual for detailed information.
- Ensure the stratification factors, HRR mutation status (HRRm [mutated], HRRwt [wild type {no mutation}]), visceral metastasis (yes, no), and ECOG performance status (0, 1, 2) are available in the IVRS/IWRS in order for the patient to be randomized.
- Determine patient eligibility (see Sections 5.1 and 5.2)
- Obtain signed informed consent for genetic research study (optional)

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

- Enter data into IVRS/IWRS to obtain a unique randomization number via the IVRS/IWRS. Numbers will start at 001 and will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 2 treatment groups per 1 of the 6 strata (HRR status results must be received from the central laboratory prior to randomization).

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

Every effort should be made to minimize the time between randomization and starting study treatment. It is recommended that patients commence study treatment as soon as possible after randomization (ie, preferably within 3 days and ideally on the same day after randomization in the IVRS system).

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

6.4.3 Procedures for handling incorrectly enrolled or randomized patients

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

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

6.4.4 Methods for ensuring blinding

The study will be conducted in a double-blind manner. The olaparib and placebo tablets will be identical in color and taste to maintain the double-blind conditions.

Olaparib/placebo treatment will be blinded to all site staff. The study medication will be labeled using a unique kit ID number, which is linked to the randomization scheme. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the study medication.

No member of the extended study team at AstraZeneca, at the investigational sites, or any contract research organization handling data will have access to the randomization scheme until the time of the primary data analysis. At such time, AstraZeneca and any Contract Research Organization handling data will have access to the randomization scheme. Exceptions are relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package the IP, and personnel analyzing the PK samples at AstraZeneca-designee laboratories. Investigators will be unblinded to treatment allocation only in cases of medical emergency.

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

The independent data monitoring committee (IDMC) will be provided with unblinded data for their review, but AstraZeneca staff and Investigators involved in the study will remain blinded.

6.4.5 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each site.

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

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment 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.

6.5 Treatment compliance

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

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

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

For olaparib and placebo, study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count, and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the 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 a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

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

6.6 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 the IP. The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

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

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer also to the Dosing Modification and Toxicity Management Guidelines in Section 8.4.5.1 for durvalumab and Section 8.4.5.2 for olaparib.

Table 6 Prohibited concomitant medications

Prohibited medication/class of drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment.
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment.
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy].)
Live attenuated vaccines	Should not be given through 30 days after the last dose of the IP.
Immunosuppressive medications, including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs. • Short-term premedication for patients receiving SoC CRT, in which the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions, nausea/vomiting, prophylaxis, etc. • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids are 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 6 Prohibited concomitant medications

Prohibited medication/class of drug	Usage
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days after the last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first-generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Herbal and natural remedies, which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor.

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

Table 7 Restricted concomitant medications

Restricted medication/ class of drug	Concern
Strong or moderate CYP3A inhibitors	Known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib. If there is no suitable alternative concomitant medication, then the dose of olaparib/placebo should be reduced for the period of concomitant administration. The dose reduction of olaparib/placebo should be recorded in the eCRF with the reason documented as concomitant CYP3A inhibitor use (see Section 6.7.2).
Strong or moderate CYP3A inducers	Strong (eg, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide, and St John's Wort) and moderate CYP3A inducers (eg, bosentan, efavirenz, and modafinil) of CYP3A should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers is considered necessary for the patient's safety and welfare, this could diminish the clinical efficacy 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.

Table 7 Restricted concomitant medications

Restricted medication/ class of drug	Concern
P-gp inhibitors	It is possible that co-administration of P-gp inhibitors (eg, amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.
Effect of olaparib on other drugs	Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2K. Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP3A4, CYP2B6, CYP2C9, CYP2C19, and P-gp. The efficacy of hormonal contraceptives may be reduced if coadministered with olaparib. Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are coadministered. Examples of substrates include: • CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, quetiapine • CYP2B6 – bupropion, efavirenz • CYP2C9 – warfarin • CYP2C19 - lansoprazole, omeprazole, S-mephenytoin • P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine • OATP1B1 - bosentan, glibenclamide, repaglinide, statins, valsartan • OCT1, MATE1, MATE2K – metformin • OCT2 - serum creatinine • OAT3 - furosemide, methotrexate
Anticoagulant therapy	Patients who are taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low-molecular-weight heparin are permitted.
Anti-emetics/ Anti-diarrheals	From screening part 2 onward, should a patient develop nausea, vomiting, and/or diarrhea, then these symptoms should be reported as AEs (see Section 8.3) and appropriate treatment of the event should be given.

Table 7 Restricted concomitant medications

Restricted medication/ class of drug	Concern
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases or symptomatic pelvic soft tissue mass(es) that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Administration of other anticancer agents	Patients must not receive any other concurrent anticancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.
Subsequent therapies for cancer	Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anticancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

AEs Adverse events; CYP Cytochrome; eCRF electronic case report form; INR International Normalized Ratio; OS Overall survival; P-gp Permeability glycoprotein; PARP Poly (ADP ribose) polymerization.

Table 8 Supportive medications

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

Inactivated viruses, such as those in the influenza vaccine	Permitted

6.6.1 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and well-being, 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.

6.6.2 Durvalumab drug-drug interactions

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

6.7 Dose modification

6.7.1 Durvalumab

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

6.7.2 Olaparib

When dose reduction is necessary, patients with CrCl ≥51 mL/min dosed with 300 mg BID will take one 150-mg tablet and one 100-mg tablet (250 mg BID) or two 100-mg tablets (200 mg BID). Patients with CrCl ≥31 mL/min but <51 mL/min dosed with 200 mg BID will take one 150-mg tablet (150 mg BID) or one 100-mg tablet (100 mg BID) (see Sections 6.7.2.1 and 8.4.5.2). Patients

initiating olaparib at 200 mg BID due to reduced CrCl may escalate the dose to 300 mg BID at the beginning of the next treatment cycle if the CrCl increases to ≥51 mL/min. Intracycle dose escalation of olaparib is not permitted.

6.7.2.1 Co-administration with CYP3A inhibitors

Known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) 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 BID for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterward.
- Moderate CYP3A inhibitors – reduce the dose of olaparib to 150 mg BID for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterward.
- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

6.8 Treatment after the end of the study

Not applicable.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from the IP (durvalumab, olaparib, or placebo) if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with the IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 7.3).

- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1 for durvalumab and Section 8.4.5.2 for olaparib).
- 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 the IP (eg, refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy including another investigational agent.
- Clinical progression with or without RECIST 1.1-defined radiological PD. Both durvalumab and olaparib/placebo must be discontinued.
- Confirmed radiological PD (Appendix F) in clinically stable patients who were treated beyond RECIST 1.1-defined radiological PD. Both durvalumab and olaparib/placebo must be discontinued.

In the event that durvalumab is discontinued due to treatment-related toxicity, olaparib/placebo may still be administered as scheduled. If olaparib/placebo is discontinued due to treatment-related toxicity, durvalumab may continue at the Investigator's discretion when toxicity resolves to Grade 2 or less. The only circumstance where only 1 agent and not the other may be discontinued is in the event of treatment-related toxicity. Note: If the Investigator feels that a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

7.1.1 Procedures for discontinuation of study treatment

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

Patients who are permanently discontinued from further receipt of the IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see Table 2). Patients who permanently discontinue 1 IP due to toxicity but continue the other IP will continue all treatment assessments (see Table 1).

Patients who permanently discontinue IP for reasons other than RECIST 1.1-defined disease progression should continue to have RECIST 1.1 scans performed q8w ±1 week beginning 8 weeks after randomization for the first 48 weeks (relative to the date of randomization), and then every 12 weeks (q12w) ±1 week thereafter until clinical progression with or without RECIST 1.1-defined radiological PD plus an additional follow-up scan (if criteria for treatment beyond progression are met) or death (whichever comes first) as defined in Table 2.

If a patient is discontinued for RECIST 1.1-defined progression, then the patient should have 1 additional follow-up scan 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.

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

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in Table 2 as an alternative.

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

If a patient is withdrawn from study, see Section 7.3.

7.2 Lost to follow-up

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

At the time of DCO, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked; this includes those patients who withdrew consent or are classified as "potentially lost to follow-up."

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

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

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

7.3 Withdrawal from the study

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

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

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

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

- all further participation in the study including any further follow-up (eg, survival contact telephone calls)
- withdrawal to the use of any samples (see Section 8.8.6 withdrawal of informed consent for donated samples)

8. STUDY ASSESSMENTS AND PROCEDURES

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

The Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

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

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

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

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

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

This study will evaluate the primary endpoint of PFS. Secondary endpoints include DoR, ORR, OS, OS18, and PFS6. Efficacy assessments of PFS, PFS6, DoR, and ORR will be derived (by AstraZeneca) using Investigator assessments according to RECIST 1.1.

Tumor assessments utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest, abdomen, and pelvis, collected during screening/baseline and at regular (follow-up) intervals during study treatment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

The RECIST 1.1 guidelines (Appendix F) provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify TLs (defined measurable) and non-target lesion (NTLs). On-study images are evaluated for TLs and NTLs chosen at baseline and for new lesions when they appear. This allows determination of follow-up TL response, NTL response, and overall timepoint tumor responses (CR, PR, SD, PD, or not evaluable [NE]).

Radiologic efficacy for all patients (both treatment arms) will be assessed on images collected q8w ±1 week for the first 48 weeks relative to the date of randomization and q12w ±1 week thereafter until RECIST 1.1-defined objective disease progression or off-study. The assessment schedule must be followed regardless of any delays in dosing (refer to Table 1). If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his/her next regularly scheduled imaging visit. Assessments of tumor response (CR, PR, or SD) must be confirmed at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks and no more than 8 weeks after the prior assessment.

8.1.1 Central reading of scans

All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization for quality control and storage. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part on the results of the RECIST 1.1 assessment conducted by the Investigator.

8.1.2 Tumor biopsies

After obtaining informed consent, patient tumor samples will be screened for HRR mutation during the screening phase by a central laboratory (details of HRR mutation assessment follow below and in the laboratory manual).

All patients must provide an FFPE tumor sample for tissue-based HRR gene panel mutation testing. The analysis will be performed at a central laboratory testing service using the DNA extracted from FFPE tissue. Tumor tissue can be either from the primary tumor or metastatic biopsy. Samples should not be collected specifically for this study but should be obtained as part of patients' routine clinical care. Archived tumor specimens are acceptable for HRR testing. The tumor sample will be tested for loss of function and alterations in 15 pre-specified HRR genes: *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. If the test results indicate that the patient has at least 1 qualifying mutation in any of these genes, the patient will be considered HRRm for the purposes of the study. Patients with a prior test result from an HRR testing laboratory panel will not have to wait for HRR testing completion to determine their biomarker status, if they provide permission for reanalysis of their data at an HRR testing laboratory (see laboratory manual for further details); however, an FFPE tumor sample is still mandatory for central confirmatory testing and exploratory biomarkers analysis. No local testing results are permitted for eligibility purposes. All tumor samples will be analyzed for a range of cancer-related genes to explore correlations between clinical response and DNA alterations. Full genetic testing results from the central laboratory testing service will be provided to the Investigator upon individual request for patients that fail screening or for treated patients upon disease progression and treatment discontinuation.

Tumor lesions used for newly acquired biopsies should not be RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy. Samples with limited tumor content and fine-needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component and should not be decalcified.

8.1.3 Survival assessments

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

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

8.1.4 Clinical outcome assessments

Patient Reported Outcome (PRO) is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. In addition to assessing clinical endpoints in oncology clinical trials, it is important to assess treatment impact on disease-related symptoms and health-related quality of life (HRQoL) of the patient to aid in characterizing treatment benefit to overall wellbeing and in making risk-benefit evaluations. Moreover, PROs assist in the documentation of symptoms and specifically what symptoms and impacts are most important to patients and how these relate to clinical outcomes. The following PROs will be administered in this study: The European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ-C30), 5-level health state utility index (EQ-5D-5L), Patient Global Impression of Change (PGIC), and the Vulnerability Elders Survey-13 (VES-13) (see Appendix G). The VES-13 will only be given at baseline to assess the patient's frailty and not to assess the efficacy of treatment (see Section 8.2.6).

8.1.4.1 EORTC QLQ-C30

The impact of treatment and disease state on symptoms and HRQoL will be assessed using the EORTC QLQ-C30, a 30-item self-administered questionnaire (see Appendix G). The rationale for selecting the EORTC QLQ-C30 is primarily because it has a good coverage of general cancer symptoms and impact concepts. The questionnaire consists of 9 multiple-item scales: 5 scales that assess aspects of functioning (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health status/Quality of Life (QoL) scale. In addition, there are 5 single-item measures assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and a single item concerning the perceived financial impact of the disease. All but 2 questions have 4-point scales: "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 (9 multiple-item scales and 6 single-item scales), final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater QoL, or greater level of symptoms (Aaronson et al 1993).

8.1.4.2 EQ-5D-5L

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

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

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

8.1.4.3 PGIC

The PGIC item is included to assess how a patient perceives overall change in health status since the start of study treatment (see Appendix G). Patients will be asked "Overall, how would you rate the change in your bladder cancer symptoms since you started this study?" and will choose from 7 response options of "very much improved" to "very much worse."

8.1.4.4 Administration of patient-reported outcomes questionnaires

Patients will perform the PRO assessments using an electronic tablet (ePRO) during clinic visits and will take approximately 15 minutes to complete. Note that the VES-13 will be performed at baseline and will not be performed at subsequent clinic visits.

Each site must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. The PRO questionnaires must be administered and completed at the clinic as per the SoAs (Table 1 and Table 2).

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

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

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

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 1 and Table 2).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and the routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

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

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

The laboratory variables measured are presented in Table 9 (clinical chemistry), Table 10 (hematology), and Table 11 (urinalysis).

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

The following laboratory variables will be measured:

Table 9 Clinical chemistry

Albumin	Lipase [b]
Alkaline phosphatase [a]	Magnesium [c]
ALT [a]	Potassium
Amylase [b]	Sodium
AST [a]	Total bilirubin [a]
Bicarbonate [c]	Total protein
Calcium	TSH [e]
Chloride [c]	T3 free [f] (reflex)
Creatinine clearance [d]	T4 free [f] (reflex)

Gamma glutamyltransferase [c]	Urea or blood urea nitrogen, depending on local practice
Glucose	
Lactate dehydrogenase	

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

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

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing is to be performed at baseline, on Day 0 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 0), and if clinically indicated.

[d] Creatinine clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

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

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

ALT Alanine aminotransferase; AST Aspartate aminotransferase, T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone.

Table 10 Hematology

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

[a] Can be recorded as absolute counts or as percentages.

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated.

Table 11 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

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

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

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

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

8.2.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see Table 1 and Table 2). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

8.2.3 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiratory rate) will be evaluated according to the assessment schedules (see Table 1 and Table 2). Body weight is also recorded at each visit along with vital signs. The following timepoints for vital signs assessments apply to infusions of durvalumab.

First infusion

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

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

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

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab. Additional monitoring with assessment of vital signs will be at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Subsequent infusions

BP, pulse, and other vital signs should be measured and collected/recorded in the 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. 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 8.3.6. For any AEs of infusion reactions, please enter the vital signs values into the eCRF.

8.2.4 Electrocardiograms

Resting 12-lead electrocardiograms (ECGs) will be recorded at screening and as clinically indicated throughout the study (see Table 1). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

Any clinically significant abnormalities detected require triplicate ECG results, including a QT interval corrected for heart rate using Fridericia's formula (QTcF) value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

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

8.2.5 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the Table 1 and Table 2 based on the following:

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

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

8.2.6 Vulnerability Elders Survey-13

The VES-13 will be used to assess frailty in patients with cancer (see Appendix G). The survey consists of 13 items: 1 item for age and 12 items that assess health, functional capacity, and physical performance (Saliba et al 2000, Saliba et al 2001). Refer to Section 8.1.4.4 for administration details.

8.3 Collection of adverse events

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

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

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

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

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of the IP) (see Table 1 and Table 2). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late-onset toxicity to study drug, then it should be reported as an AE or SAE, as applicable.

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

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

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

8.3.3 Follow-up of AEs and SAEs

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study treatment or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

'The following variables will be collect for each AE:

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

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

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

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

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

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, B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B, B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would be an SAE if it satisfies the criteria shown in Appendix B, B 2.

8.3.5 Causality collection

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

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

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

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

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

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

8.3.8 Hy's law

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

8.3.9 Disease progression

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

8.3.10 New cancers

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

8.3.11 Deaths

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

- Death clearly the result of disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of the IP should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late onset toxicity to the IP, then it should also be reported as an SAE.

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

For patients continuing to receive study treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and the investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Toxicity Management Guidelines (see Section 8.4.5.1). The most current version of the Toxicity Management Guidelines is also available through the following link: https://tmg.azirae.com. All data after the final DCO and database closure will be recorded in the patient notes but will not otherwise be reported for the purposes of this study, with the exception of SAEs.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) after the final DCO and database closure must be reported as detailed in Section 8.3.2.

8.3.13 Adverse events of special interest

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

8.3.13.1 Adverse events of special interest for durvalumab

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

If the Investigator has any questions with regard to an event being an imAE, the Investigator should promptly contact the Study Physician. AESIs observed with anti PD-L/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes

mellitus), nephritis, rash/dermatitis, myocarditis,myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.:

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

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

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

8.3.13.2 Any event of AESI should be reported to AstraZeneca Patient Safety, whether it is considered a non-serious AE or SAE and regardless of the Investigator's assessment of causality. These AEs must be reported according to the timelines for reporting an SAE to allow for timely safety monitoring. Adverse events of special interest for olaparib

AESIs for olaparib comprise the important identified risk of MDS/AML and the important potential risks of:

- new primary malignancy (other than MDS/AML)
- pneumonitis

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

8.3.13.3 Pneumonitis

If new or worsening pulmonary symptoms (eg, dyspnea or cough) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended, and further diagnostic workup should be performed to exclude pneumonitis. The differential diagnosis should include the possibility of both immune-related and non-immune-related processes. AEs of pneumonitis are of interest for AstraZeneca as pneumonitis has been observed with use of anti-PD-1 mAbs (although not with anti-PD-L1 mAbs), and instances of pneumonitis have been reported in patients undergoing olaparib treatment.

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

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

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

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

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

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

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

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

The AstraZeneca representative will advise the Investigator/study site personnel 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 an SAE, see Appendix B.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for pregnancy discovered before the study patient has received any IPs.

8.4.2.1 Maternal exposure

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

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

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

8.4.2.2 Paternal exposure

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

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

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

8.4.3 Overdose

Use of IP (durvalumab or olaparib) in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose with durvalumab or olaparib, and possible symptoms of overdose are not established for these IPs.

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

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

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

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

8.4.4 Medication error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

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

8.4.5 Management of IP-related toxicities and dose reductions

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, or infections).

- In the absence of a clear alternative etiology, all events should be considered potentially immune related, and the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1 for durvalumab and Section 8.4.5.2 for olaparib) should be followed.
- In the event that durvalumab is discontinued or delayed as part of the Dosing Modification and Toxicity Management Guidelines (Section 8.4.5), olaparib/placebo may still be administered as scheduled.
- In the event that olaparib or placebo is discontinued due to treatment-related toxicity, durvalumab may continue at the Investigator's discretion when toxicity resolves to at least Grade 2 or less. Note: If the Investigator feels that a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

If unsure how to manage a patient, please contact the Study Physician at AstraZeneca to discuss individual cases. All toxicities will be graded according to NCI CTCAE version 4.03.

8.4.5.1 Durvalumab

Comprehensive toxicity management guidelines (TMG) have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitors durvalumab [Medi4736] (PD-L1 inhibitor). Given the similar underlying mechanisms of toxicities observed with these two compounds, these guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (i.e. antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen.

The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment <<Insert relevant section which describes a non-IO regimen, if applicable>>. The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy is provided to the investigative site as an Annex document and is maintained within the Site

Master File. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Please contact the clinical study associate for information on how to gain access to this website

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

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

Following the first dose of the 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 monotherpahy regimen by the reporting Investigator.

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

8.4.5.2 Olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. For patients with CrCl ≥51 mL/min dosed with 300 mg BID, study treatment can be dose reduced to 250 mg BID as a first step and to 200 mg BID as a second step. If the reduced dose of 200 mg BID is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

For patients with CrCl ≥31 mL/min but <51 mL/min dosed with 200 mg BID, study treatment can be reduced to 150 mg BID as a first step and to 100 mg BID as a second step. If the reduced dose of 100 mg BID is not tolerable, no further dose reduction is allowed, and study treatment should be discontinued.

Dose re-escalation is permitted in the study at the discretion of the Investigator.

Table 12 Management of anemia

Hemoglobin (Hb)	Action to be taken
Hb <10 *but* ≥8 g/dL (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgment to continue study treatment with supportive treatment (eg, transfusion) *or* interrupt dose for a maximum of 4 weeks. For patients with CrCl ≥51 mL/min dosed with 300 mg twice daily: If repeat Hb **<10** ***but*** **≥8 g/dL**, interrupt dose (for maximum of 4 weeks) until Hb ≥10 g/dL, and upon recovery, dose reduction to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered. For patients with CrCl ≥31 mL/min but <51 mL/min dosed with 200 mg twice daily: If repeat Hb **<10** ***but*** **≥8 g/dL**, interrupt dose (for maximum of 4 weeks) until Hb ≥10 g/dL, and upon recovery, dose reduction to **150 mg twice daily** as a first step and to **100 mg twice daily** as a second step may be considered.
Hb <8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. For patients with CrCl ≥51 mL/min dosed with 300 mg twice daily: Interrupt study treatment for a maximum of 4 weeks until improvement to Hb ≥10 g/dL, and upon recovery, reduce dose to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease. For patients with CrCl ≥31 mL/min but <51 mL/min dosed with 200 mg twice daily: If repeat Hb **<10** ***but*** **≥8 g/dL**, interrupt dose (for maximum of 4 weeks) until Hb ≥10 g/dL, and upon recovery, reduce dose to **150 mg twice daily** as a first step and to **100 mg twice daily** as a second step may be considered.

Common treatable causes of anemia (eg, iron, vitamin B12, or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Management of prolonged hematological toxicities while on study treatment.

Table 13 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgment to continue treatment or if to interrupt study treatment; this should be for a maximum of 4 weeks; give 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. For patients with CrCl ≥51 mL/min dosed with 300 mg twice daily: If repeat CTCAE Grade 3-4 occurrence, reduce study treatment dose to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step. For patients with CrCl ≥31 mL/min but <51 mL/min dosed with 200 mg twice daily: If repeat CTCAE Grade 3-4 occurrence, reduce study treatment dose to **150 mg twice daily** as a first step and **100 mg twice daily** as a second step.

AE 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 at least 24 hours (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged hematological toxicity (≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse), refer to Management of prolonged hematological toxicities while on study treatment.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse neutropenia (ANC<1×10^9/L)
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets<50×10^9/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 a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Auto-immune causes of hematologic toxicities should be considered in the differential diagnosis. Study treatment should be discontinued if blood counts do not recover to CTCAE 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 the AstraZeneca representative. Study treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

Management of non-hematological toxicity

If this is suspected to be immune mediated, refer to the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1). The most current version of the Toxicity Management Guidelines is also available through the following link: https://tmg.azirae.com. In addition, a version of the current Toxicity Management Guidelines is maintained within the Site Master File. Please contact your clinical trial associate for information on how to gain access to this website.

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 re-occurs 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.

For patients with CrCl ≥51 mL/min dosed with 300 mg BID, study treatment can be dose reduced to 250 mg BID as a first step and to 200 mg BID as a second step. For patients with CrCl ≥31 mL/min but <51 mL/min and dosed with 200 mg BID, study treatment can

be dose reduced to 150 mg BID as a first step and to 100 mg as a second step. Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 AE occurs, which the Investigator considers to be related to the administration of study treatment.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high-resolution computed tomography[CT] scan) should be performed to exclude pneumonitis (see Section 8.3.13.3). Prompt diagnosis and treatment are essential for pneumonitis.

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. In Study D0810C00019, nausea was reported in 71% of the olaparib-treated patients and 36% of the placebo-treated patients, and vomiting was reported in 34% of the olaparib-treated patients and 14% of the placebo treated patients. These events are generally mild to moderate (CTCAE Grade 1 or 2) in severity, intermittent, and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic antiemetic treatment is required at the start of study treatment; however, patients should receive appropriate antiemetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practise 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 antiemetic use in patients with cancer (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 the 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.

Study treatment should be stopped at least 3 days prior to the planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study 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 14 Dose reductions for study treatment

Initial dose	**Following re-challenge post interruption: Dose reduction 1**	**Dose reduction 2**
Patients with CrCl ≥51 mL/min		
300 mg BID	250 mg BID	200 mg BID
Patients with CrCl ≥31 mL/min but <51 mL/min		
200 mg BID	150 mg BID	100 mg BID

BID twice daily; CrCl creatinine clearance.

8.5 Pharmacokinetics

8.5.1 Collection of samples

8.5.1.1 Durvalumab

Blood samples for the determination of durvalumab concentration in serum will be obtained according to the assessment schedules (see Table 1 and Table 2).

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

8.5.1.2 Olaparib

Blood samples for the determination of olaparib concentration in plasma will be obtained according to the assessment schedules (see Table 1 and Table 2).

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

8.5.2 Collection of samples to measure for the presence of ADAs

The presence of ADAs will be assessed in serum samples taken according to the assessment schedules (see Table 1 and Table 2).

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for durvalumab using validated assays. Tiered analyses 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.

8.5.3 Storage and destruction of PK/ADA samples

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

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

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

Olaparib PK samples will be disposed of or anonymized by pooling after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report, whichever occurs first. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any 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 an Assay Validation Report as an addendum.

Any residual back-up PK or ADA samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca-assigned Biobank).

8.6 Pharmacodynamics

Pharmacodynamic samples will not be taken during the study.

8.7 Genetics

8.7.1 Optional exploratory genetic sample

If the patient agrees to participate in the optional genetic research study, a blood sample will be collected. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study. In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent. See Appendix Dfor information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the Laboratory Manual.

8.7.2 Storage and destruction of genetic samples

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 employees or designated organizations working with the DNA.

8.8 Biomarkers

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

Based on availability of tissue, exploratory biomarkers may be evaluated as described below. Samples will be obtained according to the assessment schedules provided in Table 1.

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

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

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

8.8.1 Collection of biomarkers

8.8.1.1 Collection of tumor samples for exploratory biomarker assessments (mandatory)

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

- FFPE tumor sample at baseline: ideally a sample close to the time of study entry. The tumor specimen submitted to establish HRRm and PD-L1 status should be of sufficient quantity to allow for HRR mutation testing and PD-L1 immunohistochemistry (IHC) and other exploratory biomarker analyses, such as IFNγ gene expression signature and proteomics analysis, and is preferred in FFPE blocks. Provision of core needle biopsy material will reduce the chances of adequate DNA yield for HRRm status being obtained. Therefore, resection samples or transurethral resection of bladder tumor samples are preferred. Twenty-five sections may be provided if blocks are not available, but a minimum of 15 sections (5 μm) is requested. If no sufficient sections are available from 1 tumor block specimen, then additional sections may be provided from another block provided this is clearly indicated. Fine needle aspirates or cytology samples are not acceptable for biomarker analysis.
- FFPE tumor sample at progression (optional): patients will be given the option to consent to an optional tumor biopsy at progression. The treating physician will judge the feasibility of such a procedure.

8.8.1.2 Collection of blood-based biomarkers (mandatory)

Whole blood for gene expression analyses (PaxGene-RNA) will be collected both pre- and post-treatment in PaxGene RNA tubes to evaluate both predictive and on-treatment molecular alterations.

8.8.1.3 Collection of whole blood (mandatory)

Whole blood will be collected in a 6-mL whole blood lavender top EDTA tube, both pre- and post-treatment and will be preserved (frozen), and may be used for subsequent functional analysis, including but not limited to, flow cytometry or assessment of the diversity of the immune cell repertoire (including T-cell receptor analysis), the relationship to clinical responses, and changes in response to treatment.

8.8.1.4 Collection of urine for mutation analysis (optional)

Urine samples will be collected both pre- and post-treatment in ethylenediaminetetraacetic acid containers for analysis of genomic aberrations including homologous recombination repair gene mutations to explore the potential for use of urine to assess predictive markers and markers of disease response and progression.

8.8.1.5 Collection of plasma samples for circulating tumor DNA analyses (mandatory)

Blood samples will be collected both pre- and post-treatment to provide plasma for circulating tumor deoxyribonucleic acid (ctDNA).

8.8.2 Management of biomarker data

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

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

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

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab and olaparib to generate hypotheses to be tested in future research.

8.8.4 Labeling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix C, C 3 "International Airline Transportation Association (IATA) 6.2 Guidance Document."

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

8.8.5 Chain of custody of biological samples

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

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

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

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

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

8.8.6 Withdrawal of informed consent for donated biological samples

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

The Principal Investigator will:

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

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action is documented, and the study site is informed.

9. STATISTICAL CONSIDERATIONS

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

All statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be prepared and signed off before review of any potential treatment-revealing data is undertaken (this includes blinded delivery reviews and data monitoring committee reviews), with final amendments completed prior to reporting of the data.

The primary objective of this study is to assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in terms of PFS as determined by Investigator assessment according to RECIST 1.1 in all randomized patients. The key secondary objective of this study is to assess the efficacy of durvalumab + olaparib compared with durvalumab + placebo in terms of OS in the same population of patients. Other secondary efficacy variables include ORR, DoR, PFS6, and OS18 according to RECIST 1.1 using Investigator assessments. Additionally, the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in terms of PFS, as well as DoR, ORR, and PFS6, in the subset of patients with HHRm will also be presented.

The analyses of PFS, ORR, DoR, PFS6, and PRO endpoints will occur at 1 timepoint only, (defined as the primary analysis) when approximately 118 PFS events have occurred. A full set of outputs will be delivered at this time, including baseline characteristics, safety, and tolerability. An interim analysis of OS will also be performed based on an estimated 44 OS events (29% maturity). There will be an additional DCO after the primary analysis to evaluate OS and OS18 when approximately 100 OS events have occurred, no other efficacy outputs are planned to be updated at this timepoint.

9.1 Statistical hypotheses

The primary objective is to assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in terms of PFS for patients in the full analysis set (FAS). The secondary objective is to assess OS in the FAS. Thus, formal statistical analyses will be performed to test the main hypotheses:

- Null Hypothesis 1 (H_{10}): No difference between durvalumab + olaparib compared with durvalumab + placebo in terms of PFS
- Alternative Hypothesis 1 (H_{11}): There is a difference between durvalumab + olaparib compared with durvalumab + placebo in terms of PFS

If a statistically significant difference is observed in the study, ie, reject the null hypothesis of no difference in favor of H_{11}, then the following hypotheses can also be tested:

- Null Hypothesis (H_{20}): No difference between durvalumab + olaparib compared with durvalumab + placebo in terms of OS
- Alternative Hypothesis (H_{21}): There is a difference between durvalumab + olaparib compared with durvalumab + placebo in terms of OS

To control for type 1 error, a significance level of 5% will be used for the analysis of PFS. If the null hypothesis (H_{10}) of no effect is rejected, 100% of the alpha can be passed to the OS secondary endpoint to test H_{20}.

The study will be considered positive (ie, a success) if durvalumab + olaparib combination therapy is statistically different from durvalumab + placebo in terms of PFS.

9.2 Sample size determination

The study is sized to characterize the PFS benefit of durvalumab in combination with olaparib versus durvalumab monotherapy in first-line patients with unresectable Stage IV UC.

Approximately 150 patients globally will be randomized in a 1:1 ratio to either the durvalumab + olaparib treatment group or the durvalumab + placebo treatment group, 75 patients per arm. The randomization will be stratified based on HRR status (mutant versus wild type) and Bajorin risk index (0 versus 1 versus 2).

The DCO for the primary analysis of PFS will occur when approximately 118 PFS events have occurred across both treatment groups (79% maturity). Assuming a median survival of 3 months for durvalumab monotherapy and recruitment of 150 patients in 6 months, it is estimated that this DCO will occur 7 months following recruitment of the last patient.

If the true PFS hazard ratio (HR) is 0.55 (likely to correspond to an 82% prolongation of PFS), the study will have 90% power to demonstrate a statistically significant difference for PFS at the 2-sided 5% significance level.

The smallest treatment difference that could be statistically significant at the primary analysis of PFS is an HR of 0.69 (assuming a 2-sided p-value of 0.5).

There will be up to 2 analysis timepoints for OS. The first OS analysis will occur at the same time as the primary PFS analysis and will be based on an estimated 44 OS events across therapies (29% maturity), and the second OS analysis will occur when

approximately 100 OS events have occurred (67% maturity). With an approximate 6-month recruitment period and an assumed median OS of 16 months in the durvalumab + placebo arm, it is anticipated that the final analysis will be performed at approximately 27 months after the last patient has been recruited.

Assuming the true OS HR is 0.75, the study will have 30% power to demonstrate a statistically significant OS effect with a 5% 2-sided significance level, allowing for 2 analyses of the data. The smallest treatment difference at the second analysis of OS that could be statistically significant is an HR of 0.68.

9.3 Populations for analyses

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

Table 15 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
PFS	Full analysis set (all patients for the primary analysis and the subset of patients with HRRm for the secondary analysis)
ORR, DoR, PFS6, OS, OS18, PROs	Full analysis set (all patients; ORR, DoR and PFS6 will be repeated in the subset of patients with HRRm) DoR will be based on the subset of patients in the analysis population who achieved objective tumor response
Demography	Full analysis set
PK data	PK analysis set
Safety data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
WHO/ECOG performance status	Safety analysis set

Table 15 Summary of outcome variables and analysis populations

Outcome variable	Populations
Vital signs	Safety analysis set

AE Adverse event; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; ORR Overall response rate; OS Overall survival; OS18 patients alive at 18 months; PFS Progression-free survival; PFS6 Progression-free at 6 months; PK Pharmacokinetics; PRO Patient-reported outcome; WHO World Health Organization.

9.3.1 Full analysis set

The FAS will include all randomized patients. Treatment arms will be compared based on randomized study treatment regardless of the study treatment received. Patients who were randomized but did not subsequently go on to receive study treatment will be included in the analysis in the treatment arm to which they were randomized.

The FAS will be used for the primary efficacy analysis of PFS and all secondary efficacy analyses (including PROs).

9.3.2 Safety analysis set

The safety analysis set will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally tested but will be summarized using the safety analysis set per the treatment received, that is, erroneously treated patients (eg, patients randomized to durvalumab + placebo who receive 1 or more doses of olaparib in error, will be reported in the durvalumab + olaparib group) will be summarized per the treatment they received.

9.3.3 PK analysis set

All patients who receive at least 1 dose of study treatment 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.

9.4 Statistical analyses

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

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

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

Efficacy and PRO data will be summarized and analyzed based on the FAS. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized on the safety analysis set.

All outputs will be summarized by treatment arm.

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

9.4.1 Outcome measures for analysis

9.4.1.1 Calculation or derivation of efficacy variables

The analysis of the primary endpoint, PFS, and the analyses of the secondary endpoints, ORR, DoR, and PFS6, will be based on the site Investigator assessments per RECIST 1.1. Secondary endpoints OS and OS18 will be evaluated from all-cause mortality.

BICR may be performed at AstraZeneca’s discretion.

RECIST 1.1-based endpoints

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 assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the Investigator-reported status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to randomization. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE; unless there is evidence of progression, in which case the response will be assigned as PD.

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

Progression-free survival

PFS (per RECIST 1.1 as assessed by the site Investigator) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 1). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more 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 1.1 assessment/scan dates of the component that indicates progression.

- When censoring a patient for PFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Overall survival

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

Note: Survival calls will be made following the date of DCO for the analysis. If patients are confirmed to be alive or if the death date is after the DCO date, these patients will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

Objective response rate

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

Duration of response

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

The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

Proportion of patients alive and progression free at 6 months after randomization (PFS6)

The PFS6 will be defined as the Kaplan-Meier (KM) estimate of PFS (per RECIST 1.1 as assessed by the Investigator) at 6 months after randomization.

Proportion of patients alive at 18 months after randomization (OS18)

The OS18 will be defined as the KM estimate of OS (per RECIST 1.1 as assessed by the Investigator) at 18 months after randomization.

9.4.1.2 Calculation or derivation of safety variables

Adverse events

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred term and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. AEs observed up until 90 days following discontinuation of the immunotherapy agents (ie, the last dose of durvalumab +olaprib or durvalumab + placebo) or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. Further details will be provided in the SAP. Any AE that occurs after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days post-last dose of the latest IP will be produced. These events will not be included in the AE summaries.

Other significant adverse events (OAEs)

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

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

Safety assessments

For the change from baseline summaries for vital signs, laboratory data, and physical examination, the baseline value will be the latest result obtained prior to the start of the IP.

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

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

The denominator used in laboratory summaries will include only evaluable patients, in other words, 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 only need to have 1 post-dose value recorded.

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

9.4.1.3 Calculation or derivation of patient-reported outcome variables

All items/questionnaires will be scored according to published scoring guidelines.

EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 function scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 scoring manual (Fayers et al 2001). An outcome variable consisting of a

score from 0 to 100 will be derived for each of the symptom scales, each of the function scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 scoring manual. Higher scores on the global health status and function scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. A minimum clinically meaningful change is defined as an absolute change of ≥10 in the score from baseline for scales from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase of ≥10 in the score from baseline, whereas a clinically meaningful deterioration is defined as a decrease of ≥10 in the score from baseline. At each post-baseline assessment, the change in symptoms/ functioning from baseline will be categorized as improvement, no change, or deterioration as shown in Table 16. A patient's best overall response in symptoms, function, or global health status/QoL will be derived as the best response the patient achieved, based on evaluable PRO data collected during the study period. Additional details will be provided in the SAP.

Table 16 Mean change and visit response in health-related quality of life

Score	Change from baseline	Visit response
EORTC QLQ-C30 global quality of life score	≥+10 ≥-10 Otherwise	Improvement Deterioration No change
EORTC QLQ-C30 symptom scales	≥+10 ≥-10 Otherwise	Deterioration Improvement No change
EORTC QLQ-C30 function scales	≥+10 ≥-10 Otherwise	Improvement Deterioration No change

EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire.

For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then

that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

Time to symptom deterioration

For each of the symptoms scales in the EORTC QLQ-C30, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration (an increase of ≥10 in the score from baseline) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient discontinues study treatment or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by EORTC QLQ-C30) have 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 PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at Day 0. The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores of ≤90.

Time to health-related quality of life/function deterioration

For global health status/QoL, time to deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration (a decrease of ≥10 in the function scales or the global health status/QoL from baseline) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient discontinues study treatment or receives another anticancer therapy prior to global health status/QoL or functional deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the global health status/QoL or functional change could be evaluated.

Patients whose HRQoL or function (as measured by EORTC QLQ-C30) have 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 PRO assessment where the HRQoL/function could be evaluated. Also, if HRQoL/function deteriorates after 2 or more missed PRO assessment visits or the patient dies after 2 or more

missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where HRQoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at Day 0. The population for the analysis of time to HRQoL/function deterioration will include a subset of the FAS who have baseline scores of ≥10.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (a decrease from baseline score ≥10 for EORTC QLQ-C30 symptom scales) in that symptom from baseline. The denominator will consist of a subset of the FAS who have a baseline symptom score ≥10.

HRQoL/function improvement rate

The HRQoL/function improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (an increase from baseline score of ≥10 for EORTC QLQ-C30 function scales and global health status/QoL) in that scale from baseline. The denominator will consist of a subset of the FAS who have a baseline global health status/QoL or functional score of ≤90.

EQ-5D-5L

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

PGIC

The PGIC question is “Overall, how would you rate the change in your bladder cancer symptoms since you started this study?” with response options for the PGIC as follows: Very Much Improved (+3), Much Improved (+2), Minimally Improved (+1), No Change

(0), Minimally Worse (-1), Much Worse (-2), and Very Much Worse (-3). No scoring will be done using the assigned numerical values. Instead, the proportion of patients for each response category will be summarized descriptively at each visit.

9.4.1.4 Calculation or derivation of biomarker variables

All patients must provide an FFPE tumor sample for tissue-based HRR gene panel mutation testing. HRR mutation status has previously been shown to be predictive of response to olaparib in prostate cancer (Mateo et al 2015). The analysis will be performed at a central laboratory testing service using the DNA extracted from FFPE tissue. The tumor sample will be tested for loss of function alterations in 15 pre-specified HRR genes: *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. If the test results indicate that the patient has at least 1 qualifying mutation in any of these genes, the patient will be considered HRRm for the purposes of the study. Patients with no detected mutations will be considered HRRwt.

PD-L1 is a predictive factor for the benefit of durvalumab, with patients with low PD-L1 levels having less benefit. PD-L1 expression will be analyzed retrospectively on a regular basis and adjusted for in the analysis of PFS and OS.

PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background or by the percentage of tumor-associated immune cells with staining (IC+) at any intensity above background. The percent of tumor area occupied by any tumor-associated immune cells (Immune Cells Present [ICP]) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining. PD-L1 status is considered high if any of the following are met:

- ≥25% of tumor cells exhibit membrane staining; or
- ICP>1% and IC+ ≥25%; or
- ICP= 1% and IC+ = 100%.

9.4.1.5 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 (see Appendix D).

9.4.2 Efficacy analyses

Efficacy data will be summarized and analyzed using the FAS. All outputs will be summarized by treatment arm.

Table 17 details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses. Note: all endpoints compare durvalumab + olaparib versus durvalumab + placebo, unless otherwise indicated.

Table 17 Formal statistical analysis methods and pre-planned sensitivity analyses

Endpoints analyzed	Notes
PFS	Primary analysis using a stratified log-rank test using Investigator assessment per RECIST 1.1 with the following covariates: 1 HRR status (mutant versus wildtype) 2 PD-L1 tumor status (high versus low) 3 Bajorin risk index (0 versus 1 versus 2) Sensitivity analyses using Investigator assessments (RECIST 1.1) 1 Interval censored analysis – evaluation time bias 2 Analysis using alternative censoring rules – attrition bias
OS	Stratified log-rank test with the following covariates: 1 HRR status (mutant versus wildtype) 2 PD-L1 tumor status (high versus low) 3 Bajorin risk index (0 versus 1 versus 2) Sensitivity analysis using a KM plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias
ORR	Logistic regression using Investigator assessment per RECIST 1.1
DoR	KM estimates using Investigator assessments per RECIST 1.1
PFS6	KM estimates of patients alive and progression-free at 6 months
OS18	KM estimates of survival at 18 months

Table 17 Formal statistical analysis methods and pre-planned sensitivity analyses

Endpoints analyzed	Notes
Time to symptom deterioration (EORTC QLQ-C30 endpoints)	Stratified log-rank test
Symptom improvement rate (EORTC QLQ-C30 endpoints)	Logistic regression
Change from baseline in symptoms (EORTC QLQ-C30 endpoints)	MMRM analysis

DoR Duration of response; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; FAS Full analysis set; HR Hazard ratio; HRR homologous recombination repair; HRRm Homologous recombination repair mutant; KM Kaplan-Meier; MMRM Mixed effect model repeat measurement; ORR Objective response rate; OS Overall survival; OS18 Patients alive at 18 months; PD-L1 Programmed death ligand 1; PFS Progression-free survival; PFS6 Progression-free at 6 months; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1.

Prior to unblinding for the primary analysis, the proportion of patients in each stratification level will be reviewed, and levels may be combined or factors may be removed from the analyses, if the numbers are too small.

9.4.2.1 Primary endpoint: Progression-free survival

The primary analysis of the primary endpoint PFS will occur when it is expected that approximately 118 PFS events have occurred (79% maturity). PFS will be based on RECIST 1.1 using the Investigator tumor assessments. The analysis will be performed for patients in the FAS population using a stratified log-rank test adjusting for HRR status (mutant versus wildtype), PD-L1 tumor status (defined in Section 9.4.1.4) and Bajorin risk index (0 [defined as no risk factors for metastasis and ECOG performance status] versus 1 [defined as 1 risk factor] versus 2 [defined as 2 risk factors]). The effect of durvalumab + olaparib versus durvalumab + placebo will be estimated by the HR together with its 95% CI from a stratified Cox model (an HR less than 1 will favor durvalumab in combination with olaparib).

KM plots of PFS will be presented by treatment arm, by treatment arm and HRR status (mutant versus wildtype), by treatment arm and PD-L1 tumor status, and by treatment arm and Bajorin risk index where appropriate. Summaries of the number and percentage of patients experiencing a PFS event and type of event (RECIST 1.1 or death) will be provided along with the median PFS for each treatment.

The assumption of proportionality will be assessed.

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable RECIST 1.1 assessment will be analyzed using a stratified log-rank test as described for the primary analysis of PFS. For patients whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust even in highly asymmetric assessment schedules (Sun and Chen 2010).

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, and within the same sensitivity analysis, patients who take subsequent therapy prior to their last evaluable RECIST 1.1 assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a KM plot of the time to censoring using the PFS data from the primary analysis where the censoring indicator of the PFS analysis is reversed.

Subgroup analyses will be conducted comparing PFS between durvalumab + olaparib and durvalumab + placebo in the following subgroups of the FAS (but not limited to):

- Sex (male versus female)
- Age at randomization (<65 versus ≥65 years of age)
- HRR status (mutant versus wildtype)
- BRCA status (BRCAm versus HRRm, BRCA wildtype versus HRRwt)
- PD-L1 status (high versus low)
- WHO/ECOG performance status (0 and 1 versus 2)
- VES-13 score (<3 versus ≥3)
- Visceral disease (lymph-node-only metastasis versus metastatic disease to any other organ system)
- Bajorin risk index (0 versus 1 versus 2)

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

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

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

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

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 10 events in a subgroup), the relationship between that subgroup and PFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

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

The PFS analysis described above will be repeated for a subset of patients in the FAS with HRRm.

Censoring rules will be provided in the SAP.

9.4.2.2 Overall survival

OS in the FAS population will be analyzed using a stratified log-rank test, using the same methodology as described for the primary PFS endpoint. The effect of durvalumab + olaparib with durvalumab + placebo will be estimated by the HR together with its corresponding 95% CIs and from a stratified Cox model. KM plots will be presented by treatment arm. 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 group. Subgroup analyses maybe performed if there are a sufficient number of OS events.

9.4.2.3 OS18

OS18 will be summarized (using the KM curve) with a landmark estimate from the KM curve by treatment arm.

9.4.2.4 Objective response rate

The ORR will be based on RECIST 1.1 using the Investigator tumor data. The ORR will be compared between durvalumab + olaparib and durvalumab + placebo using logistic regression models adjusting for the same factors as the primary and secondary endpoint PFS dependent on the population being analyzed. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

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

The ORR analysis described above will be repeated for a subset of patients in the FAS with HRRm.

9.4.2.5 Duration of response

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

The DoR analysis described above will be repeated for a subset of patients in the FAS with HRRm.

9.4.2.6 PFS6

PFS6 will be summarized with a landmark estimate from the KM curve by treatment arm.

9.4.2.7 The PFS6 analysis described above will be repeated for a subset of patients in the FAS with HRRm.Patient-reported outcomes

The main PRO measures identified in the secondary objectives are global health status/QoL, physical function, pain, and fatigue scales of the EORTC QLQ-C30. Compliance rates summarizing questionnaire completion at each visit will be tabulated for each questionnaire; further details will be included in the SAP.

EORTC QLQ-C30

Time to symptom deterioration in symptom, function, and HRQoL will be analyzed respectively for each of the 3 multiple-item symptom scales (fatigue, pain, and nausea/vomiting), the 5 function scales (physical, role, cognitive, emotional, and social), and global health status/QoL. These analyses will be performed for the FAS using a log-rank test stratified by the same covariates as for the primary PFS endpoint and illustrated using a KM plot by treatment arm. Summaries of the number and percentage of patients who have an event, as well as who were censored, will be provided along with the medians for each treatment.

A summary of the symptom improvement rate for each of the 3 symptom scales will be produced. Similarly, a summary of the best HRQoL/function response rate for each of the 5 function scales and global health status/QoL will be produced. The best symptom response rate and HRQoL/function response rate will be analyzed by comparing the treatment arms using a logistic regression model as described for the analysis of ORR. The odds ratio, p-value, and 95% CI will be presented graphically on a forest plot.

Summaries of absolute and change from baseline values for each of the 3 symptom scales/items, 5 individual symptom items (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), 5 function scales and the global health status/QoL score, and each functional domain will be reported by visit for each treatment arm. The mean change from baseline will be analyzed for each symptom scale and function scale of interest using a mixed model for repeated measures and potentially a piecewise linear model to further support data interpretation. Full details of this and appropriate sensitivity analyses will be described in full in the SAP.

EQ-5D-5L

Descriptive statistics, graphs, and listings will be reported for health state utility index values (United Kingdom base case) and visual analog scale by visits as well as change in these scores from baseline. To support future economic evaluations of the study treatment, additional appropriate analyses may be undertaken, for example, mean health state utility pre- and post-dose and pre- and post-progression.

PGIC

Responses on the PGIC will be summarized descriptively as the number of patients and corresponding percentages for each category in the questionnaire at each visit by treatment arm.

9.4.3 Safety analyses

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

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 and percentage of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced. Any safety summaries examining retreatment with durvalumab will be produced separately as described in the SAP.

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

9.4.4 Pharmacokinetic analyses

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

9.4.5 Immunogenicity analyses

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab. The immunogenicity titer and presence of neutralizing ADA 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 data allow.

9.4.6 Pharmacokinetic/pharmacodynamic relationships

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

9.4.7 Biomarker data

The relationship of PD-L1 expression and, if applicable, exploratory biomarkers to clinical outcomes (including but not restricted to PFS) may be assessed.

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

9.4.8 Pharmacogenetic data

DNA variants associated with response, including AEs and/or cancer or its evolution, are exploratory. These exploratory analyses are not expected to be reported in the CSR, but any contribution to the interpretation of the results may be included and will be clearly labeled as exploratory.

9.4.9 Exploratory analyses

Associations between exploratory endpoints and OS, PFS, ORR, and DoR may be assessed. These exploratory endpoints may include, but are not limited to, HRR gene expression assessments, protein expression detected by IHC (eg, PD-L1), ctDNA, tumoral mutations beyond HRRm, and mRNA expression.

The biomarker analyses to be investigated using tumor samples may include, but not limited to, the following:

- Study the correlation of the HRRm signature with response. Retrospectively adapt/refine olaparib HRRm signature based on emerging data from clinical studies particularly in bladder cancer.
- Explore the impact of PD-L1 expression and tumor mutations on response to treatments and correlations between HRRm, mutations in other genes and PD-L1 expression.
- Explore the correlation between TMB and microsatellite instability with genetic alterations and clinical response.
- Explore association of immune-related gene expression signatures such as, but not limited to, IFNγ gene expression signature in tissue with response to treatment.
- Based on emerging scientific knowledge, further analyses yet to be defined may be undertaken.

Analyses of ctDNA include, but may not be limited to, the following:

- Exploring association of genetic variants and/or variant burden in genes in ctDNA with response to treatment and other exploratory biomarkers.
- Comparing genetic variants in FFPE to those in ctDNA, particularly, but not limited to, HRRm, and their correlative response to treatment.
- Exploring changes in ctDNA mutation frequencies, including, but not limited to, changes in mutant allele frequency over the course of treatment as an early indicator of clinical outcome.

Exploratory analyses are not expected to be reported in the CSR but any contributing to interpretation of the results may be included and will be clearly labeled as exploratory.

9.4.10 Methods for multiplicity control

Formal adjustment of alpha for multiple comparisons is not planned, but if required at the time of reporting, 100% of the alpha used for the primary PFS analysis will be used for the OS analysis if the PFS analysis is statistically significant.

For the OS endpoint, there is 1 interim analysis planned, and the alpha level will be controlled at the interim and primary analysis timepoints by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach.

9.5 Interim analyses

The study will be unblinded for the primary analysis of PFS in the FAS, which will be performed at 1 timepoint only, when approximately 118 events have occurred (79% maturity). At the time of the primary analysis, the secondary analyses of ORR, DoR, PFS6, and PRO will also be performed. An interim analysis of OS will also be performed based on an estimated 44 OS events across therapies (29% maturity). After the primary analysis, the data will continue to be collected to support the final OS analysis, when approximately 100 patients have died (67% maturity).

The primary PFS analysis, as well as any OS analyses, will be conducted by AstraZeneca or its delegate.

The available alpha will be controlled among the first and second timepoints by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the significance level applied at the first analysis (ie, at the time of 44 events) is dependent upon the proportion of information available. This proportion of information will be calculated at the

first analysis using the data available at that time. For example, if the overall alpha level is 5% and if 44% of OS events required at the time of the second OS analysis are available at the time of the interim analysis (ie, 44/100 events have occurred), the 2-sided significance level to be applied for the first OS analysis would be 0.10% and the 2-sided significance level to be applied for the final OS analysis would be 4.85%. The smallest treatment difference that could be statistically significant at the first analysis of OS is an HR of 0.38 and 0.68 at the second analysis of OS.

9.5.1 Independent data monitoring committee

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

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

An IDMC composed of independent experts will be established to perform an interim assessment of the safety of durvalumab + olaparib combination therapy in this population. The first safety review will take place approximately 6 months after the study has started. Safety reviews will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment.

The IDMC will meet approximately every 6 months, unless otherwise requested by the IDMC. IDMC members will be consulted to ensure appropriate frequency.

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

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical, and study oversight considerations

A 1 Regulatory and ethical considerations

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

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

The protocol, protocol amendments, ICF, IB, 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 or head of the study site 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 the requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

A 2 Financial disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

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

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

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

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

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

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient's partner becomes pregnant during or within 90 days after the study, where permissible, the partner is asked to sign the "Adult Study ICF for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological

samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

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

Extra precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his/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 datasets transferred to the Sponsor will contain only the identifier; patient names or any information that would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committee structure

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

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

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

The Investigator must maintain accurate documentation (source data) that supports the information entered into the eCRF.

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

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

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

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

A 8 Source documents

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

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

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

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 AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of serious adverse event

A Serious Adverse Event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up) that fulfils one or more of the following criteria:

- Results in death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical treatment to prevent one of the outcomes listed above
- Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical bjudgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization,

may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

- Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

B 3 Life threatening

"Life threatening" means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. "Life-threatening" does not mean that an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm

- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 CTCAE grade

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Appendix B, B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but not an SAE unless it meets the criteria shown in Appendix B, B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B, B 2.

B 7 A guide to interpreting the causality question

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

- Time course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class, or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as the following:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related."

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

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

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized, which could have led to an error

Examples of events to be reported in clinical studies as medication errors are as follows:

- 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 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
- Wrong participant receiving 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 are as follows:

- Errors related to or resulting from IVRS/IWRS, including those that lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missing drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failing to return unused medication or empty packaging
- Errors related to background and rescue medication or standard-of-care medication in open-label studies even if an AZ product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate).

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

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

Samples retained for further use will be stored in the 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

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

Because collection of the biological sample(s) is an integral part of the study, the patient is withdrawn from further study participation.

The Principal Investigator ensures the following:

- Patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.

- Biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action is documented.
- The organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action is documented, and the signed document is returned to the study site
- The patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action is documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

IATA classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. 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 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 or life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens (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 include hepatitis A, B, C, D, and E viruses as well as 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 includes all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(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 Genetics

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; MOA of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases, or other improvements in health care and to the discovery of new diagnostics, treatments, or medications.

In addition, collection of DNA samples from populations with well-described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient's DNA, ie, the entire genome.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on durvalumab continues but no longer than 15 years or other period 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 Clinical Study Protocol **and** provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at the screening visit prior to randomization. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE; such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at the screening visit, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the patient enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix 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 consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient, and the original filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that he/she may freely withdraw 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/her genetic data. In addition, regulatory authorities may require access to the relevant files, although the patient's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can use this information only 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 who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report cases of Hy's law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Dosing Modification and Toxicity Management Guidelines(for durvalumab).

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in the review and assessment of cases meeting PHL criteria to agree whether Hy's law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's law (PHL)

AST or ALT ≥3× ULN **together with** 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, or 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 (PHL) 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

When a patient meets any of the identification criteria, in isolation or in combination, the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw)
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met, the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Appendix E, E 2 for definition) by reviewing laboratory reports from all previous visits

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 Appendix E, E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's law (PHL) criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's law (PHL) criteria met

If the patient does meet PHL criteria, the Investigator will:

- Notify the AstraZeneca representative who will then inform the central study team

The Study Physician contacts the Investigator, to provide guidance as well as discuss and agree on an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact, the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the Hy's law laboratory kit should be used
- Complete the 3 Liver eCRF Modules as information becomes available
- If at any time, in consultation with the Study Physician, the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

E 5 Review and assessment of potential Hy's law (PHL) cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks 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. 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.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation on the ALT or AST and TBL elevations other than the IP:

- Report an 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.
  - If 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 3 weeks 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:

- Report an SAE (report term "Potential Hy's law") applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required when potential Hy's law (PHL) criteria are met before and after starting study treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met.[#]

- If there is no significant change, no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the central study team, then follow the subsequent process described in Appendix B, B 5.
- # A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL), in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

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, E 6?

If **no**, follow the process described in Appendix E, 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, E 4.

A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL), in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Appendix F Guidelines for evaluation of objective tumor response using RECIST 1.1 (Response Evaluation Criteria in Solid Tumors, version 1.1) criteria

Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009) for this study with regard to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for determination of confirmation of radiologic progression.

Definitions of measurable, non-measurable, target and non-target lesions

Only patients with measurable target disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion that has not been previously irradiated.

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 CT or 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 to <15 mm short axis diameter at baseline[2]).
- Truly non-measurable lesions, including the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions[3]
- Brain metastasis

[1] The short axis is defined as the longest axis perpendicular to the long axis of the lymph node.

[2] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

[3] Localized post-radiation changes that 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 as TLs.

Target lesions:

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) each is considered as a single organ.

Tumor 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:

All additional measurable and non-measurable lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

Methods of assessment

The same method of assessment on the same imaging technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST 1.1 assessment is provided in Table 18, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

Table 18 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred) MRI	CT (preferred) MRI Plain X-ray Chest X-ray	CT (preferred) MRI Plain X-ray Chest X-ray Bone scan FDG-PET

CT Computed tomography; FDG-PET ^{18}F-Fluoro-deoxyglucose positron emission tomography; 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 images for measurement of TL, assessment of NTL, and identification of any new lesions.

It is recommended that CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV 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 timepoints per patient.

Clinical examination

Clinical examination of tumors (ie, by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

X-ray

Chest X-ray

Chest X-ray assessment will not be used for the 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 1.1 assessment of tumors as it is not a reproducible method, does not provide an accurate assessment of tumor size, and is subjective and operator dependent. Tumors identified by ultrasound examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers

Tumor markers on cytological or histological (biopsy) samples will not be used for tumor response assessments as per RECIST 1.1.

Histology and cytology

Histology on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any fluid accumulation/effusion (eg, ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to new lesions or progression of NTLs, respectively.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions may be recorded in the event that positive hotspots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hotspot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that timepoint.

FDG-PET scan

^{18}F-Fluoro-deoxyglucose positron emission tomography/CT (FDG-PET/CT) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[4] not present on baseline or prior FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline or prior FDG-PET scan available, and no evidence of new lesions on CT/MRI scans, then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to verify new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

[4] A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed.

Tumor response evaluation

Schedule of evaluation

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient (eg, new lesions) at follow-up.

Baseline assessments should be performed no more than 28 days before the date of randomization and ideally should be performed as close as possible to the date of randomization. Efficacy by RECIST 1.1 for all patients will be assessed according to the Schedule of Assessments. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his/her regularly scheduled imaging visits.

For patients who discontinue IP due to toxicity in the absence of unequivocal radiographic evidence of objective disease progression, tumor assessments should be continued according to the original imaging schedule.

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 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 diameter 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.
- 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 TL has completely disappeared, the longest 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 2 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 1 of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention, eg, definitive radiotherapy, embolization, surgery, during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 case report form (see Not evaluable in Table 19). If a TL has been completely removed (surgery), the longest diameter should be recorded as 0 mm.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 19).

Table 19 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 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 shrinkage 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 sum on study (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.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or NE (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 NE as a TL response.

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 20).

Table 20 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of 1 or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when 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.

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 PR in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 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 1 or more new lesions is assessed as progression.

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.

If a TL has completely disappeared and a lesion appears in the same location on a subsequent scan, it will be recorded as a new lesion.

The finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 21.

Table 21 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	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
NE	Non-PD or NE	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no target and/or non-target lesions at baseline).

Confirmation of Radiological Progression

Patients who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive treatment at the discretion of the Investigator and patient. A follow-up scan is collected after the initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD and the Confirmation of Radiological Progression criteria described below are applied as tumor assessments for this follow-up scan.

For all patients who are treated through progression, the Investigator should ensure that the patient does not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient.

The criteria for continuing treatment despite RECIST 1.1-defined progression are as follows:

- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG performance status >1.
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention. Concurrent radiation treatment is not permitted. If a patient requires palliative radiation or prophylactic radiation [eg, brain], consult AstraZeneca for exception to this rule: protocol therapy will need to be held prior to and during the radiation treatment.

Confirmation of progression guidelines is set for patient management and treatment decisions in clinically stable patients continuing to receive treatment at an initial RECIST 1.1-defined PD. In the absence of clinical progression, patients may receive treatment until confirmed radiological progression according to the criteria listed below.

An immediate prior RECIST 1.1-defined radiological PD would be considered confirmed if any the following criteria are met in the subsequent follow-up scan (acquired preferably at the next regularly scheduled imaging visit but no sooner than 4 weeks after the RECIST 1.1-defined PD scan):

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir (as per RECIST 1.1 definitions)

- *and/or* significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint (as per RECIST 1.1 definitions)
- *and/or* additional (brand) new unequivocal lesions at the follow-up scan timepoint (as per RECIST 1.1 definitions)
- *and/or* significant progression (worsening) of pre-existing new lesions at the follow-up scan timepoint compared with the immediate prior timepoint (unique definition)

Note: In order to have confirmed radiological progression, there should be 2 consecutive assessments meeting the PD definition, the first PD by RECIST 1.1 and the second PD using the Confirmation of Radiological Progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, in the absence of significant clinical deterioration, then the patient may continue with imaging tumor assessments until the next PD by RECIST 1.1, which will also require a follow-up scan evaluated using the Confirmation of Radiological Progression criteria.

If the first PD (by RECIST 1.1) is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.

Central Review

All images will be collected, quality checked, and stored centrally by an Imaging contract research organization (CRO) appointed by AstraZeneca. Guidelines for image acquisition, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part on the results of the RECIST 1.1 assessment conducted by the Investigator.

Further details of the BICR will be documented in the Independent Review Charter, (also referred to as “Imaging Charter”).

Specifications for radiologic anatomical imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

If specified, all images will be collected, quality checked, and stored centrally by the imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. The management of patients will be based solely on the local assessments conducted by the Investigator.

Also if specified, further details of the BICR will be documented in the Independent Review Charter (also referred to as the "Imaging Charter").

CT scan

CT scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. **Anatomic coverage:** Optimal anatomic coverage for most solid tumors is the chest, abdomen, and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up timepoints. This will enable not only better consistency of tumor measurements but also identification of new disease.

b. **IV contrast administration**: Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type as well as on anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible.

Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible, and if not, the patient should be considered NE from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are as follows: CT thoracic (chest) examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed, then CT without IV contrast is an option for the thorax, 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 minimum 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 as well as spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies, eg, neck) with T1- and T2-weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression, and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters

for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix G Patient-report outcomes

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

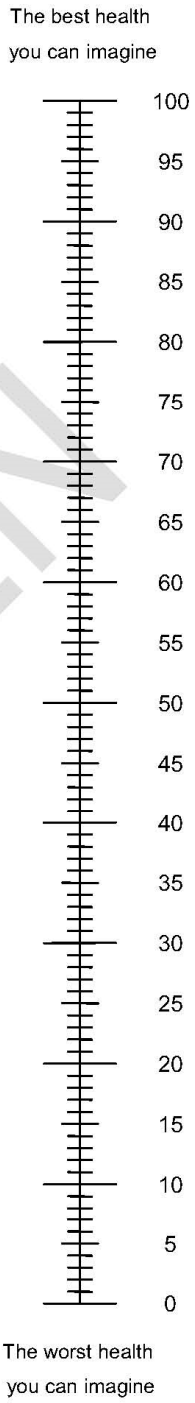
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the treatment I have received in this study, my overall health status is:

Please tick (✓) one box only:

- ☐ Very Much Improved
- ☐ Much Improved
- ☐ Minimally Improved
- ☐ No Change
- ☐ Minimally Worse
- ☐ Much Worse
- ☐ Very Much Worse

VULNERABILITY ELDERS SURVEY-13

VES-13

1. Age _____

SCORE: *1 POINT FOR AGE 75-84*
3 POINTS FOR AGE ≥ 85

2. In general, compared to other people your age, would you say that your health is:

- ☐ Poor,* *(1 POINT)*
- ☐ Fair,* *(1 POINT)*
- ☐ Good,
- ☐ Very good, or
- ☐ Excellent

SCORE: *1 POINT FOR FAIR or POOR*

3. How much difficulty, on average, do you have with the following physical activities:

	No Difficulty	A little Difficulty	Some Difficulty	A Lot of Difficulty	Unable to do
a. stooping, crouching or kneeling?	☐	☐	☐	☐ *	☐ *
b. lifting, or carrying objects as heavy as 10 pounds?	☐	☐	☐	☐ *	☐ *
c. reaching or extending arms above shoulder level?	☐	☐	☐	☐ *	☐ *
d. writing, or handling and grasping small objects?	☐	☐	☐	☐ *	☐ *
e. walking a quarter of a mile?	☐	☐	☐	☐ *	☐ *
f. heavy housework such as scrubbing floors or washing windows?	☐	☐	☐	☐ *	☐ *

***SCORE**: 1 POINT FOR EACH * RESPONSE IN Q3a THROUGH f . MAXIMUM OF 2 POINTS.*

4. Because of your health or a physical condition, do you have any difficulty:

a. shopping for personal items (like toilet items or medicines)?

- ☐ YES → Do you get help with shopping? ☐ YES * ☐ NO
- ☐ NO
- ☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

b. managing money (like keeping track of expenses or paying bills)?

- ☐ YES → Do you get help with managing money? ☐ YES * ☐ NO
- ☐ NO
- ☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

Continued

c. walking across the room? USE OF CANE OR WALKER IS OK.

☐ YES → Do you get help with walking? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

d. doing light housework (like washing dishes, straightening up, or light cleaning)?

☐ YES → Do you get help with light housework? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

e. bathing or showering?

☐ YES → Do you get help with bathing or showering? ☐ YES * ☐ NO
☐ NO
☐ DON'T DO → Is that because of your health? ☐ YES * ☐ NO

*SCORE: 4 POINTS FOR ONE OR MORE * RESPONSES IN Q4a THROUGH Q4e*

Appendix H Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{ss}	area under the concentration versus time curve at steady state
BCG	Bacillus Calmette Guerin
BICR	Blinded Independent Central Review
BID	twice daily
BoR	best overall response
BP	blood pressure
BRCA	breast cancer susceptibility gene
BRCAm	breast cancer susceptibility gene-mutated
CD	Cluster of differentiation
CI	confidence interval
$Cmax_{ss}$	maximum drug concentration at steady state
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CRT	chemoradiation therapy
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte antigen 4
CYP	cytochrome P450
DCO	data cutoff
DDR	DNA damage and response
DILI	drug-induced liver injury
DoR	duration of response
DSB	double strand break

Abbreviation or special term	Explanation
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire
ePRO	Electronic tablet
EQ-5D-5L	EuroQol 5-dimension, 5 level health state utility index
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy - General
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	F-fluoro-deoxyglucose positron emission tomography/computed tomography
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B
HCV	hepatitis C
HIV	human immunodeficiency virus
HL	Hy's law
HR	hazard ratio
HRQoL	health-related quality of life
HRR	homologous recombination repair
HRRm	homologous recombination repair mutated
HRRwt	homologous recombination repair wild type
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

Abbreviation or special term	Explanation
IFN	interferon
IFNγ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IM	intramuscular
imAE	immune-mediated adverse event
IO	Immuno-oncology
IP	investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
KM	Kaplan-Meier
LFT	liver function test
LIMS	Laboratory Information Management System
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle-invasive bladder cancer
MOA	mechanism of action
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI	National Cancer Institute
NE	not evaluable
NFBlSI-18	National Comprehensive Cancer Network - Functional Assessment of Cancer Therapy Bladder Symptoms Index-18
NFκB	nuclear factor kappa B
NK	natural killer
NMIBC	non-muscle-invasive bladder cancer
NSCLC	Non-small cell lung cancer
NTL	non-target lesion
OAE	Other significant adverse events
ORR	objective response rate

Abbreviation or special term	Explanation
OS	overall survival
OS18	patients alive at 18 months
PARP	poly (ADP ribose) polymerization
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	progression-free survival
PFS6	progression free at 6 months
PGIC	Patient Global Impression of Change
PHL	potential Hy's law
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PSR	platinum-sensitive relapsed
q12w	every 12 weeks
q28days	every 28 days
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q8w	every 8 weeks
QoL	Quality of Life
QTc	QT interval corrected for heart rate
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SoA	Schedule of Activities
sPD-L1	soluble programmed cell death ligand 1
SSB	single strand break
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TBL	total bilirubin

Abbreviation or special term	Explanation
TCC	transitional cell carcinoma
T-cell	T lymphocyte
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
TKI	tyrosine kinase inhibitor
TL	target lesion
TMB	Tumor Mutational Burden
TNF-α	tumor necrosis factor alpha
TNM	Classification of Malignant Tumors (Tumor, Lymph Nodes, Metastasis)
UC	urothelial cancer
ULN	upper limit of normal
US	United States of America
VES-13	Vulnerability Elders Survey-13
w/v	weight/volume
WBDC	Web Based Data Capture
WHO	World Health Organization

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Document ID:	CCI [redacted]	
Version Label:	4.0 CURRENT LATEST APPROVED	
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