Clinical Study Protocol	
Drug Substance	Olaparib (AZD2281) and Durvalumab (MEDI4736)
Study Codes	D081RC00001; ENGOT-ov46; AGO-OVAR 23; GOG-3025.
Version	8.0
Date	24 April 2024
EudraCT Number	2017-004632-11
EU CT Number	2022-502747-35-00

A Phase III Randomised, Double-Blind, Placebo-Controlled, Multicentre Study of Durvalumab in Combination with Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib in Newly Diagnosed Advanced Ovarian Cancer Patients (DUO-O).

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden
and (for sites in Japan): AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

Regulatory Agency Identifying Number(s):

EudraCT number: 2017-004632-11

EU CT number: 2022-502747-35-00

Clinicaltrials.gov identifier: NCT03737643

VERSION HISTORY

Version 8.0 (24 April 2024)

The main reason for this amendment is inclusion of additional extended OS follow-up for patients in the global non-*tBRCAm* cohort.

The following conventions are used to describe final OS, extended OS, and last OS in this protocol:

- **Final OS analysis:** Planned to occur at approximately 50% OS maturity across the 3 treatment arms in the non-*tBRCAm* ITT population or 5 years following randomization of the last non-*tBRCAm* patient (approximately 86 months after the first patient is randomised), whichever occurs sooner.
- **Extended OS analysis:** In the event the final OS analysis occurs when approximately 50% maturity has occurred across the 3 treatment arms in the global non-*tBRCAm* ITT population, an extended OS descriptive analysis (non-*tBRCAm* cohort only) may also be performed 5 years after the last non-*tBRCAm* patient is randomised to treatment.
- **Last OS analysis:** If the extended OS analysis is performed, this will be the last OS analysis. If the extended OS analysis is not performed, the final OS analysis will be the last OS analysis.

Applicable section number (s)/title	**Nature of revision**	**Rationale for change**
Section 1.1.3 Section 1.1.3.3 Section 1.1.3.7 Section 1.2 Section 6.7 Section 9.2 Section 9.4.1.2 Section 9.5	Update to include option for extended OS follow-up	Inclusion of option for additional extended OS follow-up for patients in the global non-*tBRCAm* cohort only, 5 years post last patient randomized in the global non-*tBRCAm* cohort, in the event final OS analysis is based on approximately 50% OS maturity across all 3 treatment arms in the non-*tBRCAm* ITT population
Section 1.1.3.6 Section 8.10	Addition of description of visits and data collection in the event of extended OS follow-up	To specify visits and data collection if there is an extended OS follow-up
Section 1.2.	Text updated to reflect the revised estimated date of last patient completed (Q2, 2026).	New information.
Table 4 footnotes	Added that survival status is to continue to be collected Q12 weeks in the global non-*tBRCAm* cohort	Clarifying requirements for the extended OS follow-up

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	only in the event of an extended OS follow-up, and clarified data collection for other assessments in the global *tBRCAm*/ non-*tBRCAm* cohorts.	
Figure 5	Addition to footnote that survival status is to continue to be collected in the event of an extended OS follow-up.	To correctly describe data to be collected in the optional extended OS follow-up
Section 4.1	Clarification that the global *tBRCAm* cohort and global non-*tBRCAm* cohort data collection will end at the last OS analysis (either the final OS analysis or extended OS analysis)	To describe when participation ends for patients in these 2 cohorts
Section 4.4	Addition of extended OS follow-up after final OS analysis. Removal of previous description of end of study.	Inclusion of an option for the study to continue after final OS analysis into extended OS follow-up.
Section 7.1.1	Clarification added for extended OS follow-up data collection.	Further clarifying when to collect data and required data points.
Section 8.4.3.1	Maternal exposure updated from 3 months to 6 months after the last dose of study medication.	To make compliant with new FDA and EMA CTFG guidelines.
Section 8.4.4 Appendix B4	Change from study drug to IMP or NIMP	To comply with EU CTR regulation
Section 8.4.6.3	New section added for management of olaparib in combination with durvalumab toxicities.	Addition of PRCA as an ADR and AIHA as a potential risk when olaparib is used in combination with durvalumab.
Appendix A, A1	Introduce medical device text under regulatory reporting.	Alignment with updated regulatory EU requirement.
Appendix A, A4	Data Protection text introduction.	To align with EU CTR requirements.
Appendix I, I 1	Update to toxicity management guidance, to include action to be taken with olaparib and durvalumab	To align with latest olaparib IB edition 23.0, which includes the addition of new ADR of PRCA and

Applicable section number (s)/title	Nature of revision	Rationale for change
	in the event of pure red cell aplasia (PRCA) or autoimmune haemolytic anaemia (AIHA)	new potential risk of AIHA when olaparib is used in combination with durvalumab

Version 7.0, 24 January 2023

Applicable section number(s)/title	Nature of revision	Rationale for change
Tilte page	The EU CT number of the study was added	To provide the appropriate regulatory identifiers for the study.
Section 1.2, Section 3.2	Overall survival (OS) was added to the endpoints for the secondary objective relating to the clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of *tBRCAm* patients with newly diagnosed advanced ovarian cancer.	For consistency with the analyses described in Section 9.4.5.
Section 4.4	Update to end-of-study definitions.	Alignment with updated regulatory requirements.
Section 6.7	Update on continued access to interventional treatments after the end of the study.	For consistency with current AstraZeneca processes.
Section 8.3.13	Update to AESI section to change pneumonitis from an important potential risk to a potential risk for olaparib.	To align with the latest edition of the olaparib IB.
Section 8.4.2 Appendix A1	Information on reporting of SAEs moved to Appendix A1.	For consistency with current AstraZeneca processes.
Section 8.4.5 Appendix B4	Guidance on Drug Abuse and Drug Misuse added to existing Medication Error section.	For consistency with current AstraZeneca processes.
Table 13 Appendix I1	Updates to olaparib toxicity management guidelines to include pre-transfusion laboratory investigations in the event of severe anaemia for studies with olaparib and durvalumab combination.	To provide further evaluation of the cause of severe anaemia in olaparib/durvalumab combination studies.

Appendix A1	Reporting guidance for serious and potential serious protocol breaches added.	To comply with updated regulatory requirements.
Appendix A6	Minor update to dissemination of study results.	To align with EU CTR requirements.
Appendix A7	Minor update to study oversight requirements.	For consistency with current AstraZeneca processes.
Appendix A7	The retention period for records and documents has been extended from 15 to 25 years after study completion.	To align with EU CTR requirements.
Appendix F1	Duration of abstinence updated from at least 1 month to at least 6 months post-olaparib.	Error corrected to provide consistency with the rest of the protocol.

Version 6.0, 11 June 2021

Applicable section number(s)/title	**Nature of revision**	**Rationale for change**
Section 1.2 Section 3.1 Section 3.2 Section 9.1 Section 9.3.1	Objectives updated with the primary comparisons now being Arm 3 vs Arm 1 in non-*tBRCAm* HRD positive population and non-*tBRCAm* ITT population. The comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population is now a key secondary endpoint.	HRD status has been established as a clinically important biomarker in first-line advanced ovarian cancer patients (data from the PAOLA-1 study). Thus, the primary endpoint allows for assessment of effect in the non-*tBRCAm* HRD positive population and the non-*tBRCAm* ITT population.
Section 1.2 Section 3.2	Removal of reference to olaparib from the secondary objective to determine the proportion of patients with pCR in patients undergoing IDS.	To clarify this endpoint as IDS occurs prior to receipt of olaparib/placebo within the study.
Section 1.2 Section 3.2	Clarification that secondary endpoints of OS, PFS2, TFST and TSST will be assessed in the populations described for PFS.	To clarify the populations to be assessed in these secondary endpoints.
Section 1.2 Section 9.5.1 Appendix A5	Clarification that IDMC review will include patients in the China cohort during regular data reviews and that the IDMC will review the PFS interim analysis results and will make	To clarify IDMC activities regarding China and the PFS interim analysis.

Applicable section number(s)/title	Nature of revision	Rationale for change
	recommendations to the sponsor on the future conduct of the study.	
Section 1.1.3.5 Section 1.2 Section 9.2 Section 9.4.1.2	Clarification of event numbers and data maturity required to trigger PFS analysis in the two populations of interest (ie, the non-*tBRCAm* HRD positive population and the non-*tBRCAm* ITT population).	Event numbers and data maturity required to trigger analyses have been updated to align with the primary endpoint comparing Arm 3 vs Arm 1 in the non-*tBRCAm* HRD positive population and the non-*tBRCAm* ITT population.
Section 1.2 Section 8.8.1.1 Section 9.4.1.2	Updates to subgroups by HRD status (HRD positive vs HRD negative vs HRD unknown), and PD-L1 expression (high vs low vs unknown).	Clarification of subgroups for analysis.
Section 2.1.1.3	Updated with details of current US durvalumab approvals.	Updates made to ensure text is up to date and accurate.
Section 2.3.1	Updates to the Javelin and IMagyn050 studies.	These new data provide a justification for the change to the primary analysis of the DUO-O study.
Section 2.3.2	Update on PAOLA-1 study results to provide justification for the change to the primary analysis for DUO-O.	These new data provide a justification for the change to the primary analysis of the DUO-O study.
Section 2.3.4 Section 2.3.5.	Updated to include results of the MEDIOLA study.	To provide updated data on triplet therapy.
Section 2.4 Section 4.5	Addition of cross reference to new Appendix L on guidance during the COVID-19 outbreak.	Cross reference to new information to comply with AstraZeneca requirements for clinical studies ongoing during the COVID-19 pandemic.
Section 1.2 Section 3.2 Section 3.4	Clarification that objectives apply to IMPs (durvalumab and olaparib).	To use consistent terminology throughout to describe the treatment arm.
Section 4.2	Section updated to clarify that DUO-O will provide a robust assessment of the benefit-risk of the combination of durvalumab and olaparib in both the non-*tBRCAm* HRD positive	To align with the updates made to the primary endpoint.

Applicable section number(s)/title	Nature of revision	Rationale for change
	population and the non-*tBRCAm* ITT population.	
Section 4.4	Clarification of end of study procedures to confirm that patients may enter a roll-over study, if such a study was available at the time of the final DCO and database closure.	To comply with standard wording for description of end of study procedures in AstraZeneca study protocols.
Section 6.5	Updated instructions provided for specific categories of restricted concomitant mediations.	Clarification based on latest available data.
Section 8.3.13	Updated risk language for durvalumab to include "pemphigoid (reflected as rash/dermatitis [pemphigoid]) and immune thrombocytopenia".	To align with updates to the Durvalumab IB Edition 16.
Section 8.8.1	Clarification that the Myriad myChoice HRD Plus assay will be used to determine HRD status in non *tBRCAm* patients. In the non-*tBRCAm* patients, HRD status will be defined according to GIS score. A patient with a GIS ≥ 42 is defined as HRD positive, GIS < 42 as HRD-negative or, when GIS testing fails, as HRD-unknown.	The patient's HRD status (either positive, negative or unknown) will be used for analysis purposes to determine the analysis. population for the primary endpoint of the study.
Section 1.2 Section 9.2	Update to include sample size determination calculations for the non-*tBRCAm* HRD positive population.	To provide sample size information for the new primary objective comparing Arm 3 vs Arm 1 in the non-*tBRCAm* HRD positive population.
Section 9.4.4	Update to methods for multiplicity control to account for changes in the alpha spending across endpoints/populations including the primary endpoint comparing Arm 3 vs Arm 1 in non-*tBRCAm* HRD positive population and the non-*tBRCAm* ITT population.	To align with revisions to the primary endpoint..
Section 9.4	Updated to clarify potential for changes to study analyses as a result of the COVID-19 pandemic.	To comply with AstraZeneca requirements for clinical studies ongoing during the COVID-19 pandemic.
Section 9.4.6	Update to analysis plans for China cohort to align with Global population (analyses will be conducted for the non-*tBRCAm* HRD positive	To align analyses for China cohort with the Global population.

Applicable section number(s)/title	Nature of revision	Rationale for change
	population and the non-*tBRCAm* ITT population).	
Section 1.2 Section 9.5	Inclusion of an interim PFS analysis when approximately 50% or more maturity has been observed for the comparisons of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and non-*tBRCAm* ITT population.	To include an interim analysis when sufficient maturity and information has occurred in the trial.
Appendix F	Minor update of contraceptive wording to confirm acceptable methods of birth control.	Changes made in response to Health Authority feedback on an update to the olaparib IB.
Appendix L	New appendix providing guidance on new patient enrollment and management for patients with confirmed or suspected COVID-19 who are being treated with olaparib/placebo and durvalumab/placebo.	New information to comply with AstraZeneca guidance for clinical studies ongoing during the COVID-19 pandemic.

Version 5.0, 01 February 2021

Applicable section number(s)/title	Nature of revision	Rationale for change
Title page	Addition of Sponsor details for sites in Japan: AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan	To comply with updated AstraZeneca clinical study template.
Table 2 Table 3 Table 4 (footnote b) Table 12	Clarification that the schedule for CT/MRI scans in the maintenance phase is set from the date of the end of chemotherapy assessment scan, rather than the visit date.	As the assessment scans may not be concurrent with the end of chemotherapy visit, it is important to clarify that the schedule for subsequent scans is set from the date of the end of chemotherapy scan, rather than the visit date.
Table 2 Table 3	Amended to show that optional plasma biomarker samples are collected at the start of maintenance (Visit 8) and then aligned with the imaging assessment visit (Q12W for 3 years then Q24W until disease progression)	To align Table 2 and Table 3 with the sampling requirements shown in Table 16.
Section 1.1.2.2 Section 1.2	Text updated to describe the inclusion of a China cohort of approximately	To support regulatory submissions in China.

Applicable section number(s)/title	Nature of revision	Rationale for change
Section 4.1 Section 9.3	120 non *tBRCAm* patients randomised (1:1:1) to study treatments from sites in China.	
Section 1.1.2.3 Section 8.1.1 (footnote to Table 12)	To confirm scan schedule for patients unable to complete the minimum number of cycles of chemotherapy	Clarification text.
Section 1.2 Section 9.4.1.2	Addition of patients with NED to the subgroup analysis by response status at the end of chemotherapy.	To account for patients who enter without disease at study entry.
Sections 2.1.1.1 and 6.1.2	Text updated to clarify which bevacizumab biosimilars will be permitted on the study and to permit individual patients to switch between Avastin® and a bevacizumab biosimilar if required. Since bevacizumab biosimilars start to replace bevacizumab as standard of care locally, text is updated to allow individual patients to be treated with either bevacizumab or a single one of the FDA-, EMA- or PMDA-approved biosimilars in this study (for China only, a CDE-approved biosimilar also may be used). Although it is preferable for an individual patient to remain on the originator product Avastin® or a single one of the FDA-, EMA- or PMDA-approved biosimilars for the duration of their treatment, under certain circumstances, individual patients will be allowed to switch	To clarify which bevacizumab biosimilars will be permitted on the study and to permit individual patients to switch between Avastin® and a bevacizumab biosimilar if required.
Section 1.2 Section 2.1.1.1 Section 4.1 Section 6.1.2	"Suitable biosimilar" has been changed to "an FDA-, EMA- or PMDA-approved biosimilar"	To clarify use of bevacizumab biosimilars
Section 1.2	Clarification that the single arm, open-label cohort is for *tBRCAm* patients only and that bevacizumab is optional.	Clarification of study design
Section 1.2	Duration of response reference has been removed from section regarding testing at a two-sided significance level of 5%.	Since duration of response endpoint will be summarised only.
Section 1.2.2.2 Section 4.1 Section 6.3.1 Section 9.4.1.2	Aligned the stratification wording in the PFS statistical model of by timing and outcome of cytoreductive surgery (no macroscopic residual disease after upfront primary surgery vs all others [macroscopic residual disease after upfront primary surgery or planned IDS]) with	Clarified text to align with stratification factors.

Applicable section number(s)/title	Nature of revision	Rationale for change
	the stratification factor wording applied in the randomisation scheme.	
Section 1.1.3	Clarification of post-discontinuation schedule of assessments	To improve clarity.
Section 1.1.3.4	Clarification that second progression can be based on clinical progression to align with study objectives	To improve clarity.
Table 4	Clarification that subsequent anticancer therapy, PFS2 and overall survival should be assessed Q12W relative to the date of first progression.	To improve clarity.
Section 1.2 Section 3.2 Section 9.4.1.1	To clarify that all analyses of ORR will be assessed in patients with evaluable disease at baseline.	To align wording and ensure use of a consistent population for ORR analyses.
Section 2.4	Addition of new text regarding the COVID-19 pandemic.	New information and to enable mitigation strategies to be implemented in clinical studies ongoing during the COVID-19 pandemic if required.
Section 3.4 Section 9.4.3	Clarified that patients with CR at end of chemotherapy are included in the analysis of the exploratory objectives of relapse free survival in patients who have no disease at the end of chemotherapy CT scan.	To account for patients who enter with disease at study entry and who are CR (without disease) at end of chemotherapy.
Section 4.5	New section describing study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis.	New information to enable mitigation strategies for clinical studies ongoing during the COVID-19 pandemic, if required, as per AstraZeneca requirements.
Section 5.1	Clarification on postmenopausal status according to age	To align with AstraZeneca CSP template definition of postmenopausal
Section 5.3.2, Appendix F	Minor update of contraceptive wording to require only one highly effective form of contraception.	To align with AstraZeneca CSP template definitions
Section 6.3.1	Update to clarify that the randomisation scheme used for the China cohort will be the	Added for clarification.

Applicable section number(s)/title	Nature of revision	Rationale for change
	same as the randomisation scheme used for the Global Population.	
Section 6.3.1.1	New section clarifying the procedures for handling incorrectly enrolled or randomised patients (cross references have been added to this section from Section 5, Section 5.2 and Section 7.3).	Added for clarification of procedures for patients randomised in error.
Section 6.5	Clarification that EGFR TKIs are a prohibited medicine for patients receiving olaparib/placebo as well as durvalumab/placebo. Removal of dexamethasone from table of restricted concomitant medications for olaparib/olaparib placebo.	To align with olaparib IB Edition 19. Dexamethasone is no longer considered a moderate CYP inhibitor and has been removed from the table of olaparib restricted concomitant medications.
Section 7.1	Pregnancy or intent to become pregnant added to list of reasons to discontinue study treatment	To align with olaparib IB Edition 19.
Section 8.1.2.1	Minor changes to EORTC-QLQ-OV28	To reflect latest scoring manual.
Section 8.2.5.3	Clarification of the actions to follow for confirmed AEs of pneumonitis	To align with the durvalumab TMG.
Section 8.3.13	Update to AESI section to change MDS/AML from important potential risk to important identified risk	To align with olaparib IB Edition 19
Section 8.4.6.2 Appendix I2	Link to Dosing Modification and Toxicity Management Guidelines (TMG) portal removed	TMG portal decommissioned end September 2020; TMG for durvalumab is provided to sites as an annex to the protocol
Section 9	Standard text added relating to the potential to generate additional summaries to determine the impact of COVID-19 on the study.	New information to comply with AstraZeneca requirements for clinical studies ongoing during the COVID-19 pandemic.
Section 9.1	Clarification that an exploratory analysis comparing Arm 3 and Arm 2 will also be undertaken, where required.	Addition of exploratory analysis comparing Arm 2 and Arm 3 to provide information on the contribution of components

Applicable section number(s)/title	Nature of revision	Rationale for change
Section 9.2 Section 9.4.1.2 Section 1.1.3.5 Section 1.2	Update to clarify that the PFS DCO will occur when events are achieved in both PFS comparisons. In addition, event numbers/maturity have been corrected to accurately account for the 15% drop out rate across the entire period of the study.	To clarify timings of PFS/OS analysis and maturity.
Section 9.2	Update to power calculations for the further analysis of OS to accurately account for the 15% drop out rate across the entire period of the study.	To clarify the OS power at the time of the further OS analysis.
Section 9.3.2	Clarified the reporting of safety data by treatment groups is as randomised, due to the administration of olaparib/placebo post-baseline in the maintenance phase. This will provide a summary of the underlying safety profile that patients should expect when initially prescribed to treatment. Removal of wording around the exploratory biomarker analysis sets as the definitions will be dependent on the emerging scientific and clinical data at the time of analysis. ADA analysis set defined to support reporting of ADA data.	To clarify reporting of safety data by treatment groups. Clarified analysis set definitions to be applied to support reporting.
Section 9.3	Text added to clarify that all populations and planned analyses described, relate to the Global population unless otherwise stated and to clarify that standalone safety and efficacy analyses of the China cohort will be performed.	To support regulatory submissions in China.
Section 9.4.1	Clarification that post-baseline RECIST assessments do not need to be evaluable, due to the planned on study surgery (lesion intervention) in IDS patients.	Updated to reflect planned on study interventions and patient population entered (ie, ovarian cancer patients with upfront primary surgery vs IDS).
Section 9.4.6	New section describing the inclusion of a China cohort of approximately 120 non-*tBRCAm* patients randomised (1:1:1) to study treatments from sites in China and the statistical analysis to be undertaken.	To support regulatory submissions in China.
Appendix K	New appendix describing changes related to mitigation of study disruptions due to cases of civil crisis, natural disaster, or public health crisis.	New information to comply with AstraZeneca requirements for clinical

Applicable section number(s)/title	Nature of revision	Rationale for change
		studies ongoing during the COVID-19 pandemic.
Other administrative changes	Minor formatting changes and correction of typographical errors including 'IWRS' changed to IRT system throughout and ir-AEs changed to im-AEs throughout.	To comply with updated AstraZeneca clinical study template.

Version 4.0, 08 June 2020

Applicable section number(s)/title	**Nature of revision**	**Rationale for change**
Sections 1 (Figure 1), 1.1.2.2, 1.2, 2.2, 4.1, and 6.1.1, and Tables 2 and 3.	Update of the duration of durvalumab dosing from 22 cycles (15 months) to up to 35 cycles (24 months).	Optimise the duration of treatment with durvalumab.
Section 1.1.2.2, 4.1 and 6.1.1.	Note added to clarify that patients who have already completed 22 cycles of durvalumab (*tBRCAm* positive cohort) or durvalumab/placebo (non-*tBRCAm* cohort) can restart durvalumab/ placebo to receive up to a total of 35 cycles, providing no more than 12 weeks have elapsed between the last durvalumab/placebo dose and treatment restart, and only if deemed appropriate by the Investigator.	Optimise the duration of treatment with durvalumab and provide clarity on the options for patients who have completed 22 cycles of durvalumab at the time of implementation of this amendment.
Sections 1 (Figure 1), 1.1.2.2, 1.1.3.5, 1.2, 4.1. 9.2, 9.4.1.2.	The number of patients in the non-*tBRCAm* cohort has been increased by 198 patients to approximately 1104 patients and the total number of patients to approximately 1254. The analysis for the primary objective will be performed when approximately 707/1104 PFS events have occurred across the 3 treatment arms (approximately 64% maturity). This will be approximately 52 months after the first patient has been randomised.	Following the results of the PAOLA-1 study, the assumptions of the performance of the control arm in DUO-O were revisited with expected median PFS (mPFS) updated from 16 months to 18 months. To maintain an improvement in mPFS to 24 months in treatment Arm 2, the assumed average treatment effect hazard ratio for PFS for Arm 2 (chemotherapy, bevacizumab and durvalumab arm) has been updated to 0.74, requiring an increase in sample size in the non-*tBRCAm* cohort by 198 patients.
Sections 1.1.3.6, 1.2, 4.1, 9.4.1.2.	The study will continue until 552/1104 OS events have occurred (50% maturity) across the 3 treatment arms of the non-*tBRCAm* cohort or 5 years following randomisation of the last non-*tBRCAm* patient, whichever occurs sooner.	For consistency with the changes made to patient sample size as a result of the revision of median expected PFS (see above).

Applicable section number(s)/title	Nature of revision	Rationale for change
Section 2.1.1.3 and 2.3.2.	Text updated to add the results obtained from the PAOLA-1 study.	To include the most recent relevant information from PAOLA-1.
Section 2.3.1	Text updated to add additional background information from the CheckMate 153 and PACIFIC studies.	To include the most recent relevant information
Sections 1, 1.1.2.2, 1.1.2.3 (Tables 2 and 3) and Figures 1 and 2.	Update to text to confirm the *tBRCAm* cohort of the study is now closed to recruitment.	The 150 patient allocation for the arm has been reached.
Section 1.1.2.1, 4.1 and 6.1.2.	Clarification on the start of bevacizumab after major surgery.	To clarify the use of bevacizumab after major surgery.
Sections 1.1.2.2, 1.1.2.3 (Tables 2 and 3), 2.2, 4.1 and 6.1.2.	Clarification that the duration of treatment with bevacizumab is for up to a total of 22 cycles (15 months).	To improve clarity.
Sections 1.1.2.3 (Tables 2 and 3), 1.2, 1.3 and 6.1.1.	Patients who have evidence of residual disease that remains stable (ie, no evidence of disease progression) after completing the maintenance phase of treatment may continue to receive blinded durvalumab or placebo treatment until PD if, in the opinion of the investigator, it is in patient's best interest.	Optimise the duration of treatment with durvalumab.
Sections 1.1.2.2, 1.1.2.3 (Tables 2 and 3), 1.1.3.6 (Table 4), 8.1.2.1, 8.1.2.2, 8.1.2.3, and 8.1.2.4.	Clarification that the ePRO questionnaires will be collected at 30 days AND 90 days post treatment discontinuation visit.	To ensure correct procedures are followed.
Sections 2.1.1.3 and 2.2.	Section updated to reflect current status of olaparib approvals based on SOLO1.	New information.
Section 2.1.1.3.	Section updated to reflect durvalumab approvals as of the data cut-off of 12 July 2019 in Edition 15 of the durvalumab Investigator's Brochure (dated 08 October 2019).	New information.
Section 2.3.5.	Section updated to reflect the Phase II expansion study NCT02484404 is ongoing.	To update text based on the current status of clinical trial.
Section 8.4.2.	Addition of new regulatory reporting requirements for SAEs.	New requirement for all clinical study protocols.
Section 1.2.	Text updated to reflect the actual date of first patient enrolled (January 2019) and the revised estimated date of last patient completed (Q3, 2025).	New information.

Applicable section number(s)/title	Nature of revision	Rationale for change
Sections 6.5 (Table 8) and 8.2.1.1.	Update to restricted medications.	Guidance on Non-vitamin K antagonist oral anticoagulants and alignment to revised olaparib protocol template.
Sections 1, 1.1.2.2, 1.3, and, Appendix H4.	Clarification of the definition of IDS patients so it clearly states that this includes patients who have undergone partial or unsuccessful primary surgery and are also planned to have IDS.	To make clearer the scope of the IDS patient population.
Section 5.1 (inclusion criterion 8).	Addition of timing for screening of creatinine clearance.	Clarity on the timing window for creatinine clearance.
Section 5.2 (exclusion criterion 8).	Clarification on HBV and HCV testing.	Allow additional time for HBV and HCV testing prior to randomisation.
Section 1.1.3.6 (Table 4).	Clearly define the patient population for CCI collection in follow up visits.	To clearly define the patient population for the collection of CCI during follow-up.
Section 1.1.3.6 (Table 4).	The visit window for safety follow-up Day 30 has been changed from ±3 days to ±7 days.	To allow alignment of the durvalumab 30 day safety visit with the established visit schedule.
Section 1	Confirmation that all patients MUST be eligible to start first-line platinum-based chemotherapy in combination with bevacizumab (previously “should”).	To improve clarity.
Section 1.1.3.6 (Table 4).	Update to the optional plasma biomarker collection.	Provide clarity on the timings of the optional plasma collection.
Sections 1.1.2.2, 1.1.2.3 (Tables 2 and 3), 5.1, 6, 6.3.1, and 7.3.	Updated wording to ensure that patients must be able to receive bevacizumab at Day 1 of Cycle 2 to be eligible for randomisation and any patient who is unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure.	To ensure the appropriate patients capable of receiving all the study treatments enter the study.
Appendix A8.	Updated wording regarding study and site closures.	New requirement for all clinical study protocols.

Applicable section number(s)/title	Nature of revision	Rationale for change
Sections 6.6 and 8.4.6.2 Appendix I.	Update guidance on durvalumab toxicity management.	Refinement of durvalumab toxicity management guidance due to an update in the Investigator's Brochure in October 2019.
Section 1.1.3.	Post-discontinuation, where the decision to discontinue treatment occurs after the window for the 30-day or 90-day safety visit, then the relevant safety visit should take place as soon as possible and within 7 days of the decision.	Refinement of post-discontinuation safety visits.
Sections 1.1.1, 5.1, 5.2, and 6.3.1.	Clarification that Inclusion/Exclusion criteria marked with an asterisk in Sections 5.1 and 5.2 MUST (previously "should") be met prior to the patient signing the Pre-screen ICF.	To ensure correct procedures are followed.
Section 1.1.2.2.	Clarification that Inclusion/Exclusion criteria MUST (previously "should") be met in order to receive Cycle 1 of chemotherapy.	To ensure correct procedures are followed.
Section 6 and 6.1.2.	Clarification for carboplatin administration, that in patients with low serum creatinine, the creatinine clearance MUST (previously "should") be estimated using a minimum value of 0.7 mg/dl (equivalent to 62 µmol/L).	To ensure correct procedures are followed.
Sections 1.1.2.3 and 6.1.1.	Updated to state that the maximum delay permitted for patients to receive olaparib/placebo is 9 weeks from the last day of chemotherapy infusion. It is also clarified that if a patient cannot start olaparib/placebo maintenance within 9 weeks from the last day of chemotherapy infusion, the patient should continue durvalumab/placebo and bevacizumab maintenance (these should also continue during the 3 to 9 week window after the last day of chemotherapy infusion, if the olaparib/placebo start criteria have not yet been met). In addition, the criteria required for the start of olaparib maintenance has been included and it is also clarified that prior to the start of maintenance treatment with olaparib/placebo, the patient MUST (previously "should") have her haematological and clinical chemistry parameters re-checked.	Clarification on the criteria required for patients to start olaparib and the maximum permitted delay for the start of olaparib dosing and the use of durvalumab/placebo and bevacizumab until olaparib/placebo starts.

Applicable section number(s)/title	Nature of revision	Rationale for change
Section 5.4.	Update to wording on retesting of blood screening samples.	Clarity that repeated blood tests are permitted within the 28-day screening period without rescreening.
Section 1.1.2.3.	Clarification that visits stay 3 weekly until 12 months of olaparib treatment have elapsed.	To improve clarity.
Sections 1.1.2.2, 1.1.2.3 (Table 2) and 5.	Clarification that eligibility MUST (previously "should") be confirmed prior to treatment allocation/randomisation at Cycle 2 Day 1.	To improve clarity.
Section 1.1.2.3 (Tables 2 and 3).	Table reformatted to separate out the start of maintenance, completion of bevacizumab and completion of durvalumab treatment.	To improve clarity.
Sections 1.1.2.3 (Tables 2 and 3) and Section 8.2.1 (Table 13).	Confirmation that on treatment, TSH should be measured every 6 weeks and aligned with the treatment cycle.	For clarity.
Section 8.2.1 (Table 13).	Clarification that TSH, glucose, LDH, amylase and lipase collection no longer required following the 90-day durvalumab safety visit.	For clarity
Sections 1.1.2.3 (Tables 2 and 3).	Footnote added to clarify that resourcing use at Visit 7 captures information from the time of Screening to the last dose of chemotherapy.	For clarity.
Sections 1.1.2.3 (Tables 2 and 3) and Section 8.8.1.2 (Table 16).	Confirmation that an optional plasma sample should also be collected at disease progression.	For clarity.
Section 6.4.	Clarification that study staff will make tablet counts at every visit (previously "regular intervals").	To ensure correct procedures are followed.
Throughout the document.	Correction of minor typographical errors including rewording, spelling and formatting.	To improve readability.

Version 3.0, 02 Oct 2019

Applicable section number(s)/title	Nature of revision	Rationale for change
Section 1.1 Section 1.3 Section 8.1.1	Refinement of the definition of IDS patients so it includes patients who have undergone partial or unsuccessful primary surgery and are planned to have IDS .	To clarify the scope of the IDS patient population.

Applicable section number(s)/title	**Nature of revision**	**Rationale for change**
Section 1.1.2.1; Section 6 Section 6.1.2	Recommendation that for patients from Asian sites, AUC5 is used for the carboplatin dose calculation.	To reduce the risk of haematological toxicity.
Section 1.1.2.2 Section 1.1.2.3 Table 2 footnotes Table 3 footnotes Section 8.1 Table 12 Appendix H	Updated: • Timing of surgery and chemotherapy restart in IDS • Timing of discontinuation visits from date of allocation/randomisation • CT/MRI timings from end of chemotherapy assessment visit • Timings of blood assessments in relation to visit dates while on study • Clarification that vital signs should be performed on the day of treatment	Clarify timings of IDS and chemotherapy restart after surgery To clarify inconsistencies within earlier versions of the protocol. Allow sites to have flexibility in the collection of assessments and to reduce burden on patient
Section 1.1.2.2 Table 2 Table 3 Section 5	Updated so that for a patient to be allocated/randomised, they must meet all inclusion criteria except for criteria 7, 8 and 9 and meet none of the exclusion criteria except for criteria 24.	Clarification on patient populations eligible for study.
Section 5.2	Correction of exclusion criteria 23 to Patients with Nephrotic Syndrome	Correction of error in exclusion criteria as there is no Grade 4 proteinuria.
Section 6 Section 6.1.2	• Addition of mandatory lowest creatinine level to use when calculating the Creatinine Clearance using the Cockcroft-Gault formula to be used in the Calvert Formula for the calculation on carboplatin dose • Addition of maximum carboplatin dosing recommendations according to AUC • Inclusion of the The Calvert Formula for carboplatin dose calculation	To reduce the risk of haematological toxicity.
Section 6	Clarification of infusions time of carboplatin	Give sites flexibility to follow local guidelines for infusion times.

Applicable section number(s)/title	Nature of revision	Rationale for change
Section 6.1.1 Section 6.3.2 Table 6	Updated durvalumab infusion procedures: • use of transparent coloured sleeve as an alternative to an opaque sleeve will be allowed • alternative methods of securing an opaque/amber sleeve to the infusion bag will be acceptable (use of tamper evident tape is not mandatory)	Simplification of the durvalumab blinding process.
Section 6.1.2 Section 6.6 Section 7.1 Section 8.4.5.3	Protocol amended to permit the use of desensitisation protocols in the event of carboplatin hypersensitivity or the use of alternative platinum-based SoC regimens in the event of paclitaxel or carboplatin hypersensitivity reactions that require discontinuation of the agent, where SOC chemotherapy is locally sourced (substitution with cisplatin in the event of carboplatin hypersensitivity reaction; substitution with another taxane (nab-paclitaxel or docetaxel) or anthracycline (Pegylated Liposomal Doxorubicin) in the event of paclitaxel hypersensitivity reaction.	To enable patients to continue on study with a doublet platinum-based chemotherapy in the event of a hypersensitivity reaction to carboplatin or paclitaxel, and so ensure optimal SOC treatment in this patient group.
Section 6.3.2	Guidance on unblinding of IMP and patient continuation within the study	Inclusion of guidance on IMP unblinding
Section 6.3.2	Removal of ADA samples from the requirement to be unblinded	Update of analytical procedures removing the requirement for unblinding
Section 6.6 Section 8.4.5.3	The addition of recommended actions in the event of: • neutropenia on the day before or on the day of chemotherapy • febrile neutropenia during chemotherapy	To reduce the risk of repeated events of febrile neutropenia during chemotherapy.

Applicable section number(s)/title	**Nature of revision**	**Rationale for change**
Section 6.6 Section 8.4.5.2 Section 8.4.5.3 Appendix I2	Protocol amended to include the following regarding treatment interruptions: • Clarify that 12 weeks is the maximum duration permitted for a durvalumab delay before durvalumab must be discontinued; • Guidance that in the event of a chemotherapy delay due to toxicity, and if further chemotherapy is planned, then bevacizumab and durvalumab should also be held; • Guidance that 12 weeks is the maximum duration permitted for a bevacizumab hold before bevacizumab must be discontinued (unless otherwise agreed with the Study Physician).	Clarification on dose modifications allowed in cases of toxicity.
Section 8.1.2.1-4 Table 2 Table 3 Table 4	Indicated that PROs are collected at the start of maintenance and Q6W thereafter until treatment discontinuation, at treatment discontinuation, 30-days post discontinuation and Q12W thereafter up to 36 months post visit 2 or DCO.	To clarify the administration schedule and that maintenance phase triggers a new schedule.
Section 8.1.2.5 Table 2 footnotes Table 3 footnotes	Amended so that : • in the event of ePRO device failure, paper questionnaires may be used when completion of the questionnaire is scheduled during a site visit. • ePRO may be assigned up to 3 days before Cycle1 Day 1, although ideally at C1D1	Facilatate the capture of PRO data.
Section 8.2.4.1	ECG timings clarified for consistency with corresponding tables	Resolve inconsistencies within protocol.
Section 8.4.5.2	Inclusion of the durvalumab toxicity management guidelines (TMGs) as an Annex to the Protocol.	For operational ease and to ensure investigators have the most up to date version of the durvalumab TMGs with the protocol.
Section: 8.5.1, Table 2 footnotes Table 4 footnotes	Reduction in number of patients for PK/ADA analysis	PK samples from China are no longer required.

Applicable section number(s)/title	**Nature of revision**	**Rationale for change**
Section 8.7.1. Table 2 footnotes Table 3 footnotes	Amended so gBRCA sample may be collected at Cycle 2 or at later visits	Gives sites flexibility to collect sample.
Table 1 footnotes Appendix D	Amended so the Genomics Initative sample may be collected at Screening or at later visits	Gives sites flexibility to collect sample.
Appendix I2	Durvalumab TMG will also be provided as an Annex to the Protocol	For operational ease and to ensure investigators have the most up to date version of the durvalumab TMGs with the protocol.
Section 8.3.8 Appendix E	Details regarding reporting PHL cases have been added.	To be consistent with new requirements.
Other changes	Minor corrections and clarifications.	To improve readability of the CSP and to correct errors noted in Version 2.0

Version 2.0, 18 September 2018

Applicable section number(s)/title	Nature of revision	Rationale for change
Global change	The Clinical Study Protocol (CSP) was extensively revised prior to any patients being recruited, to restrict recruitment to the placebo-controlled double-blinded arms of the study to patients who do not carry *BRCA* mutations. A separate cohort was created to ensure all patients who do carry a *BRCA* mutation receive optimal treatment (ie, oral olaparib as a maintenance therapy once they complete their chemotherapy phase).	The rationale for this change is based on data from the SOLO1 study, which has demonstrated a statistically significant and clinically meaningful improvement in PFS for olaparib compared with placebo for patients who carry a *BRCA* mutation.
1.1.1 Screening schedule of activities	Results of central tumour *BRCA* (*tBRCA*) test now required before patients can be enrolled to start investigational treatment. All patients can receive 1 cycle of platinum-based chemotherapy while central *tBRCA* testing is ongoing (study run-in period). Additional optional tumour sample for research purposes also added.	The *tBRCA* mutation (*tBRCAm*) status must be known prior to start of investigational treatment to ensure all patients who carry a *tBRCAm* receive optimal treatment with olaparib as maintenance treatment.
1.1.2 On-study schedule of activities	As a result of the global change, the schedule of activities tables have been updated to provide clarification of study run-in period. For all patients, durvalumab treatment will now start on Day 1 of Cycle 2. Patients will be allocated to a treatment cohort (either non-*tBRCAm* or *tBRCAm*) on Day 1 of Cycle 2 and non-*tBRCAm* patients will be randomised to 1 of 3 treatment arms. Table footnotes updated to reflect global change to the CSP.	Changes have been made to deal with operational challenges with obtaining central *BRCA* result ahead of randomisation
	Additional blood sample added to test germline *BRCA* mutation (*gBRCAm*) status of all patients, retrospectively.	Additional sample required to confirm how many *tBRCAm* patients also have a *gBRCAm* status and how many non-*tBRCAm* patients do not have a *gBRCAm* status
1.1.3 Post-discontinuation follow-up	Clarification of follow-up period.	To reflect global change.

Applicable section number(s)/title	Nature of revision	Rationale for change
1.2 Synopsis	Updated throughout to reflect global change to the study based on enrolment *tBRCAm* status. Objectives updated to clarify that the primary objective only applies to the non-*tBRCAm* cohort.	Study is only sized for the non-*tBRCAm* cohort.
1.3 Schema	Updated throughout to reflect global change to the study based on enrolment *tBRCAm* status.	For consistency with global change.
2.1 Background and rationale	Updated to reflect changes to standard of care (SoC) since Version 1 of the CSP.	Updated to reflect current clinical practice.
2.2 Study rationale	Updated throughout to reflect global change to the study based on enrolment *tBRCAm* status.	For consistency with global change.
2.3.2 The combination of a PARP inhibitor and an anti-angiogenic agent	Updated to add data on 2 clinical studies with this combination.	To provide rationale for optional use of bevacizumab in *tBRCAm* patients
3 Objectives and endpoints	Updated throughout to reflect global change to the study based on enrolment dependent on *tBRCAm* status. Objectives updated to clarify that the primary objective only applies to the non-*tBRCAm* cohort.	Study is only sized for the non-*tBRCAm* cohort.
4 Study design	Updated throughout to reflect global change to the study based on enrolment dependent on *tBRCAm* status.	For consistency with global change.
5 Study population	Updated to require confirmation of *tBRCAm* status prior by the end of the run-in period. Exclusion criteria related to olaparib treatment have been moved from this section as these only need to be met at the start of the maintenance phase, not at study enrolment.	For consistency with global change.
5.4 Screen failures	Clarification that patients without a valid central *tBRCA* test result are screen failures.	For consistency with global change.
6 Study treatments	Updated to reflect use of study run-in period and to confirm that durvalumab will be blinded in the open-label cohort, for operational consistency.	For consistency with global change.
6.3.1 Procedures for enrolment and allocation/randomisation	Updated throughout to reflect global change to the study based on enrolment dependent on *tBRCAm* status and to add details on the study run-in period.	For consistency with global change.
8.4.5.2 Management of Durvalumab toxicities	Details have been removed and replaced with a link to an online description of the durvalumab toxicity management guidelines (TMGs).	For operational ease and to ensure investigators always access the most up to date version of the durvalumab TMGs.

Applicable section number(s)/title	Nature of revision	Rationale for change
8.5 Pharmacokinetics	Updated to confirm samples are only required in non-*tBRCAm* patients and to allow more flexibility in pre-dose sampling.	For consistency with global change.
8.8.1 Sample requirements	Updated throughout to reflect global change to the study based on enrolment *tBRCAm* status. Additional optional tumour sample for research purposes also added.	For consistency with global change.
	Additional clarification wording added for CCI sample requirements. Footnotes in Tables 2, 3 and 4 updated in accordance with changes made in this section.	Clarification of sample requirements.
9 Statistical consideration	Updated throughout to describe analyses to be performed to reflect global change to the study based on enrolment *tBRCAm* status.	For consistency with global change.
Appendix A	Updated to describe site closure details	To align with global template text.
Appendix I2 Durvalumab TMGs	Details have been removed and replaced with a link to an online description of the durvalumab TMGs.	For operational ease and to ensure investigators always access the most up to date version of the durvalumab TMGs.
Other changes	Minor corrections and clarifications.	To improve readability of the CSP and to correct errors noted in Version 1.0

Initial creation: 1.0, 13 April 2018

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 Standard - Bioethics and in compliance with prevailing laws and regulations.

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Abbreviations: GOG Gynecologic Oncology Group.

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Dosing Modification and Toxicity Management Guidelines for Immune–Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy)

1. PROTOCOL SUMMARY

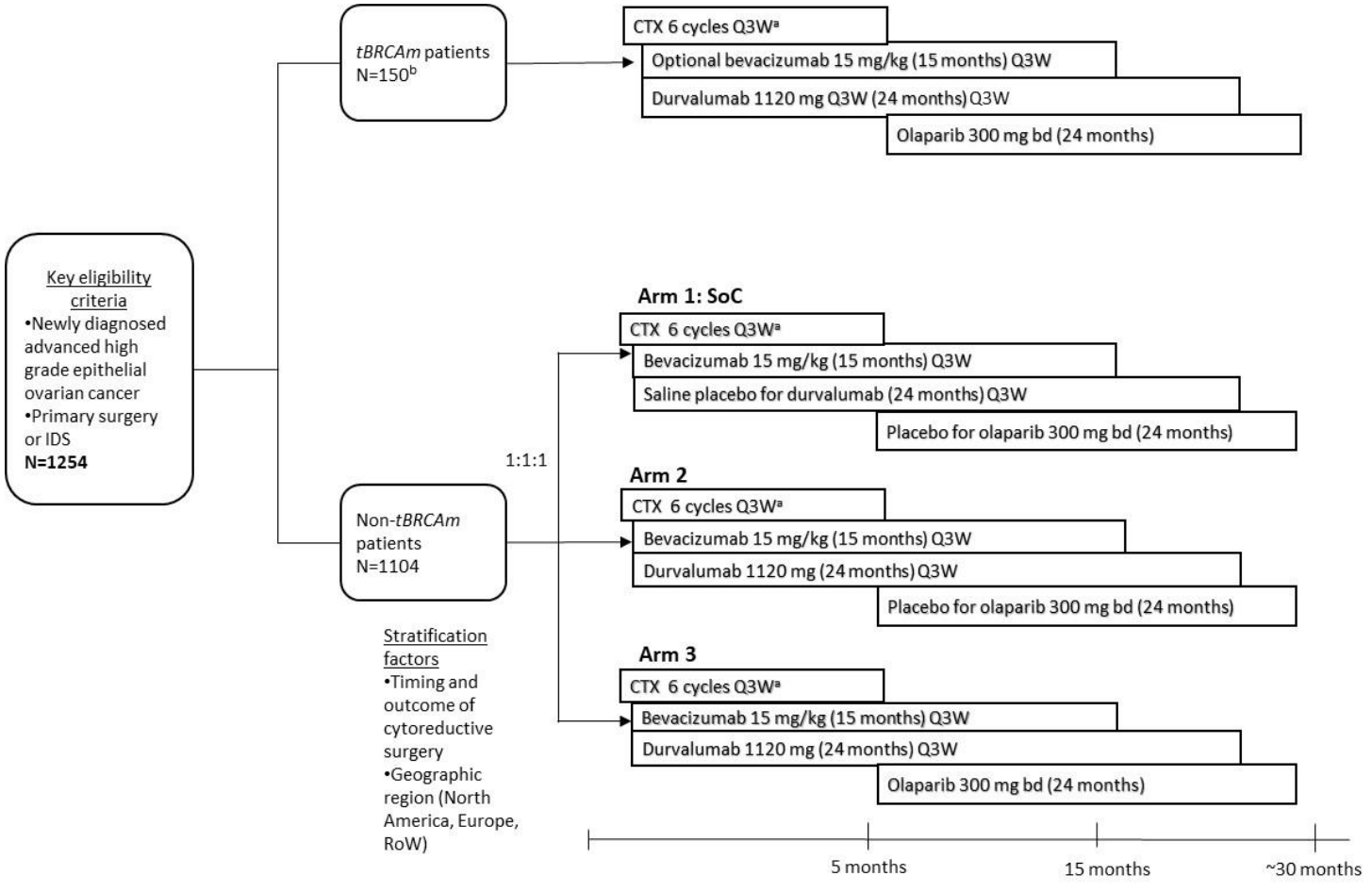
The Phase III DUO-O study will assess the efficacy and safety of durvalumab and olaparib when added to standard of care (SoC) in patients with newly diagnosed advanced ovarian cancer. The study consists of 2 independent cohorts which are defined by the breast cancer sensitivity gene (*BRCA*) mutated (*BRCAm*) status, based on testing of tumour tissue (ie, *tBRCAm* status) of the patients.

- **Non-*tBRCAm* cohort**: Patients who do not have a *tBRCA* mutation will be allocated to the non-*tBRCAm* cohort and be further randomised to 1 of 3 double-blind, placebo-controlled treatment arms to receive SoC plus investigational treatments as described in Section 1.2.
- ***tBRCAm* cohort**: Patients who have a *tBRCA* mutation will be allocated to a single arm cohort to assess the safety and potential additional clinical benefit of durvalumab added to SoC and olaparib.
  Note: The *tBRCAm* cohort was closed to recruitment as of November 2019 as the 150 patient allocation was reached.

Target Patient Population: patients with newly diagnosed advanced (FIGO Stage III-IV) high grade epithelial ovarian, fallopian or primary peritoneal cancer who have either undergone upfront primary surgery or plan to start chemotherapy followed by interval debulking surgery (IDS), with the planned IDS population including patients who have undergone partial or unsuccessful primary surgery and are also planned to have IDS. All patients must be eligible to start first line platinum-based chemotherapy in combination with bevacizumab.

A study schematic is provided in Figure 1:

Figure 1 Study D081RC00001: Study schematic



Abbreviations: bd = twice daily; *BRCA* = Breast cancer susceptibility gene; CTX = Chemotherapy; IDS = Interval debulking surgery; RoW = Rest of World; *tBRCAm* = Tumour *BRCA* mutated; SoC = Standard of care; Q3W = Every 3 weeks.

Note: For bevacizumab, 15 months of treatment is equivalent to 22 cycles and for durvalumab, 24 months of treatment is equivalent to 35 cycles.

[a] Chemotherapy should be administered for a minimum of 4 cycles and a maximum of 6 cycles.

[b] This cohort is now closed to recruitment.

1.1 Schedule of Activities (SoA)

In this study, all patients undergo a common screening procedure (Table 1). However, there are separate schedules of activities (SoAs) for patients, depending on whether they have had upfront primary cytoreductive surgery prior to study entry (Table 2), OR whether they will be considered for interval debulking surgery (IDS) during the chemotherapy phase of the study (this includes patients who have undergone partial or unsuccessful primary surgery and are also planned to have IDS) (Table 3). The post-discontinuation SoA is the same, regardless of timing of surgery (Table 4).

All patients regardless of *tBRCAm* status have common:

- Inclusion/exclusion criteria
- Lifestyle restrictions
- Concomitant therapy guidance
- Dose modification guidance
- Treatment discontinuation
- CT and MRI scan assessments
- Patient reported outcomes
- Safety assessments
- Collection of genetic and biomarker samples

Depending on the patient's *tBRCAm* status there are differences in:

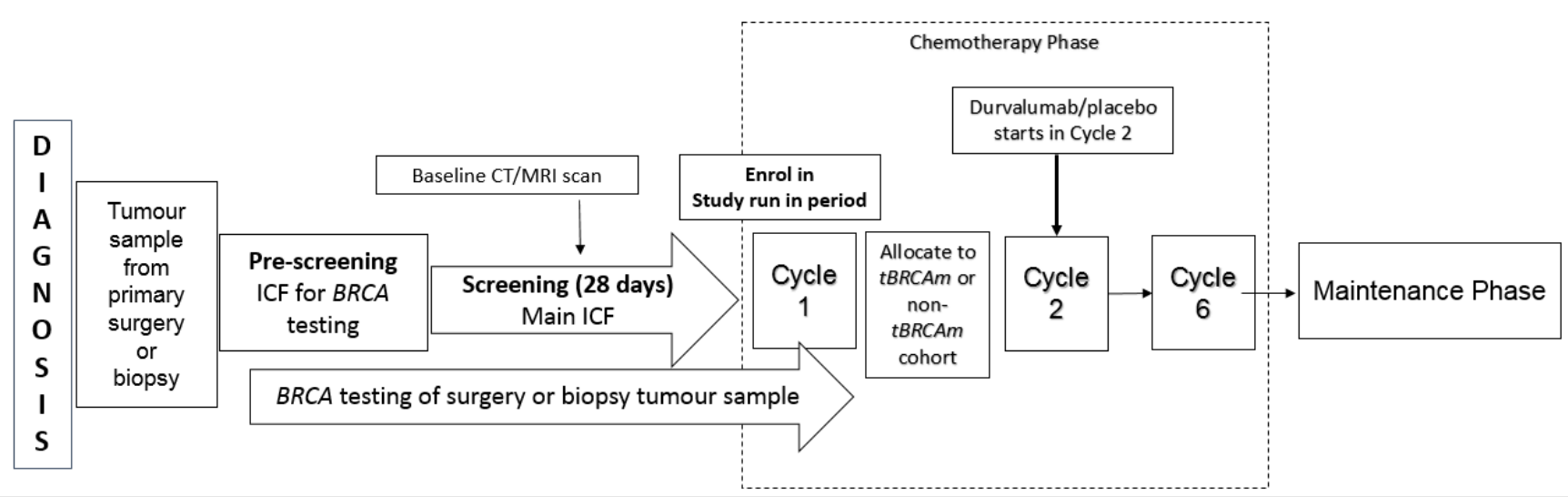
- Allocation to non-*tBRCAm* or *tBRCAm* cohort
- Investigational treatments administered
- Pharmacokinetic sample collection

1.1.1 Screening Schedule of Activities

A flowchart for the screening process is provided in Figure 2.

All patients must sign the (Pre-screen) informed consent form (ICF). The Pre-screen ICF provides consent for provision of tumour tissue sample and for prospective *tBRCAm* status analysis. Also the study inclusion and exclusion criteria marked with an asterisk in Sections 5.1 and 5.2 MUST be met prior to the patient signing the Pre-screen ICF. If a patient is assigned to primary upfront cytoreductive surgery, a sample from the primary cytoreductive surgery should be provided, or, if not available, a biopsy tumour sample previously obtained at diagnosis may be provided.

Figure 2 Screening flowchart



Abbreviations: *BRCA* = Breast cancer susceptibility gene; CT = Computed tomography; ICF = Informed consent form; MRI = Magnetic resonance imaging.
Note: The *tBRCAm* cohort was closed to recruitment as of November 2019 as the 150 patient allocation was reached.

Determination of breast cancer susceptibility gene (*BRCA)* status: Subject to local regulations, all patients must provide a formalin-fixed paraffin embedded (FFPE) tumour specimen sample for tissue-based *BRCA1/2* gene testing using the clinical trial assay (CTA) known as the myChoice HRD Plus assay. Prospective screening will be implemented at Myriad Genetics, who will provide the myChoice HRD Plus test, a next generation sequencing (NGS) based assay, that will be performed as a single laboratory testing service using DNA extracted from FFPE tissue.

Provided the patient has signed the Pre-screen ICF, and a suitable tumour sample has been provided, the screening process can continue. If all the screening criteria are met, the patient can enter the run-in period (see Section 1.1.2.1).

The following assessments and procedures should be performed prior to Day 1 of Cycle 1 as per Table 1.

Table 1 Screening schedule (all patients)

	Pre-screening (all patients)	**Main Screening (all patients)**
Day	**Diagnosis to Day 0**	**Day -28 to Day 0**
Patient signs pre-screen consent for *BRCA* testing of tumour tissue	X	X
Patient signs main consent form (including optional consent for Genomics Initiative sample)		X[a]
FFPE tumour sample from the primary cytoreductive surgery of ovarian cancer, primary peritoneal cancer or fallopian-tube cancer for patients that have had primary surgery or, if not available, a biopsy tumour sample previously obtained at diagnosis may be provided for patients planned to have IDS for central *BRCA* testing of tumour tissue (see Section 8.8.1.1).	X (prospective)	
Optional tumour sample for academic research[b]	X	
Assignment of E-code	X	
Demographics	X	X
Medical and surgical history	X	X
Inclusion/exclusion criteria	X[c]	X
ECOG Performance Status (0-1)		X
Physical examination		X
Vital signs, body weight, height (Includes BP, pulse and temperature)		X
ECG		X
Haematology/clinical chemistry[d]		X

Table 1 Screening schedule (all patients)

	Pre-screening (all patients)	Main Screening (all patients)
Day	**Diagnosis to Day 0**	**Day -28 to Day 0**
CCI		
Thyroid function tests (TSH, T3 [reflex], T4 [reflex])[e]		X
Screen for HBV, HCV and HIV[f]		X
Urinalysis		X
Pregnancy test for women of childbearing potential[g]		X
Disease specific marker (CA125)		X
Tumour Assessment (CT or MRI according to modified RECIST v1.1)[h]		Within 28 days of the start of Cycle 1 of platinum based chemotherapy
SAEs from time of signing the main consent		X
Concomitant medications		X
Genomics initiative sample (optional)		X[a]

Abbreviations: AE = Adverse Event; BP = Blood pressure; *BRCA* = Breast cancer susceptibility gene; CA125 = Cancer antigen 125; CCI; CT = Computed tomography; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = Formalin fixed, paraffin embedded; HBV = Hepatitis B virus; HCV = Hepatitis C virus; IDS = Interval debulking surgery; MRI = Magnetic resonance imaging; RECIST = Response evaluation criteria in solid tumours; SAE = serious adverse event; T3 = Triiodothyronine; T4 = Throxine; TSH = Thyroid stimulating hormone.

[a] Consent for provision of a blood sample for the Genomics Initiative programme is optional for all patients; consent for this sample will be provided as part of the main consent form. Patients who cannot be allocated/randomised because of delayed *tBRCA* test results may still be able to provide samples for the Genomics Initiative programme. Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or for receipt of non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection. If the Genomics Initiative sample cannot be collected during screening period, it can be collected anytime after Cycle 1 Day 1.

[b] If available, an additional tumor sample from the primary cytoreductive surgery or biopsy obtained at diagnosis should be provided for academic research, subject to local regulations (see Section 8.8.1.3).

[c] Selected criteria only (those marked with an asterisk [*] in Section 5.1 and Section 5.2).

[d] Coagulation test is required at screening only for patients receiving anticoagulant therapy or when clinically indicated. For a list of all required laboratory tests please refer to Section 8.2.1.

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

[f] Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc], followed by a negative hepatitis B virus DNA test and absence of HBsAg) are eligible provided these tests are confirmed as negative prior to Cycle 2 Day 1. Patients positive for HCV antibody are eligible only if the polymerase chain reaction is confirmed as negative for HCV RNA prior to Cycle 2 Day 1.

[g] Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test before treatment on Day 1.

[h] Baseline RECIST assessments will be performed using CT or MRI scans of chest, abdomen and pelvis. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of the individual patient. The baseline scans should be performed within the 28 days prior to or on Day 1 of Cycle 1 of chemotherapy and ideally as close as possible before the start of chemotherapy. For patients who have undergone primary cytoreductive surgery, the baseline scan must be performed following primary cytoreductive surgery.

1.1.2 On-study Schedule of Activities

There are separate SoAs for patients, depending on whether they have had primary cytoreductive surgery prior to study entry (Table 2), OR whether they will be considered for IDS during the chemotherapy phase of the study (Table 3). There are also minor differences in the SoAs depending on whether patients are in the *tBRCAm* cohort or non-*tBRCAm* cohort (these differences are shown in the SoA tables and table footnotes). All patients must have a baseline RECIST scan conducted within 28 days prior to or on Day 1 of Cycle 1 of platinum based chemotherapy (before the start of chemotherapy). For the statistical analysis, this scan will be regarded as the baseline scan for all patients.

The treatment period will consist of the chemotherapy treatment phase, followed by the maintenance phase and a follow-up period. The treatment options for patients are dependent on their *tBRCA* mutation status (Figure 1).

1.1.2.1 Study run-in period

If a patient has completed screening and meets all eligibility criteria, she will then receive Cycle 1 of platinum-based chemotherapy (carboplatin area under the plasma concentration-time curve [AUC] 5 or 6 and paclitaxel 175mg/m^2 Q3W), while the determination of central *tBRCAm* status is ongoing. This is the study 'run-in' period.

- Patients who have had primary upfront surgery must receive Cycle 1 of chemotherapy within a maximum of 8 weeks of upfront primary surgery; it is recommended that Cycle 1 starts a minimum 3 weeks after the surgery, however, Cycle 1 can also start as soon as their surgical wound is fully healed.
- Cycle 1 of chemotherapy may also include bevacizumab, according to local practice. In line with the European Summary of Product Characteristics (SmPC) and the US prescribing information it is recommended that bevacizumab should not be administered within the first 28 days following major surgery. If bevacizumab is not routinely used by the site, then bevacizumab should be started at Cycle 2. Once a patient's *tBRCAm* status is known, based on central *tBRCA* testing (and prior to Day 1 of Cycle 2), patients will be allocated to either the *tBRCAm* cohort or the non-*tBRCAm* cohort (provided the patient continues to meet the study inclusion and exclusion criteria listed in Sections 5.1 and 5.2).
- Should the central *tBRCA* assay fail to determine the presence or absence of a deleterious/suspected deleterious mutation prior to the start of Cycle 2, due to technical failure or delay in testing the patient cannot continue on the study, even if she fulfils all

other eligibility criteria: these patients will be withdrawn and receive SoC treatment outside the study.

Note: For patients from Asian sites, it is recommended to use AUC5 for the carboplatin dose calculation.

1.1.2.2 Start of investigational study treatment and timing of surgery

Patients should have completed the first cycle of chemotherapy as part of the study run-in period as described in Section 1.1.2.1. Each patient MUST meet all of the inclusion criteria and none of the exclusion criteria for this study in order to receive Cycle 1 of chemotherapy. Eligibility must be confirmed prior to allocation/randomisation at Cycle 2 Day 1 when patients must meet all inclusion criteria except for criteria 7, 8 and 9 and meet none of the exclusion criteria except for criteria 24. In addition, non-*tBRCAm* patients must be able to receive bevacizumab at Day 1 of Cycle 2 to be randomised and continue on study (any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure). Prior to Day 1 of Cycle 2 of platinum-based chemotherapy, patients with a valid central *tBRCAm* test result will be treated as follows:

Non-*tBRCAm* cohort

Approximately 1104 patients with no deleterious/suspected deleterious mutations in *BRCA1*, and *BRCA2* will be randomised 1:1:1 to receive a further 5 cycles of platinum-based chemotherapy (in combination with bevacizumab followed by bevacizumab maintenance for up to a total of 22 cycles [15 months] of treatment). A China cohort, of approximately 120 patients randomised (1:1:1) from sites in China will also be recruited. If necessary, the China cohort will continue recruiting patients after recruitment to the Global population closes at approximately 1104 patients.

Investigational treatments will be given as specified below:

(i) Arm 1 (SoC): Patients in Arm 1 will receive saline IV Q3W as a placebo for durvalumab from Day 1 of Cycle 2 for up to a total of 35 cycles (24 months) of treatment. At the end of chemotherapy, patients will also receive placebo tablets, matched to olaparib for up to a total of 24 months.

(ii) Arm 2: Patients in Arm 2 will receive durvalumab 1120 mg Q3W from Day 1 of Cycle 2 for up to a total of 35 cycles (24 months) of treatment. At the end of chemotherapy, patients will also receive placebo tablets, matched to olaparib for up to a total of 24 months.

(iii) Arm 3: Patients in Arm 3 will receive durvalumab 1120 mg Q3W from Day 1 of Cycle 2 for a total of up to 35 cycles (24 months) of treatment. At the end of chemotherapy, patients will also receive olaparib tablets, 300 mg twice daily (bd) for up to a total of 24 months.

NOTE: Patients who have already completed 22 cycles of durvalumab/placebo are permitted to restart durvalumab/placebo in order to receive up to a total of 35 cycles, providing no more than 12 weeks have elapsed between the last durvalumab/placebo dose and treatment restart, and only if deemed appropriate by the Investigator.

The randomisation scheme will be stratified according to:

- Timing and outcome of cytoreductive surgery: no macroscopic residual disease after upfront primary surgery vs all others (macroscopic residual disease after upfront primary surgery OR planned IDS)
- Geographic region: North America vs Europe vs RoW.

***tBRCAm* cohort**

Note: The *tBRCAm* cohort was closed to recruitment as of November 2019 as the 150 patient allocation was reached.

Approximately 150 patients with deleterious/suspected deleterious mutations in *BRCA1* or *BRCA2* as identified by central *tBRCA* testing will be allocated to a single arm cohort. Once olaparib becomes available as part of clinical practice for first-line maintenance treatment of ovarian cancer in a country, then this cohort may be closed to further recruitment within that country. Patients will receive a further 5 cycles of platinum-based chemotherapy (and optional bevacizumab for up to a total of 22 cycles (15 months) of treatment according to standard local practice). Investigational treatments will be given as specified below:

(i) Durvalumab 1120 mg Q3W from Day 1 of Cycle 2 for up to a total of 35 cycles (24 months). At the end of chemotherapy, patients will also receive olaparib tablets, 300 mg twice daily (bd) for up to a total of 24 months.

NOTE: Patients who have already completed 22 cycles of durvalumab are permitted to restart durvalumab in order to receive up to a total of 35 cycles, providing no more than 12 weeks have elapsed between the last durvalumab dose and treatment restart, and only if deemed appropriate by the Investigator.

For all patients, chemotherapy will be given for 6 cycles in total (a minimum of 4 cycles is required to continue to the maintenance phase).

Timing of surgery

All patients should have had, or be candidates for cytoreductive surgery, which was conducted as upfront primary surgery following diagnosis or as IDS, to be conducted during the study after initiation of platinum-based neoadjuvant chemotherapy.

Patients who have had upfront primary surgery

From Cycle 2 onwards, patients who have undergone primary surgery will be treated as follows:

- All non-*tBRCAm* patients will receive chemotherapy plus bevacizumab (this is mandatory in non-*tBRCAm* patients and MUST be administered if not given in Cycle 1- any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure) and durvalumab/saline in the chemotherapy phase, followed by durvalumab/saline and olaparib/placebo in the maintenance phase, according to the randomised treatment arm.
- All *tBRCAm* patients will receive chemotherapy and durvalumab in the chemotherapy phase, followed by durvalumab and olaparib in the maintenance phase. Bevacizumab is optional according to local practice.

The study plan for these patients is shown in Table 2.

Patients planned for IDS

From Cycle 2 onwards, patients planned for IDS (includes patients who have undergone partial or unsuccessful primary surgery and are also planned to have IDS) will be treated as for patients who have undergone primary surgery (includes the mandatory administration of bevacizumab at Cycle 2 – any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure); however, the following differences apply:

- Surgery should then ideally take place within 14 days (and no later than 28 days) after Day 21 of Cycle 3. All patients receiving bevacizumab, MUST have bevacizumab treatment omitted from the cycle prior to IDS.
- Following recovery from IDS, further cycles of chemotherapy will be given (resulting in a minimum of 4 cycles up to a maximum of 6 cycles in total). Following IDS, chemotherapy should be restarted ideally within 4 weeks but no later than 8 weeks from the date of IDS.
- If chemotherapy is started within 4 weeks after surgery then bevacizumab (if receiving) must be omitted from the first cycle post IDS.
- Patients having IDS surgery will have a Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) assessment scan pre-surgery.

Please note:

- In certain circumstances patients may have an additional 4th cycle of chemotherapy prior to surgery if deemed clinically appropriate, this should be discussed with the AstraZeneca Study Physician first and bevacizumab treatment must be omitted from this treatment cycle.

The study plan for these patients is shown in Table 3.

1.1.2.3 On-study assessments

The visit schedule is based on 3 week (21-day) cycles. Patients will attend the clinic on Day 1, Day 22, and every 3 weeks (Q3W) thereafter for as long as they continue to receive intravenous (IV) treatment. Once all IV treatments have stopped, the visit schedule is every 6 weeks (Q6W; relative to date of allocation/randomisation) unless the patient has received less than 12 months of olaparib, when the visit schedule remains every 3 weeks.

Start of maintenance treatment

Prior to the start of maintenance treatment with olaparib/placebo (a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion), the patient MUST have her haematological and clinical chemistry parameters re-checked. The patient MUST meet the following requirements within 3 days prior to dosing in order to receive olaparib/placebo:

- Patients must have normal organ and bone marrow function as defined below:
  - Haemoglobin (Hb) ≥10.0 g/dL
  - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
  - Platelet count ≥100 x 10^9/L
  - Total bilirubin ≤1.5 × institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed to participate in the study, in consultation with their physician.
  - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤2.5 × institutional ULN unless liver metastases are present in which case they must be ≤5 × ULN.

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

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

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

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

Once all IV treatments are discontinued, patients will attend the required follow up visits and attend the clinic Q6W (relative to date of allocation/randomisation), until discontinuation of olaparib/placebo treatment OR their disease progresses (RECIST 1.1 progression). If discontinuation of IV infusions is earlier than planned duration, clinic visits should be every 3 weeks (Q3W) until patients have been on olaparib for 12 months, at which point, the interval between study visits can increase to Q6W.

If patients discontinue olaparib/placebo, but are continuing with IV infusions, then clinic visits should be every 3 weeks (Q3W) until treatment discontinuation or disease progression.

If patients have discontinued all study treatments and have not had disease progression (RECIST 1.1 progression), patients will attend the clinic Q12W for up to 3 years and every 24 weeks (Q24W) thereafter (relative to end of chemotherapy assessment RECIST visit), until disease progression. The assessments will be performed at time points specified in the study schedules. Any patient unable to complete the minimum 4 cycles of platinum-based chemotherapy required to continue to the maintenance phase should have their 'End of Chemotherapy' imaging assessment performed at Week 15 (or as soon as possible after Week 15 in the case of IDS patients) relative to randomisation; subsequent scans will then be performed every 12 weeks ± 2 weeks for the first 3 years (156 weeks) and then every 24 weeks ± 2 weeks relative to this End of Chemotherapy assessment (see Table 12).

Patients will continue with study treatments until objective radiological disease progression by RECIST version 1.1 or until they have completed the stated durations of treatment. Note: any patient receiving combination treatment who has an AE that contraindicates further dosing and is considered to be attributable to 1 of the study treatments but not the others, may continue on study and continue to receive the therapies that have not been considered to be the

cause of the AE (a discontinuation of 1 drug should not affect the dosing schedule of the other drugs) and continue following the on-treatment SoA.

Once patients have been discontinued from all study treatments, other treatment options will be at the discretion of the investigator. Within this study patients are not permitted to switch over to the other arms from the one to which they were randomised.

Table 2 On-treatment study plan for patients who have had prior primary cytoreductive surgery

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'						Maintenance Phase			Treatment discontin-uation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**	**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**	**10**	**13**	**16+**	**Q3W**	**Q3W**	**Q6W**		
Screening assessments complete	X see Table 1											1.1.1
tBRCAm status by central test result[a]		X[a]										8.8.1.1
Allocation to either *tBRCAm* or non-*tBRCAm* cohort[a]		X[a]										6.3.1
Allocation / randomisation (of non-*tBRCAm* patient) to study treatment [b]			X									6.3.1
Blood sample for retrospective germline *BRCA* testing[c]			X									8.7.1

Table 2 On-treatment study plan for patients who have had prior primary cytoreductive surgery

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'						Maintenance Phase			Treatment discontin-uation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**	**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**	**10**	**13**	**16+**	**Q3W**	**Q3W**	**Q6W**		
Administration of study treatments												
Durvalumab or saline (placebo) by IV infusion			X[d]	X	X	X	X	X[d]	X[d]			6.1
Bevacizumab		X[e]	X	X	X	X	X	X[e]				6.1.2
Platinum-based chemotherapy		X[f]	X	X	X	X	X[f]					6.1.2
Olaparib or placebo (tablets PO, twice daily)								X[g] (twice daily treatment for up to 24 months)				6.1
Safety assessments												
Concomitant medication		X	X	X	X	X	X	X	X	X	X	6.5
Adverse event review (AEs and SAEs)		X	X	X	X	X	X	X	X	X	X	8.3
Blood samples for haematology and clinical chemistry[h]		X	X	X	X	X	X	X	X	X	X	8.2.1

Table 2 On-treatment study plan for patients who have had prior primary cytoreductive surgery

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'						Maintenance Phase			Treatment discontin-uation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**	**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**	**10**	**13**	**16+**	**Q3W**	**Q3W**	**Q6W**		
Thyroid function[i]		X (prior to Cycle 2 and every 6 weeks thereafter)						X	X	X	X	8.2.1
Urinalysis		X	X	X	X	X	X	X	X	X	X	8.2.1
ECG		As clinically indicated										8.2.4
Vital signs, BP and body temperature[j]		X	X	X	X	X	X	X	X	X	X	8.2.2 and 8.2.3
ADA (durvalumab; non-*tBRCAm* patients only)[k]			X		X		X	X (third cycle of maintenance phase)				8.5.1.1
Women of childbearing potential ONLY: Pregnancy test (serum or urine)[l]		X	X	X	X	X	X	X	X	X	X	8.2.5.1

Table 2 On-treatment study plan for patients who have had prior primary cytoreductive surgery

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'						Maintenance Phase			Treatment discontin-uation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**	**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**	**10**	**13**	**16+**	**Q3W**	**Q3W**	**Q6W**		
Efficacy assessments												
CT/MRI[m]	within 28 days of Cycle 1							End of chemotherapy assessment scan and then every 12 weeks[m]	every 12 weeks for the first 3 years and then every 24 weeks until disease progression[m]			8.1.1
CA125		X	X	X	X	X	X	X[n]	X[n]	X[n]	X	8.2.1.3
Other assessments												
Blood samples for PK (durvalumab; non-*tBRCAm* patients only)[o]			X		X		X	X (third cycle of maintenance phase)				8.5.1
Blood samples for PK (olaparib; non-*tBRCAm* patients only)[o]								X (third cycle of maintenance phase)				8.5.1
CCI [redacted]												8.8.1.2

Table 2 On-treatment study plan for patients who have had prior primary cytoreductive surgery

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'					Maintenance Phase			Treatment discontin-uation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**	**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**	**10**	**13**	**16+**	**Q3W**	**Q3W**	**Q6W**		
Tumour sample[r]											X (optional at progression)	8.8.1.3
CCI												8.8.1.4
												8.8.1.4
Resource Use							X[u]	X[n]	X[n]	X[n]	X	8.9
EORTC-QLQ-C30 (by e-device)[t]		X	Q6W (±3d) until discontinuation of all study treatments or start of maintenance phase					At start of maintenance (+3 days) and Q6W (±3d) until discontinuation of all study treatments			X	8.1.2.1
EORTC-QLQ-OV28 (by e-device)[t]		X	Q6W (±3d) until discontinuation of all study treatments or start of maintenance phase					At start of maintenance (+3 days) and Q6W (±3d) until discontinuation of all study treatments			X	8.1.2.1

Table 2 On-treatment study plan for patients who have had prior primary cytoreductive surgery

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'						Maintenance Phase			Treatment discontin-uation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**	**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**	**10**	**13**	**16+**	**Q3W**	**Q3W**	**Q6W**		
EQ5D-5L (by e-device)[t]		X	Q6W (±3d) until discontinuation of all study treatments or start of maintenance phase					At start of maintenance (+3 days) and Q6W (±3d) until discontinuation of all study treatments			X	8.1.2.4
PRO-CTCAE (by e-device)[t]		X	Weekly (±3 days) for the first 12 weeks from Visit 2, and Q6W (±3d) thereafter until discontinuation of all study treatments or start of maintenance phase					At start of maintenance (+3 days) and weekly (±3 days) for the first 6 weeks and Q6W (±3d) thereafter until discontinuation of all study treatments			X	8.1.2.2
PGIS (by e-device)[t]		X	Q6W (±3d) until discontinuation of all study treatments or start of maintenance phase					At start of maintenance (+3 days) and Q6W (±3d) until discontinuation of all study treatments			X	8.1.2.3

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; BP = Blood pressure *BRCA* = Breast cancer susceptibility gene; CA125 = Cancer Antigen 125; CCI [redacted]; CR = Complete response; CT = Computed tomography; ECG = Electrocardiogram; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28; ePRO = electronic Patient reported outcome; EQ-5D-5L = EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index; IV = Intravenous; MRI = Magnetic resonance imaging; PGIS = Patient Global Impression of Severity; PK = Pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; *tBRCAm* = Presence of a deleterious or suspected deleterious mutation in tumour breast cancer sensitivity gene; Q3W = Every 3 weeks; Q6W = Every 6 weeks; Q12W = Every 12 weeks; RNA = Ribonucleic acid

Note: The visit schedule is based on 3-week (21-day) cycles. Patients will attend the clinic on Day 1, Day 22, and every 3 weeks (Q3W) thereafter for as long as they continue to receive intravenous (IV) treatment. Once all IV treatments have stopped, the visit schedule is every 6 weeks (Q6W; relative to date of allocation/randomisation). If discontinuation of IV infusions is earlier than planned duration, clinic visits should be every 3 weeks (Q3W) until patients have been on olaparib/placebo for 12 months, at which point, the visit schedule can increase to Q6W.

[a] All patients will receive Cycle 1 of platinum-based chemotherapy provided they have supplied a tumour sample for central *tBRCAm* testing and meet all of the study selection criteria (see Sections 5.1 and 5.2) with the exception of the criterion related to *tBRCAm* status. Central evaluation of *tBRCAm* status should occur prior to Day 1 of Cycle 2. Once a successful *tBRCAm* test result is available, patients will be allocated to either the *tBRCAm* cohort or the non-*tBRCAm* cohort. If there is notification of a failed central *tBRCA* test, a second tumour sample suitable for Myriad testing can be submitted for another *tBRCA* test, if a suitable time period is available before results are required for allocation/randomisation at Cycle 2. If the test results have not been received before Cycle 2 then the patient cannot be allocated and should continue standard of care outside the study. Patients in the non-*tBRCAm* cohort will be further randomised to 1 of 3 treatment arms; patients in the *tBRCAm* cohort will receive treatment with durvalumab and olaparib. Note: The *tBRCAm* cohort was closed to recruitment as of November 2019 as the 150 patient allocation was reached.

[b] Provided the patient continues to meet all the study selection criteria except for inclusion criteria 7, 8 and 9; and exclusion criteria 24. In addition, non-*tBRCAm* patients must be able to receive bevacizumab at Day 1 of Cycle 2 to be randomised and continue on study (any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure).

[c] The *gBRCA* sample may be collected at Cycle 2 or at later visits.

[d] All *tBRCAm* patients will receive durvalumab; all non-*tBRCAm* patients will be randomised to receive either durvalumab or IV saline (placebo). Treatment will start from Day 1 of Cycle 2 and continued as a maintenance treatment to complete up to 35 cycles (24 months) of total treatment. Patients who have evidence of macroscopic residual disease that remains stable (ie, no evidence of disease progression) after completing the maintenance phase of treatment may continue to receive blinded durvalumab or placebo treatment (or unblinded durvalumab for patients in the *tBRCAm* cohort) until PD if, in the opinion of the investigator, it is in patient's best interest.

[e] Bevacizumab is optional in Cycle 1 for all patients. Bevacizumab remains optional throughout the study for *tBRCAm* patients. For non-*tBRCAm* patients, bevacizumab is mandatory from Day 1 of Cycle 2 to complete up to a total of 22 cycles (15 months).

[f] Chemotherapy must start a maximum of 8 weeks after primary cytoreductive surgery and should be continued for 6 cycles. Patients must have received a minimum of 4 cycles of the platinum regimen for the patient to be able to continue into the maintenance treatment phase.

[g] All *tBRCAm* patients will receive olaparib; non-*tBRCAm* patients will be randomised to receive either olaparib or placebo. Treatment will be self-administered and will commence after chemotherapy is completed (a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion). Patients will receive 24 months of olaparib (or placebo) maintenance treatment but may also continue to receive study treatment after this if they have evidence of macroscopic residual disease that remains stable and in the opinion of the investigator, it is in the patient's best interest. Following discontinuation of IV infusions, clinic visits are scheduled every 6 weeks (Q6W). If discontinuation of IV infusions is earlier than planned duration, clinic visits should be every 3 weeks (Q3W) until patients have been on olaparib for 12 months, at which point, the visit schedule can increase to Q6W.

[h] Regular blood lab assessments can be done 1-3 days before infusions. Not all laboratory tests are required to be conducted at each visit; please see Table 13 for more details

[i] If TSH is measured within 14 days prior to Day 1 of Cycle 2 (first durvalumab/saline infusion day), it does not need to be repeated at Day 1, Cycle 2. 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. On treatment, TSH should be measured every 6 weeks and aligned with the treatment cycle; if there is an abnormality, follow-up should also occur at the next scheduled visit.

[j] BP, pulse and temperature should be measured on the day of treatment and prior to the start of the infusion. In addition, for the first infusion of durvalumab/saline (placebo), BP and pulse will be collected from patients before, during, and after the infusion – see Section 8.2.3 for timings.

[k] ADA samples will be taken in up to 100 patients who are scheduled for PK sampling (see footnote o). Samples will be taken pre-infusion at Cycle 2, Cycle 4 and Cycle 6; pre-infusion at the third cycle of the maintenance phase (usually Cycle 9). A sample should be taken at any time during the 90-day safety follow-up visit (see Table 4).

[l] Pregnancy tests on serum or urine samples will be performed for women of childbearing potential within 28 days prior to Day 1 of Cycle 1, on Day 1 of Cycle 1 prior to commencing treatment, at the time points shown in Table 2 during study treatment and at the 30 day follow up visit. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

[m] RECIST 1.1 assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at baseline. Follow-up CT/MRI of the chest, abdomen and pelvis. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. Baseline assessments should be performed after the cytoreductive surgery, no more than 28 days before Day 1 of Cycle 1, and ideally should be performed as close as possible to the start of chemotherapy. The end of chemotherapy assessment scan will be performed within 3 weeks ±1 week after the last dose of chemotherapy and before the start of the maintenance treatment. During the maintenance phase assessments will be performed every 12 weeks ±2 weeks for the first 3 years (156 weeks) and then every 24 weeks ± 2 weeks, relative to the date of end of chemotherapy assessment scan, until objective disease progression as defined by modified RECIST 1.1. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. The schedule for post-progression assessments is provided in Table 4.

[n] Follow-up assessments will be performed every 12 weeks ±2 weeks for the first 3 years (156 weeks) then every 24 weeks ± 2 weeks, relative to the date of Visit 8 (start of maintenance phase/end of chemotherapy visit), until objective disease progression. The schedule for post-progression assessments is provided in Table 4.

[o] PK sampling for durvalumab and olaparib will be carried in up to 100 randomised non-*tBRCAm* patients, who have received all scheduled treatments (durvalumab + bevacizumab + SoC chemotherapy during the chemotherapy phase and 2 cycles of bevacizumab + durvalumab +olaparib in the maintenance phase) at those sites that are able to take PK assessment samples. PK sampling will not be performed in *tBRCAm* patients. Approximately 33 evaluable non-*tBRCAm* patients per arm will be required. Durvalumab PK sampling will be carried out at the following timepoints: up to 1 hour after the end of infusion for Cycle 2; pre-dose for Cycle 4; pre-dose and up to 1 hour after the end of infusion in Cycle 6; pre-dose and at up to 1 hour after the end of infusion for the third cycle of the maintenance phase and at any time during the 90 day follow-up visit (ie, the visit which occurs 90 days post discontinuation of durvalumab). PK sampling for determination of olaparib in plasma will be performed on Day 1 of the third cycle of the maintenance phase (ie after 2 cycles of bevacizumab + durvalumab +olaparib) pre-dose and post dose at: 0.5 hour to 1 hour; 1 hour to 3 hours; 3 hours to 6 hours; 6 hours to 12 hours. All olaparib PK samples should be taken at least 1 hour apart; see the schedules in Section 8.5.1.

[p] CCI

CCI

CCI

CCI

[q] CCI

CCI

[r] A tumour sample should be taken at progression (optional).

[s] CCI

CCI CCI

CCI

[t] ePRO LogPads will be assigned to patients before or on Day 1 of Cycle 1 of chemotherapy; baseline ePROs should be completed by patients prior to dosing on Day 1 of Cycle 1 and before any study procedures are conducted (exception may be made for blood draws), when they are still in the clinic, to ensure that the device is correctly set up and working properly; however it is permitted for the baseline ePROs to be completed prior to C1D1 as long as treatment is given within 3 days of ePRO completion. If a site wishes to perform both blood draws and ePRO before C1D1, then ideally the ePRO should be performed prior to the blood draws. In the event of device failure at a site visit, paper questionnaires may be used at that visit. Subsequent ePROs should be completed by the patients at home or at the site if site visit coincides with ePRO visit, but prior to any study procedures including treatment, with the exception of blood draws. PRO-CTCAE will be administered only in the languages where a linguistically validated version exists. Questionnaires will be collected at the times shown in the study plan, at the discontinuation of study treatment visit (discontinuation of all study treatments), 30 days and 90 days post treatment discontinuation visit and every 12 weeks (±14 days) from 30 day post treatment discontinuation visit (discontinuation of all study treatments) thereafter up to a maximum of 36 months post Visit 2 or primary data cut-off date [DCO], whichever comes first).

[u] Resourcing use at Visit 7 captures information from the time of Screening to the last dose of chemotherapy.

Table 3 On-treatment study plan for patients who require interval debulking surgery (IDS)

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'							Maintenance Phase			Treatment discon-tinuation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**IDS post Cycle 3**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**		**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**		**10**	**13**	**16**	**Q3W**	**Q3W**	**Q6W**		
Screening assessments complete	X see Table 1												1.1.1
tBRCAm status by central test result[a]		X[a]											8.8.1.1
Allocation to either *tBRCAm* or non-*tBRCAm* cohort[a]		X[a]											6.3.1
Allocation/randomisation (of non-*tBRCAm* patients) to study treatment [b]			X										6.3.1
Blood sample for retrospective germline *BRCA* testing[c]			X										8.7.1

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Visit	**1**	**2**	**3**	**4**	**IDS post Cycle 3**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**		**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**		**10**	**13**	**16**	**Q3W**	**Q3W**	**Q6W**		
Administration of study treatments													
Durvalumab or saline (placebo) as IV infusion			X	X		X	X	X	X[d]	X[d]			6.1
Bevacizumab		X[e]	X[e]			X[e]	X	X	X[e]				6.1.2
Platinum-based chemotherapy		X[f]	X	X		X	X	X[f]					6.1.2
Olaparib or placebo (tablets po, twice daily)									X[g] (twice daily treatment for up to 24 months)				6.1
Safety assessments													
Concomitant medication		X	X	X		X	X	X	X	X	X	X	6.5
Adverse event review (AEs and SAEs)		X	X	X		X	X	X	X	X	X	X	8.3
Blood samples for haematology and clinical chemistry[h]		X	X	X		X	X	X	X	X	X	X	8.2.1

Table 3 On-treatment study plan for patients who require interval debulking surgery (IDS)

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'							Maintenance Phase			Treatment discon-tinuation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**IDS post Cycle 3**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**		**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**		**10**	**13**	**16**	**Q3W**	**Q3W**	**Q6W**		
Thyroid function[i]		X (prior to Cycle 2 and every 6 weeks thereafter)							X	X	X	X	8.2.1
Urinalysis		X	X	X		X	X	X	X	X	X	X	8.2.1
ECG		As clinically indicated											8.2.4
Vital signs, BP and body temperature[j]		X	X	X		X	X	X	X	X	X	X	8.2.2 and 8.2.3

Table 3 On-treatment study plan for patients who require interval debulking surgery (IDS)

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'							Maintenance Phase			Treatment discon-tinuation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**IDS post Cycle 3**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**		**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**		**10**	**13**	**16**	**Q3W**	**Q3W**	**Q6W**		
Women of childbearing potential ONLY: Pregnancy test (serum or urine)[k]		X	X	X		X	X	X	X	X	X	X	8.2.5.1
Efficacy assessments													
CT/MRI[l]	within 28 days of Cycle 1			X					End of chemotherapy assessment scan and then every 12 weeks[l]	every 12 weeks for the first 3 years and then every 24 weeks until disease progression[l]			8.1.1
CA125		X	X	X		X	X	X	X[m]	X[m]	X[m]	X	8.2.1.3
Other assessments													
CCI													8.8.1.2

Table 3 On-treatment study plan for patients who require interval debulking surgery (IDS)

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'							Maintenance Phase			Treatment discon-tinuation visit (when ALL study treatments have been discontinued)	For details see section
Visit	1	2	3	4	IDS post Cycle 3	5	6	7	Visit 8 onwards: start of maintenance phase and end of chemo assessment	Visit 25 onwards (once bevacizumab treatment completed)	Visit 38 onwards (once durvalumab treatment completed)		
Treatment cycle		1 (run-in)	2	3		4	5	6	Cycle 7 onwards	Cycle 24 onwards	Cycle 37 onwards		
Study week ± 3 day visit window	-28 to Day 0	1	4	7		10	13	16	Q3W	Q3W	Q6W		
Tumour sample[p]					X							X (optional at progression)	8.8.1.1 and 8.8.1.3
CCI													8.8.1.4
													8.8.1.4
Resource Use								X[s]	X[m]	X[m]	X[m]	X	8.9
EORTC-QLQ-C30 (by e-device)[r]		X	Q6W (±3d) until discontinuation of all study treatments or start of maintenance phase						At start of maintenance (+3 days) and Q6W (±3d) until discontinuation of all study treatments			X	8.1.2.1
EORTC-QLQ-OV28 (by e-device)[r]		X	Q6W (±3d) until discontinuation of all study treatments or start of maintenance phase						At start of maintenance (+3 days) and Q6W (±3d) until discontinuation of all study treatments			X	8.1.2.1

Table 3 On-treatment study plan for patients who require interval debulking surgery (IDS)

	Screen-ing Phase	Chemotherapy phase (Cycle 1 to Cycle 6) including 'Study run-in'							Maintenance Phase			Treatment discon-tinuation visit (when ALL study treatments have been discontinued)	For details see section
Visit	**1**	**2**	**3**	**4**	**IDS post Cycle 3**	**5**	**6**	**7**	**Visit 8 onwards: start of maintenance phase and end of chemo assessment**	**Visit 25 onwards (once bevacizumab treatment completed)**	**Visit 38 onwards (once durvalumab treatment completed)**		
Treatment cycle		**1 (run-in)**	**2**	**3**		**4**	**5**	**6**	**Cycle 7 onwards**	**Cycle 24 onwards**	**Cycle 37 onwards**		
Study week ± 3 day visit window	**-28 to Day 0**	**1**	**4**	**7**		**10**	**13**	**16**	**Q3W**	**Q3W**	**Q6W**		
EQ-5D-5L (by e-device)[r]		X	Q6W (±3d) until discontinuation of all study treatments or start of maintenance phase						At start of maintenance (+3 days) and Q6W (±3d) until discontinuation of all study treatments			X	8.1.2.4
PRO-CTCAE (by e-device)[r]		X	Weekly (±3 days) for the first 12 weeks from Visit 2, and Q6W (±3d) thereafter until discontinuation of all study treatments or start of maintenance phase						At start of maintenance (+3 days) and weekly (±3 days) for the first 6 weeks and Q6W (±3d) thereafter until discontinuation of all study treatments			X	8.1.2.2
PGIS (by e-device)[r]		X	Q6W (±3d) until discontinuation of all study treatments or start of maintenance phase						At start of maintenance (+3 days) and Q6W (±3d) until discontinuation of all study treatments			X	8.1.2.3

Abbreviations: AE = Adverse event; BP = Blood pressure; *BRCA* = Breast cancer susceptibility gene; CA125 = Cancer antigen 125; [redacted]; CT = computed tomography; ECG = electrocardiogram; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28; ePRO = electronic Patient-Reported Outcomes; EQ-5D-5L = EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index; IDS = Interval debulking surgery; IV = Intravenous; po = per os (oral administration); MRI = Magnetic resonance imaging; Q3W = Every 3 weeks; Q6W = Every 6 weeks; PGIS = Patient global impression of severity; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RECIST = Response Evaluation Criteria In Solid Tumours; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = Thyroid stimulating hormone; RNA = Ribonucleic acid.

Note: The visit schedule is based on 3 week (21-day) cycles. Patients will attend the clinic on Day 1, Day 22, and every 3 weeks (Q3W) thereafter for as long as they continue to receive intravenous (IV) treatment. Once all IV treatments have stopped, the visit schedule is every 6 weeks (Q6W; relative to date of allocation/randomisation). If discontinuation of IV infusions is earlier than planned duration, clinic visits should be every 3 weeks (Q3W) until patients have been on olaparib/placebo for 12 months, at which point, the visit schedule can increase to Q6W.

[a] All patients will receive Cycle 1 of platinum-based chemotherapy provided they have supplied a tumour sample for central *tBRCAm* testing and meet all of the study selection criteria (see Sections 5.1 and 5.2) with the exception of the criterion related to *tBRCAm* status. Central evaluation of *tBRCAm* status should occur prior to Day 1 of Cycle 2. Once a successful *tBRCAm* test result is available, patients will be allocated to either the *tBRCAm* cohort or the non-*tBRCAm* cohort. If there is notification of a failed central *tBRCA* test, a second tumour sample suitable for Myriad testing can be submitted for another *tBRCA* test, if a suitable time period is available before results are required for allocation/randomisation at Cycle 2. If the test results have not been received before Cycle 2 then the patient cannot be allocated and should continue standard of care outside the study. Patients in the non-*tBRCAm* cohort will be further randomised to 1 of 3 treatment arms; patients in the *tBRCAm* cohort will receive treatment with durvalumab and olaparib. Note: The *tBRCAm* cohort was closed to recruitment as of November 2019 as the 150 patient allocation was reached.

[b] Provided the patient continues to meet all of the study selection criteria except for inclusion criteria 7, 8 and 9; and exclusion criteria 24. In addition, non-*tBRCAm* patients must be able to receive bevacizumab at Day 1 of Cycle 2 to be randomised and continue on study (any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure).

[c] The *gBRCA* sample may be collected at Cycle 2 or at later visits.

[d] All *tBRCAm* patients will receive durvalumab; all non-*tBRCAm* patients will be randomised to receive either durvalumab or IV saline (placebo). Treatment will start from Day 1 of Cycle 2 and continued as a maintenance treatment to complete up to 35 cycles (24 months) of total treatment. Patients who have evidence of macroscopic residual disease that remains stable (ie, no evidence of disease progression) after completing the maintenance phase of treatment may continue to receive blinded durvalumab or placebo treatment (or unblinded durvalumab for patients in the *tBRCAm* cohort) until PD if, in the opinion of the investigator, it is in patient's best interest.

[e] Bevacizumab is optional in Cycle 1 for all patients. Bevacizumab remains optional throughout the study for *tBRCAm* patients according to local practice. For non-*tBRCAm* patients, bevacizumab is mandatory from Day 1 of Cycle 2 to complete up to a total of 22 cycles (15 months). Bevacizumab must be omitted from Cycle 3 (cycle immediately before IDS). If chemotherapy is started within 4 weeks after surgery then bevacizumab must be omitted from the first cycle post IDS.

[f] Patients who are not considered candidates for primary cytoreductive surgery at the time of the diagnosis or have undergone unsuccessful primary surgery and planned for IDS, should have 3 cycles of neoadjuvant chemotherapy prior to IDS. Depending on their allocation to either the *tBRCAm* or non-*tBRCAm* cohort (and subsequent allocation/randomisation), patients will also receive bevacizumab and durvalumab/saline during Cycle 2 and durvalumab/saline during Cycle 3. IDS should ideally take place within 14 days (and no later than 28 days) after Day 21 of Cycle 3. Following IDS, a further 3 cycles of chemotherapy will be given and should be restarted ideally within 4 weeks but no later than 8 weeks from the date of IDS. Patients must have received a minimum of 4 cycles of the platinum regimen for the patient to be able to continue their maintenance treatment. Bevacizumab must be omitted from Cycle 3 (cycle immediately before IDS). If chemotherapy is started within 4 weeks after surgery then bevacizumab must be omitted from the first cycle post IDS.

[g] All *tBRCAm* patients will receive olaparib; all non-*tBRCAm* patients will be randomised to receive either olaparib or placebo. Treatment will be self-administered and will commence after chemotherapy is completed (a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion). Patients will receive 24 months of olaparib or placebo maintenance treatment but may also continue to receive study treatment after this if they have evidence of macroscopic residual disease that remains stable and in the opinion of the investigator, it is in the patient's best interest. Following discontinuation of IV infusions, clinic visits are scheduled Q6W. If discontinuation of IV infusions is earlier than planned duration, clinic visits should be every 3 weeks (Q3W) until patients have been on olaparib for 12 months, at which point, the visit schedule can increase to Q6W.

[h] Regular blood lab assessments can be done 1-3 days before infusions. Not all laboratory tests are required to be conducted at each visit; please see Table 13 for more details.

[i] If TSH is measured within 14 days prior to Day 1, Cycle 2 (first durvalumab/saline infusion day), it does not need to be repeated at Day 1, Cycle 2. 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. On treatment, TSH should be measured every 6 weeks and aligned with the treatment cycle; if there is an abnormality, follow-up should also occur at the next scheduled visit.

[j] BP, pulse and temperature should be measured on the day of treatment and prior to the start of the infusion. In addition, for the first infusion of durvalumab/saline (placebo), BP and pulse will be collected from patients before, during, and after the infusion – see Section 8.2.3 for timings.

[k] Pregnancy tests on serum or urine samples will be performed for women of childbearing potential within 28 days prior to Day 1 of Cycle 1, on Day 1 of Cycle 1, at the time points shown in Table 3 during study treatment and at the 30 day follow up visit. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

[l] RECIST 1.1 assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at baseline. Follow-up CT/MRI of the chest, abdomen and pelvis. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before Day 1 of Cycle 1 and ideally should be performed as close as possible to the start of chemotherapy. Patients having IDS surgery will have a RECIST 1.1 assessment scan prior to IDS (any time after the last dose of the neoadjuvant chemotherapy but prior to IDS). The end of chemotherapy assessment scan will be performed within 3 weeks ±1 week after the last dose of chemotherapy and before the start of the maintenance treatment. During the maintenance phase assessments will be performed every 12 weeks ±2 weeks for the first 3 years (156 weeks) and then every 24 weeks ± 2 weeks, relative to the date of end of chemotherapy assessment scan, until objective disease progression as defined by modified RECIST 1.1. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. The schedule for post-progression assessments is provided in Table 4.

[m] Follow-up assessments will be performed every 12 weeks ± 2 weeks for the first 3 years (156 weeks) then every 24 weeks ±2 weeks, relative to the date of Visit 8 (start of maintenance phase/end of chemotherapy visit), until objective disease progression. The schedule for post-progression assessments is provided in Table 4.

[n] CCI

[o] CCI

[p] A tumour sample is required at IDS surgery (mandatory). A tumour sample should be taken at progression (optional).

[q] CCI

[r] ePRO LogPads will be assigned to patients before or on Day 1 of Cycle 1 of chemotherapy; baseline ePROs should be completed by patients prior to dosing on Day 1 of Cycle 1, and before any study procedures are conducted (exception may be made for blood draws), when they are still in the clinic, to ensure that the device is correctly set up and working properly; however it is permitted for the baseline ePROs to be completed prior to C1D1 as long as treatment is given within 3 days of ePRO completion. If a site wishes to perform both blood draws and ePRO before C1D1, then ideally the ePRO should be performed prior to the blood draws. In the event of the device failure at a site visit, paper questionnaires may be used at that visit. ePROs should be completed by the patients at home or at the site if the site visit coincides with the ePRO visit, but prior to any study procedures including treatment, with the exception of blood draws. PRO-CTCAE will be administered only in the languages where a linguistically validated version exists. Questionnaires will be collected at the times shown in the study plan, at discontinuation of study treatment visit (discontinuation of all study treatments), 30 days and 90 days post treatment discontinuation visit and every 12 weeks (±14 days) from 30 day post treatment discontinuation visit (discontinuation of all study treatments) thereafter (up to a maximum of 36 months post Visit 2 or primary data cut-off date [DCO], whichever comes first).

[s] Resourcing use at Visit 7 captures information from the time of Screening to the last dose of chemotherapy.

1.1.3 Post-discontinuation Schedule of Activities

The post-discontinuation SoA applies to all patients (Table 4); however, the initial safety follow-up visits differ, depending on whether the patient discontinues durvalumab/saline treatment (in which case a 30-day and a 90-day follow-up visit from the last dose of durvalumab/saline treatment is required, even if the patient is still receiving olaparib/placebo treatment) or whether the patient discontinues olaparib/placebo treatment only (in which case a 30-day follow-up visit from the last dose of olaparib/placebo treatment is required even if the patient is still receiving IV treatment). If discontinuing both durvalumab/saline and olaparib/placebo at the same time patients will have both the 30-day and the 90-day follow-up visits. Where the decision to discontinue treatment occurs after the window for the 30-day or 90-day safety visit, then the relevant safety visit should take place as soon as possible and within 7 days of the decision.

Patients who are permanently discontinued from all study treatments, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (see Table 4).

Patients who permanently discontinue all study treatments for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 scans performed Q12W ± 2 weeks (relative to the date of the end of chemotherapy scan) for the first 3 years, then every 24 weeks ± 2 weeks until objective disease progression (as per RECIST 1.1). Copies of scans from all patients will be collected until disease progression and stored centrally (see Section 8.1.1).

All procedures to be conducted during the follow-up period will be performed according to the assessment schedules (see Table 4).

1.1.3.1 Treatment Discontinuation Visit

Patients can be discontinued from an individual study treatment if any discontinuation criteria are fulfilled (see Section 7.1) but the treatment discontinuation visit will only occur when all treatments have been discontinued. The assessments to be carried out at the visit are detailed in the study schedule (Table 2 and Table 3).

1.1.3.2 Follow-up after last dose of study medication (safety follow-up visit)

The safety follow-up visits are as follows:

- 30 days from the last dose of olaparib/placebo treatment (the follow-up period for olaparib) AND
- 30 days and 90 days from the last dose of durvalumab/saline (the follow-up period for durvalumab)

NOTE: Where the decision to discontinue treatment occurs after the window for the 30-day or 90-day safety visit, then the relevant safety visit should take place as soon as possible and within 7 days of the decision.

All safety follow-up visits are required even if a patient is still receiving some of the other study treatments. Therefore depending on when a patient discontinues study treatment, the follow-up period will be between 30 days and 90 days. Any serious and/or non-serious adverse events (AEs) ongoing at the time of the Discontinuation Visit or which have occurred during the defined follow-up period must be followed-up (in accordance with Section 8.3.3). Any serious adverse events (SAEs) which occur on treatment or within the relevant follow-up period will be reported to AstraZeneca Patient Safety. Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the electronic case report form (eCRF). The assessments to be carried out at the follow-up visit are detailed in the study schedule (Table 4).

1.1.3.3 Survival

Assessments for survival should be made Q12W following objective radiological disease progression according to RECIST 1.1. Survival information may be obtained via telephone contact with the patient, patient's family, contact with the patient's current physician or by checking publicly available death registries. Survival data will be collected up to the data cut-off time of the final OS analysis, except in the event of the extended OS analysis where survival data for the global non-*tBRCAm* cohort will be collected up to the DCO of the extended OS analysis. In addition, attempts will be made to contact patients in the week following the data cut-off for the primary progression-free survival (PFS) and final survival analyses to provide complete survival data.

Following the data cut-off for the primary analysis of PFS, patients will continue to be followed up as detailed in the study schedule (Table 2, Table 3 and Table 4) to the point of the last survival analysis (either the final OS analysis or the extended OS analysis, see Section 1.1.3.6). At this point investigators will be notified that no further data collection for the study will be required. Monitoring and recording of SAEs will continue as per Section 8.4.1. Since some cases of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) or new primary malignancies develop after discontinuing treatment with olaparib/placebo, investigators will be asked during the regular follow up for OS if the patient has developed MDS/AML or a new primary malignancy and prompted to report any cases even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm.

1.1.3.4 Second progression

Following the primary objective radiological progression, copies of the patient's radiological scans are no longer required to be collected. Patients will be assessed Q12W for a second progression (using the patient's status at first progression as the reference for assessment of second progression). A patient's second progression status is defined according to the local standard clinical practice and may involve any of; investigator assessment of radiological progression, cancer antigen 125 (CA125) progression, clinical/symptomatic progression or death. RECIST 1.1 measurements will not be collected for assessment of time to second progression (PFS2). The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

1.1.3.5 Patient management post primary analysis

The analysis for the two comparisons of interest for the primary objective of the study (Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population) will be performed when approximately 149 PFS events have occurred (58% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and approximately 453 PFS events (62% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population. At the time of the PFS primary analysis approximately 480 PFS events (65% maturity) are expected to have occurred for the comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population. This will be approximately 52 months after the first patient has been randomised (see Section 9.2).

Patients on study treatment at the time of the data cut-off will continue to receive study treatment until they meet any discontinuation criteria as per Section 7.1.

Patients on study treatment will be followed for core safety assessments and disease progression (haematology, clinical chemistry, AEs/SAEs and concomitant medications (including any subsequent cancer therapy), study treatment dosing details, objective radiological disease progression according to RECIST 1.1). These patients should be followed according to routine clinical practice but visits should take place at least every 12 weeks.

All patients (patients still on study treatment and patients discontinued from study treatment) will be followed for survival and disease progression.

1.1.3.6 Patient management post final OS analysis (global *tBRCAm* & non-*tBRCAm* cohorts only)

Global *tBRCAm*/non-*tBRCAm* cohorts: Patients in the global cohorts who are on study treatment at the final OS analysis DCO should continue to receive their assigned treatment if, in the opinion of the Investigator, it is in the patient's best interest and in accordance with CSP requirements (see Section 6.1.1). For patients continuing to receive olaparib/placebo and/or durvalumab/placebo following the final OS analysis DCO, it is recommended that patients

continue the scheduled site visits and safety assessments so Investigators can monitor safety associated with ongoing treatment.

Global non-*tBRCAm* cohort only: Patients in the non-*tBRCAm* cohort who have discontinued treatment by the final OS analysis DCO should continue survival assessment every 12 weeks (±2 weeks) during extended OS follow up, which may be performed via phone contact and does not require an in-person visit.

Data collected during extended OS follow-up

Post final OS analysis, limited data should be collected as outlined below.

- Global *tBRCAm* and non-*tBRCAm* cohorts: Olaparib and/or durvalumab administration must continue to be reported if patients continue study treatments during extended OS follow-up.

- Global *tBRCAm* and non-*tBRCAm* cohorts: All SAEs, AEs, and pregnancies occurring on treatment or within the safety follow-up periods, must continue to be reported to the Sponsor within the usual timelines (ie, for SAEs immediately, or no later than 24 hours of when the site become aware of the SAE) directly in the EDC. For patients who have completed treatment, AEs should be reported as described in Section 8.3.2.1.

- Global non-*tBRCAm* cohort only: Survival status will be collected for all patients in the global non-*tBRCAm* cohort only during extended OS follow-up, and information of subsequent anti-cancer therapy will be collected if patients started anti-cancer therapy during extended OS follow-up. Survival information may be obtained via telephone contact with the patient, patient's family, by contact with the patient's current physician, local death registries as described per local rules and regulations, and/or medical records.

- No sample collections, images, or PFS2 data are required for any patients in the extended OS follow up.

1.1.3.7 Patient management post last analysis (all cohorts)

The study will continue until approximately 552/1104 OS events (~50% maturity) have occurred across the 3 treatment arms of the non-*tBRCAm* cohort or 5 years following randomisation of the last non-*tBRCAm* patient, whichever occurs sooner. In the event final analysis of OS occurs when approximately 552/1104 OS events (~50% maturity) have occurred across the 3 treatment arms in the non-*tBRCAm* ITT population, an extended OS descriptive analysis for the non-*tBRCAm* cohort only, may also be performed 5 years after the last non-*tBRCAm* patient is randomised to treatment.

At the time of DCO for the last OS analysis, the clinical study database will close to new data and post the database lock, all non-*tBRCAm* patients will be unblinded.

Patients who are receiving active treatment can either choose to discontinue treatment or where the investigator believes patients are gaining clinical benefit; patients may continue to receive active treatment, but outside of the study setting. All patients will receive follow up care in accordance with standard local clinical practice.

Patients that are on placebo will not be offered durvalumab or olaparib as treatments within the study setting. AstraZeneca will work with investigators on the proper transition of patients to alternative therapies if possible.

SAEs will continue to be reported to AstraZeneca Patient Safety Department, to the end of the appropriate follow-up period, in accordance with Section 8.4.1. Investigators will be asked during the regular follow up for OS if the patient has developed MDS/AML or a new primary malignancy and prompted to report any cases even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm.

Additionally, any SAE or non-serious AE, that is ongoing at the end of the study, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to one or more of the products used in this study, the investigator should notify AstraZeneca, Patient Safety.

Drug accountability should continue to be performed until the patient stops study treatment completely, in accordance with Section 6.2.

Table 4 Post-discontinuation schedule of assessments

Evaluation	Time since last dose of study treatment		Off treatment follow up to 1st progression • Study treatment discontinued due to reasons other than disease progression • Tumour assessment visits every 12 weeks or 24 weeks[b]	Time to second progression (PFS2) and survival for: • Patients who have discontinued study treatment due to disease progression • Patients who have progressed off treatment • Patients who were on study treatment after primary (PFS) analysis who subsequently discontinued study treatment • Assessments every 12 weeks	For details see Section
	Safety follow-up Day 30 (post olaparib/placebo or post durvalumab/saline treatment discontinuation)	Safety Follow-up Day 90[a] (post durvalumab/saline treatment discontinuation)			
Visit window	**±7 days**	**±7 days**	**±14 days**	**±14 days**	
AE/SAE assessment[c]	X	X			8.3
Vital Signs (including weight)	X	X			8.2.2 and 8.2.3
Concomitant medications	X	X			6.5
ECOG performance status	X	X			8.2.2
Haematology	X	X			8.2.1
Clinical chemistry	X	X			8.2.1
Thyroid function (TSH, free T3 [reflex], free T4 [reflex][d])	X	X			8.2.1
Women of childbearing potential: Pregnancy test (serum or urine)	X	As clinically indicated			8.2.5.1
Durvalumab PK assessment (non-*tBRCAm* patients only)[e]		X			8.5.1

Table 4 Post-discontinuation schedule of assessments

Evaluation	Time since last dose of study treatment		Off treatment follow up to 1st progression • Study treatment discontinued due to reasons other than disease progression • Tumour assessment visits every 12 weeks or 24 weeks[b]	Time to second progression (PFS2) and survival for: • Patients who have discontinued study treatment due to disease progression • Patients who have progressed off treatment • Patients who were on study treatment after primary (PFS) analysis who subsequently discontinued study treatment • Assessments every 12 weeks	For details see Section
	Safety follow-up Day 30 (post olaparib/placebo or post durvalumab/saline treatment discontinuation)	Safety Follow-up Day 90[a] (post durvalumab/saline treatment discontinuation)			
Durvalumab ADA sample (non-*tBRCAm* patients only)[e]		X			8.5.1.1
Tumour assessment (CT or MRI) (RECIST 1.1)[f]			Every 12 weeks for 3 years then every 24 weeks until PD[n]		8.1.1
Tumour biopsy on progression (optional)			X[n]		8.8.1.3
CA125			X[h, n]		8.2.1.3
CCI					8.8.1.2 8.8.1.4
EORTC-QLQ-C30 (by e-device)[i]	30 days and 90 days post treatment discontinuation visit (discontinuation of all study treatments) and Q12W (±14 days) from 30 day post treatment discontinuation visit thereafter up to a maximum of 36 months post Visit 2 or primary DCO, whichever comes first				8.1.2.1

Table 4 Post-discontinuation schedule of assessments

Evaluation	Time since last dose of study treatment		Off treatment follow up to 1st progression • Study treatment discontinued due to reasons other than disease progression • Tumour assessment visits every 12 weeks or 24 weeks[b]	Time to second progression (PFS2) and survival for: • Patients who have discontinued study treatment due to disease progression • Patients who have progressed off treatment • Patients who were on study treatment after primary (PFS) analysis who subsequently discontinued study treatment • Assessments every 12 weeks	For details see Section
	Safety follow-up Day 30 (post olaparib/placebo or post durvalumab/saline treatment discontinuation)	Safety Follow-up Day 90[a] (post durvalumab/saline treatment discontinuation)			
EORTC-QLQ-OV28 (by e-device)[i]	30 days and 90 days post treatment discontinuation visit (discontinuation of all study treatments) and Q12W (±14 days) from 30 day post treatment discontinuation visit thereafter up to a maximum of 36 months post Visit 2 or primary DCO, whichever comes first				8.1.2.1
EQ5D-5L (by e-device)[i]	30 days and 90 days post treatment discontinuation visit (discontinuation of all study treatments) and Q12W (±14 days) from 30 day post treatment discontinuation visit thereafter up to a maximum of 36 months post Visit 2 or primary DCO, whichever comes first				8.1.2.4
PRO-CTCAE (by e-device)[i]	30 days and 90 days post treatment discontinuation visit (discontinuation of all study treatments) and Q12W (±14 days) from 30 day post treatment discontinuation visit thereafter up to a maximum of 36 months post Visit 2 or primary DCO, whichever comes first				8.1.2.2
PGIS (by e-device)[i]	30 days and 90 days post treatment discontinuation visit (discontinuation of all study treatments) and Q12W (±14 days) from 30 day post treatment discontinuation visit thereafter up to a maximum of 36 months post Visit 2 or primary DCO, whichever comes first				8.1.2.3
Resource use			X [h, n]		8.9
Subsequent anticancer therapy, and second progression assessment[j]			X [h]	X [l]	NA

Table 4 Post-discontinuation schedule of assessments

Evaluation	Time since last dose of study treatment		Off treatment follow up to 1st progression • Study treatment discontinued due to reasons other than disease progression • Tumour assessment visits every 12 weeks or 24 weeks[b]	Time to second progression (PFS2) and survival for: • Patients who have discontinued study treatment due to disease progression • Patients who have progressed off treatment • Patients who were on study treatment after primary (PFS) analysis who subsequently discontinued study treatment • Assessments every 12 weeks	For details see Section
	Safety follow-up Day 30 (post olaparib/placebo or post durvalumab/saline treatment discontinuation)	Safety Follow-up Day 90[a] (post durvalumab/saline treatment discontinuation)			
Survival status[k]				X [l, m]	NA

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse event of special interest; *BRCA* = Breast cancer susceptibility gene; CA125 = Cancer antigen 125; CCI [redacted]; CT = Computed tomography; DCO = Data cut-off; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28; EQ-5D-5L = EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index; MRI = Magnetic resonance imaging; NA Not applicable; PK = Pharmacokinetic; Q3W = Every 3 weeks; Q12W = Every 12 weeks; Q24W = Every 24 weeks; PD = Progressive disease; PFS = Progression-free survival; PFS2 = time to second progression; PGIS = Patient global impression of severity; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RECIST = Response Evaluation Criteria In Solid Tumours; SAE = serious adverse event; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid-stimulating hormone; WHO = World Health Organisation.

[a] Samples at these timepoints are only required for patients when patients discontinue durvalumab/saline treatment.

[b] Follow-up assessments will be performed Q12W (±2 weeks), for the first 3 years (156 weeks) then Q24W ± 2 weeks (relative to the date of the end of chemotherapy assessment scan). Follow-up CT or MRI assessments will be by chest, abdomen and pelvis. Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until RECIST 1.1 disease progression). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Following disease progression further RECIST 1.1 assessments will not be performed and assessment of disease will be as per local clinical practice.

[c] Only SAEs for MDS/AML or new primary malignancy should be recorded after the safety follow-up period (see Section 8.3.2.1).

[d] 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.

[e] PK and immunogenicity (ADA) samples for each durvalumab (or saline) will only be taken from the 100 non-*tBRCAm* patients who have had samples collected on treatment (see Table 2); these samples are collected 90 days (3 months) (± 7 days) after treatment ends.

[f] For patients who discontinue their assigned study treatment following RECIST 1.1 progression, available readings of CT/MRI from local practice will be collected from patients' medical charts while information on subsequent anticancer treatment and/or PFS2 is collected.

g CCI

h

i The ePROs should be completed by the patients at home or at the site if the site visit coincides with an ePRO visit. PRO-CTCAE will be administered only in the languages where a linguistically validated version exists. Questionnaires will be collected at the times shown in the study plan, at the discontinuation of study treatment visit (discontinuation of all study treatments), 30 days and 90 days post treatment discontinuation visit and every 12 weeks (±14 days) from 30 day post treatment discontinuation visit (discontinuation of all study treatments) thereafter up to a maximum of 36 months post Visit 2 or primary data cut-off date [DCO], whichever comes first).

j All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigators opinion of response to them plus the date of progression, post discontinuation of study treatment need to be recorded.

k Patients may be contacted in the week following data cut-offs to confirm survival status.

l Assessments should be aligned to the date of first progression (see Section 1.1.3.4).

m In the event of an extended OS follow-up after the final OS analysis, survival follow-up will continue in the global non-*tBRCAm* cohort only.

n CCI

1.2 Synopsis

International co-ordinating investigator	GOG co-ordinating investigator
PPD Department of Gynecology and Gynecologic Oncology Kliniken-Essen-Mitte Henricistrasse 92 45136 Essen Germany	PPD PPD Medical Oncology Service Memorial Sloan Kettering Cancer Center 1275 York Avenue New York NY 10065 USA

Abbreviations: GOG = Gynecologic Oncology Group.

Protocol Title: A Phase III Randomised, Double-Blind, Placebo-Controlled, Multicentre Study of Durvalumab in Combination with Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib in Newly Diagnosed Advanced Ovarian Cancer Patients (DUO-O).

Short Title: DUO-O Study

Rationale:

Ovarian cancer is the leading cause of death from gynaecological cancers in women. Cytoreductive surgery followed by 6 cycles of platinum-based chemotherapy in combination with bevacizumab is established as the standard first-line treatment for newly diagnosed advanced ovarian cancer patients. Despite optimal cytoreductive surgery and high response to first line platinum-based chemotherapy, approximately 70% of patients subsequently relapse in the first 3 years. Once disease relapse is diagnosed, patients remain largely incurable. Therefore, there is a need for a more effective first line treatment that will significantly extend the progression free interval in this patient population, leads to long term remission and potentially improve the cure rate.

Poly (ADP-ribose) polymerase inhibitors (olaparib) and immune checkpoint inhibitors (durvalumab) are established cancer therapies and there is growing evidence that these therapies can be combined together and with the vascular endothelial growth factor (VEGF) inhibitors (bevacizumab) to gain synergistic anti-tumour effects while minimising the potential for significant side-effects. DUO-O study will assess the efficacy and safety of durvalumab and olaparib when added to SoC (platinum-based chemotherapy ± bevacizumab) in patients with newly diagnosed advanced ovarian cancer.

The SOLO1 study, investigating the efficacy and safety of maintenance treatment with olaparib vs placebo in patients with newly-diagnosed *BRCAm* advanced ovarian cancer who were in response to first line platinum based chemotherapy, has demonstrated a statistically significant and clinically meaningful improvement in PFS for olaparib compared with

placebo. Given the results of SOLO1, this study has been redesigned to focus on the assessment of a potential clinical benefit in patients who do not carry *BRCAm*. Current SoC for non-*tBRCAm* patients remains platinum-based chemotherapy in combination with bevacizumab; therefore, non-*tBRCAm* patients will be randomised in 1:1:1 ratio to one of 3 treatment arms (as described in Section 1.1.2.2), all of which include SoC.

Given the results of the SOLO1 study of olaparib as maintenance treatment in patients with newly-diagnosed advanced *BRCAm* ovarian cancer, to ensure that all patients who carry a *BRCA* mutation receive optimal treatment, all *tBRCAm* patients in DUO-O will receive oral olaparib as a maintenance therapy once they complete their chemotherapy phase. These patients will be studied as a separate single arm, open-label cohort to investigate the potential benefit of adding durvalumab and olaparib treatment to current SoC platinum-based chemotherapy in combination with optional bevacizumab.

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To determine the efficacy of durvalumab and olaparib assessed by PFS in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	PFS by investigator assessment using modified RECIST 1.1 – time from randomisation to first progression or death. This will be assessed via: • Determining the efficacy of durvalumab in combination with platinum-based chemotherapy and bevacizumab and continued as maintenance in combination with bevacizumab and olaparib versus SoC platinum-based chemotherapy in combination with bevacizumab in the following populations: ° non-*tBRCAm* HRD positive population ° non-*tBRCAm* ITT population.

Abbreviations: HRD = homologous recombination deficiency; ITT = intention to treat; *tBRCAm* = Presence of a deleterious or suspected deleterious mutation in tumour breast cancer sensitivity gene; PFS = Progression free survival; RECIST = Response Evaluation Criteria In Solid Tumours; SoC = Standard of care

Secondary objectives:	**Endpoint/variable:**
To determine the efficacy of durvalumab assessed by PFS in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	PFS by investigator assessment using modified RECIST 1.1 – time from randomisation to first progression or death. This will be assessed via: • Determining the efficacy of durvalumab in combination with platinum-based chemotherapy and bevacizumab and continued as maintenance in combination with bevacizumab versus SoC platinum-based chemotherapy in combination with bevacizumab in the non-*tBRCAm* ITT population
To determine the efficacy of durvalumab and olaparib assessed by OS in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	OS – time from date of randomisation to death This will be assessed via: ° Arm 3 vs Arm 1 in non-*tBRCAm* HRD positive population ° Arm 3 vs Arm 1 in non-*tBRCAm* ITT population ° Arm 2 vs Arm 1 in non-*tBRCAm* ITT population.
To assess the efficacy of durvalumab and olaparib in terms of PFS2, ORR, ORR pre-surgery in IDS group, duration of response, TFST, TSST and TDT in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	• Time from date of randomisation to second progression by investigator assessment of radiological, clinical or CA125 progression or death (PFS2) • ORR (CR + PR) by investigator assessment by modified RECIST 1.1 ° in all patients with evaluable disease at baseline ° prior to surgery in those patients planned to have IDS with evaluable disease at baseline. • Duration of response • TFST • TSST • TDT All endpoints will be assessed in the populations described for PFS and OS.
To determine the effects on HRQoL, global health status and ovarian cancer symptoms of the combination of durvalumab and olaparib in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	• Changes in the subscales from baseline of the EORTC-QLQ-C30; and EORTC-QLQ-OV28 questionnaires • Health state utility derived from the HRQoL instrument, the EuroQOL EQ5D-5L • Q-TwiST • QAPFS All endpoints will be assessed in the populations described for PFS and OS.

Secondary objectives:	**Endpoint/variable:**
To determine the effects on pCR for the combination of durvalumab with platinum-based chemotherapy and bevacizumab in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	• Proportion of patients with pCR in patients undergoing IDS
• To characterize the PK and immunogenicity of durvalumab in combination with bevacizumab and olaparib • To determine olaparib plasma concentrations via sparse sampling for population PK analyses.	Only in non-*tBRCAm* patients with primary cytoreductive surgery • Serum concentrations of durvalumab and plasma concentrations of olaparib (samples to be taken in the non-*tBRCAm* cohort only) • ADA to durvalumab
• To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of *tBRCAm* patients with newly diagnosed advanced ovarian cancer.	OS, PFS, PFS2, ORR, ORR pre-surgery in IDS group, duration of response, TFST, TSST, TDT EORTC-QLQ-C30 and EORTC-QLQ-OV28, EQ5D-5L, Q-TwiST, QAPFS, proportion of patients with pCR in patients undergoing IDS

Abbreviations: ADA = Anti-drug antibody; CA125 = Cancer antigen 125; CR = Complete response; EORTC-QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ5D-5L = EuroQoL five dimensions, five level health state utility index; HRQoL = health-related quality of life; IDS = Interval debulking surgery; ORR = Objective response rate; OS = Overall Survival; pCR = Pathological complete response; PFS = Progression free survival; PFS2 = Time to second progression; PK = Pharmacokinetic; PR = Partial response; QAPFS = Quality-adjusted progression-free survival; Q-TwiST = Quality-adjusted time without symptoms of disease or toxicity; RECIST = Response Evaluation Criteria In Solid Tumours; SoC = Standard of care; *tBRCAm* = Presence of a deleterious or suspected deleterious mutation in tumour breast cancer sensitivity gene; TDT = Time to discontinuation or death; TFST = Time to first subsequent therapy; TSST = Time to second subsequent therapy.

Safety objectives:	Endpoint/variable: All patients
• To evaluate the safety and tolerability of the combination of durvalumab and bevacizumab given in combination with platinum-based chemotherapy and continued as maintenance in patients with newly diagnosed advanced ovarian cancer • To evaluate the safety and tolerability of durvalumab in combination with platinum based chemotherapy+/- bevacizumab and continued as maintenance in combination with olaparib +/-bevacizumab in patients with newly diagnosed advanced ovarian cancer	• AEs / SAEs, physical examination, vital signs including BP, pulse, ECG and laboratory findings including clinical chemistry / haematology parameters • imAEs – given the intended mechanisms of action of durvalumab, particular attention will be given to AEs that may follow enhanced T-cell activation, or other imAE

Abbreviations: AE = Adverse event; BP = blood pressure; ECG = Electrocardiogram; imAE = Immune-mediated adverse event; SAEs = Serious adverse events.

Exploratory objectives are listed in Section 3.4

Overall design:

This is a prospective randomised, double-blind, placebo-controlled, multi-centre Phase III study evaluating the efficacy and safety of SoC platinum-based chemotherapy and bevacizumab followed by maintenance bevacizumab either as monotherapy, or in combination with durvalumab (MEDI4736), or in combination with durvalumab and olaparib (AZD2281) in non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer. The study will also include a single arm, open-label *tBRCAm* cohort to determine the potential benefit of adding durvalumab treatment to SoC platinum-based chemotherapy and olaparib in the maintenance setting (bevacizumab optional).

Note applicable to all patients: bevacizumab dosing may be achieved via use of the originator product (Avastin®) or an FDA-, EMA- or PMDA-approved biosimilar (for China only, a CDE-approved biosimilar also may be used). For the purposes of this Clinical Study Protocol (CSP), the generic name bevacizumab is used throughout and taken to apply to either Avastin or an FDA-, EMA- or PMDA-approved biosimilar.

Study period:

Date of first patient enrolled: January 2019

Estimated date of last patient completed Quarter 2, 2026

Number of patients:

This study will allocate/randomise approximately 1254 patients with newly diagnosed advanced ovarian cancer patients at approximately 225 study sites worldwide as follows:

- Patients **without** detected deleterious/suspected deleterious mutations in tumour *BRCA1/2* (hereafter referred to as the non-*tBRCAm* cohort; approximately 1104 patients).
  - Note: A China cohort of approximately 120 non-*tBRCAm* patients from sites in China will be randomised 1:1:1 to study treatments. If necessary, the China cohort will continue recruiting patients after recruitment to the Global population closes at approximately 1104 patients.
- Patients **with** deleterious/suspected deleterious mutations in *tBRCA1/2 (*hereafter referred to as the *tBRCAm* cohort; approximately 150 patients).

The 2 cohorts will be treated as described in Section 1.1.2.2.

Treatments and treatment duration:

Patients will receive treatments as specified in Section 1.1.2.1 and Section 1.1.2.2 until progressive disease (PD) is confirmed, unacceptable toxicity occurs, withdrawal of consent, or some other discontinuation criterion is met. If after 35 cycles (24 months) of treatment with durvalumab, macroscopic residual disease is still present that remains stable (ie, no evidence of disease progression), the patient may continue to receive durvalumab/placebo IV treatment until PD if, in the opinion of the investigator, it is deemed to be in the patient's best interests. Olaparib/placebo treatment may also be continued for longer than 24 months provided the patient has macroscopic residual disease that remains stable and in the opinion of the investigator, it is in the patient's best interest.

Data Monitoring Committee:

This study will use an external Independent Data Monitoring Committee (IDMC) to perform interim reviews of accumulating study safety data. The IDMC will be composed of therapeutic area experts and a statistician, who are not employed by the Sponsor, and do not have any major conflict of interest. Following each review, the IDMC will recommend whether the study should continue unchanged as designed, be modified in any way, or terminated.

The IDMC will meet regularly to review accumulated study safety data, by cohort and treatment arm, with the initial review planned to take place prior to the first dosing with the combination of bevacizumab, durvalumab/saline, and olaparib/placebo to examine available safety data. During regular data reviews, the IDMC will also separately assess the safety of the combination therapy in Japanese patients as well as review safety data for patients in the China cohort.

Furthermore, the IDMC will meet for the PFS interim analysis, which will occur when approximately 86% of the target number of PFS events for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and non-*tBRCAm* ITT population have been

reached (approximately 43.5 months after the first patient has been randomised). See Section 9.5.

Further details are in the IDMC charter.

Statistical methods:

The primary objective of this study is to determine the efficacy by PFS (using investigator assessment of scans according to modified RECIST v1.1) of durvalumab and olaparib in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer. This will be assessed via:

- Determining the efficacy of Arm 3 (durvalumab in combination with SoC platinum-based chemotherapy and bevacizumab and continued as maintenance in combination with bevacizumab and olaparib) versus Arm 1 (SoC platinum-based chemotherapy in combination with bevacizumab) in the following populations:
  - non-*tBRCAm* HRD positive population
  - non-*tBRCAm* ITT population.

A key secondary comparison is to compare PFS (per modified RECIST 1.1 as assessed by investigator) for Arm 2 vs Arm 1 in all non-*tBRCAm* patients. This will be assessed via:

- Determining the efficacy of Arm 2 (durvalumab in combination with SoC platinum-based chemotherapy and bevacizumab and continued as maintenance in combination with bevacizumab) versus Arm 1 (SoC platinum-based chemotherapy in combination with bevacizumab) in the non-*tBRCAm* ITT population.

Analysis of PFS (Primary Objective and Key Secondary Endpoint) in non-*tBRCAm* cohort

In the non-*tBRCAm* cohort, the PFS comparisons are adequately powered for both experimental arms vs chemotherapy and bevacizumab combination. For the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population, the power is expected to be >90% at a two-sided alpha level of 5%. For the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population, the power is expected to be >90% at a two-sided alpha level of 5.0%. For the comparison of Arm 2 vs Arm 1, in the non-*tBRCAm* ITT population, the power is expected to be >80% at a two-sided alpha level of 2.5%. The sample size is based on an assumed median PFS duration of 18 months for the chemotherapy + bevacizumab arm and is based on the results seen in the PAOLA-1 study (Ray-Coquard et al 2019) in addition to the expected average time for chemotherapy and the inclusion of the stable disease population in the DUO-O study. The original assumed median PFS for the control arm was 16 months and was based on the data reported in the GOG-218, ICON7 and GOG262 clinical trials with bevacizumab in the first-line setting, including subgroup analysis from the GOG218 study

based on *BRCA*/HRR wild type status (Perren et al 2011; Burger et al 2013; Norquist et al 2018).

The sample size has been derived on the assumption of a 3 month delay in separation of the PFS curves between Arm 2 vs Arm 1 and between Arm 3 vs Arm 1. The assumed average hazard ratio for PFS for the chemotherapy, bevacizumab, durvalumab + olaparib arm in the non-*tBRCAm* HRD-positive population is 0.49 (approximately 39 months median PFS), in the non-*tBRCAm* ITT population is 0.61 (approximately 30 months median PFS) and for the chemotherapy, bevacizumab and durvalumab arm in the non-*tBRCAm* ITT population it is 0.74 (approximately 24 months median PFS). In addition, the sample size has been derived on the assumption that 15% of patients will drop out.

In order to strongly control the type I error at the 5% two-sided level, a multiple testing procedure will be employed. The overall 5% type I error rate will be allocated to the primary PFS comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population. If the PFS analysis for this comparison is statistically significant, 5% alpha (two-sided) will be allocated to the next level in a pre-defined hierarchical order; ie, the PFS comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population. For further details on the complete hierarchical testing procedure across the key comparisons of interest of PFS and OS in the non-*tBRCAm* HRD-positive population and non-*tBRCAm* ITT population, see Section 9.4.4.

In order to describe the nature of the benefits of durvalumab and durvalumab + olaparib compared with comparator arm, ORR, PFS2, time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), time to discontinuation (TDT), change from baseline score in the physical functioning subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 30 (EORTC-QLQ-C30) will be tested at a two-sided significance level of [redacted]%.

The data cut off (DCO) for the analysis of PFS for the two comparisons of interest (Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population) will be undertaken at the same calendar time. The primary PFS analysis will be undertaken when approximately 149 PFS events have occurred (58% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and approximately 453 PFS events (62% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population. At the time of the PFS primary analysis approximately 480 PFS events (65% maturity) are expected to have occurred for the comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population. Assuming a non-linear recruitment period of 26 months, the data cut-off for the analysis of PFS will take place at approximately 52 months after the first patient is randomised.

An interim PFS analysis is planned and will be undertaken when approximately 86% of the target number of PFS events is expected to be reached for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and non-*tBRCAm* ITT population (ie, approximately 128 of 149 PFS events across Arm 3 and Arm 1 in non-*tBRCAm* HRD-positive population and 390 of 453 PFS events in non-*tBRCAm* ITT population). It is anticipated that approximately 86% of the target number of PFS events (ie, approximately 414 of 480 PFS events) will be available for the comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population at that time. This interim will occur approximately 43.5 months after the first patient is randomised.

PFS will be analysed using a log rank test stratified by timing and outcome of cytoreductive surgery (no macroscopic residual disease after upfront primary surgery vs all others [macroscopic residual disease after upfront primary surgery or planned IDS]), and geographic region (North America vs Europe vs RoW). The hazard ratio together with its 95% confidence interval (CI) and p-value will be presented (a hazard ratio less than 1 will favour the comparator arm). The hazard ratio and confidence interval will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron and the stratification variables as strata) and the CI will be calculated using a profile likelihood approach. The primary analyses will be based on investigator-recorded assessment of disease progression by RECIST 1.1. Sensitivity analyses will be performed, including using the Blinded Independent Central Review (BICR) assessment of disease progression.

Subgroup analyses will be conducted for PFS to assess consistency of treatment effect across potential or expected prognostic factors including:

- Timing and outcome of cytoreductive surgery (no residual macroscopic disease after upfront primary surgery vs residual macroscopic disease after upfront primary surgery OR planned IDS, including patients who have undergone partial or unsuccessful primary surgery and are also planned to have IDS),
- Geographic region (North America vs Europe vs RoW);
- Age (<65 years vs ≥65 years);
- ECOG performance status (PS0 vs PS1);
- Stage of disease at diagnosis (Stage III vs Stage IV);
- CR/PR/NED vs non CR/PR/NED at the end of chemotherapy;
- Homologous Recombination Deficiency (HRD) status (HRD positive vs HRD negative vs HRD unknown), as required;
- Homologous recombination repair related gene mutation (HRRm) status (HRRm vs non HRRm);
- PD-L1 expression (high vs low vs unknown).

Other biomarker subgroups may be added prior to database lock based on emerging clinical trial evidence. An analysis will not be performed if there are too few events available for a meaningful analysis of a particular subgroup (ie, if there are less than 5 events in a stratum). Other subgroups of exploratory interest will be defined in the SAP.

At the time of the primary analysis of PFS an interim analysis of OS will be performed. It is anticipated that 81 OS events will have occurred (31% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and 231 OS events will have occurred (31% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population at that time. A final analysis of OS may be performed when approximately 552/1104 OS events (~50% maturity) have occurred across the 3 treatment arms in the non-*tBRCAm* ITT population or 5 years after the last non-*tBRCAm* patient is randomised to treatment, whichever occurs sooner. In the event final analysis of OS occurs when approximately 552/1104 OS events (~50% maturity) have occurred across the 3 treatment arms in the non-*tBRCAm* ITT population, an extended OS descriptive analysis (non-*tBRCAm* cohort only) may also be performed 5 years after the last non-*tBRCAm* patient is randomised to treatment.

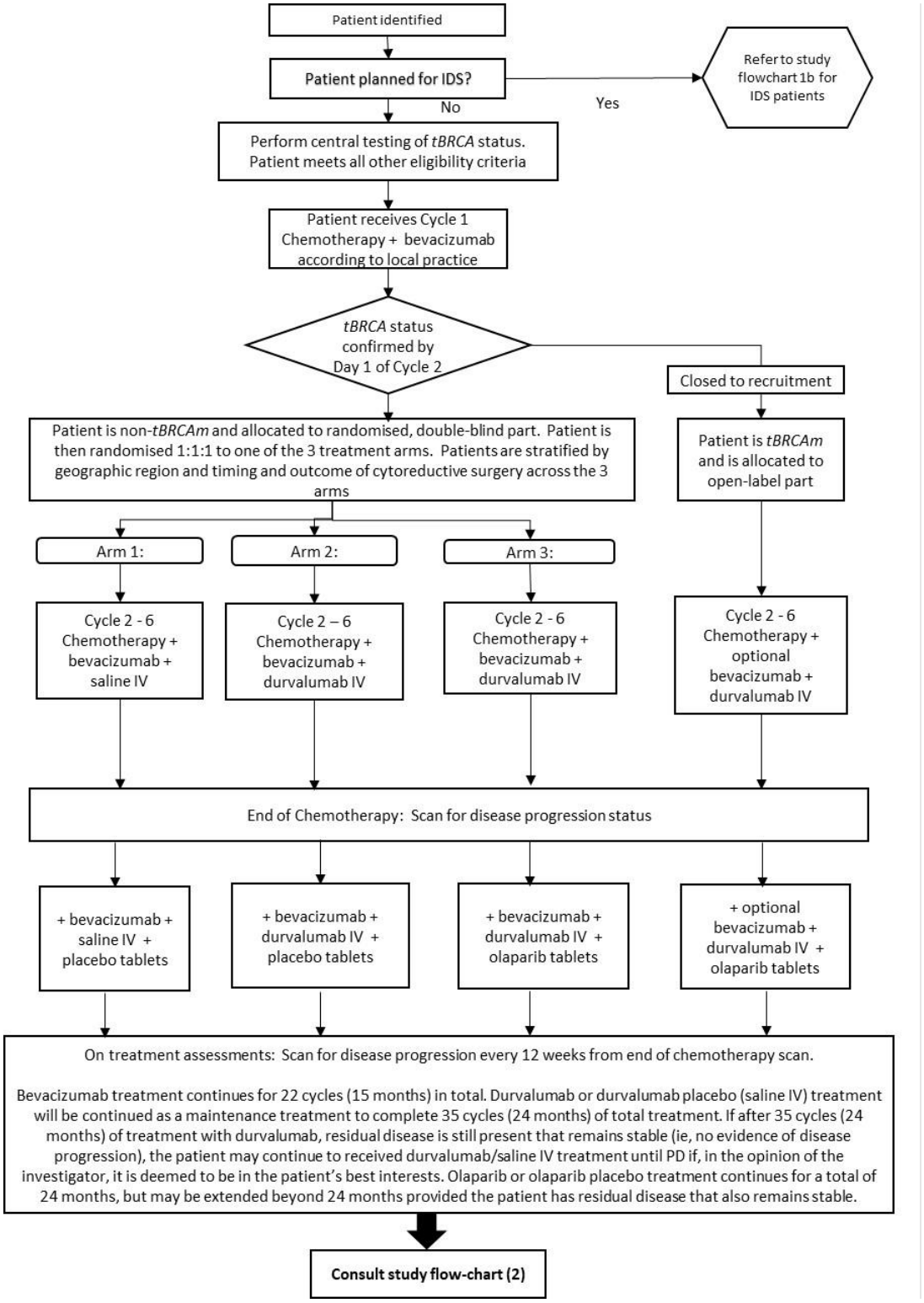
At the time of the DCO and unblinding of PFS analysis of the non-*tBRCAm* cohort, the data collected from the *tBRCAm* cohort will be appropriately summarised.

1.3 Schema

The general study design is summarised in Figure 1.

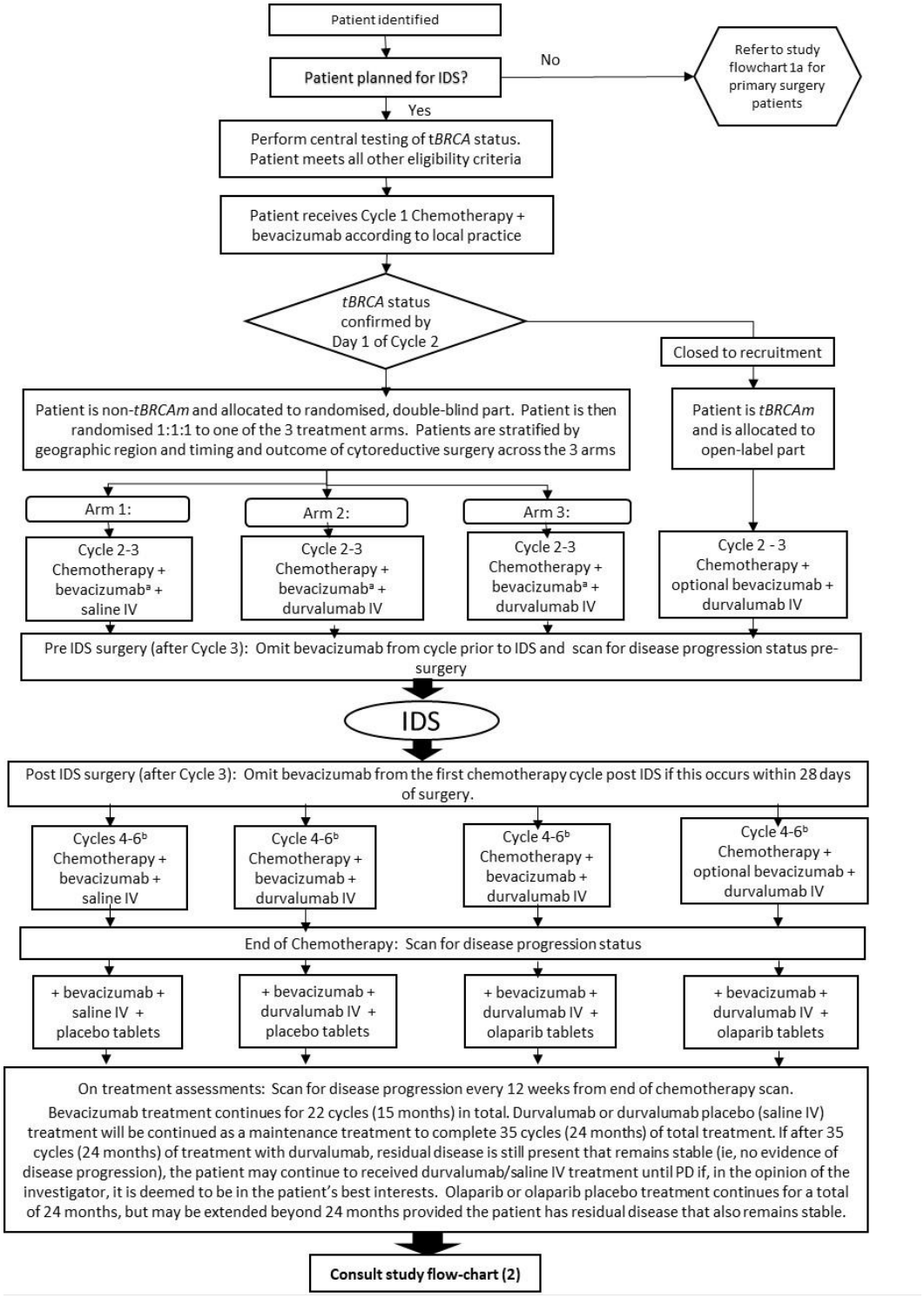
Specific flow-charts are provided in Figure 3, Figure 4 and Figure 5. For patients who have had primary cytoreductive surgery at study entry, follow the flowcharts in Figure 3 and Figure 5; for patients planned for IDS (this includes patients who have undergone partial or unsuccessful primary surgery and are also planned to have IDS), follow the flowcharts in Figure 4 and Figure 5.

Figure 3 Study flow chart 1a: Patients with primary cytoreductive surgery



Abbreviations: *BRCA* = Breast cancer susceptibility gene; IDS = Interval debulking surgery; IV = intravenous.
Chemotherapy should be administered for a minimum of 4 cycles and a maximum of 6 cycles.

Figure 4 Study flow chart 1b: Patients requiring interval debulking surgery (IDS)

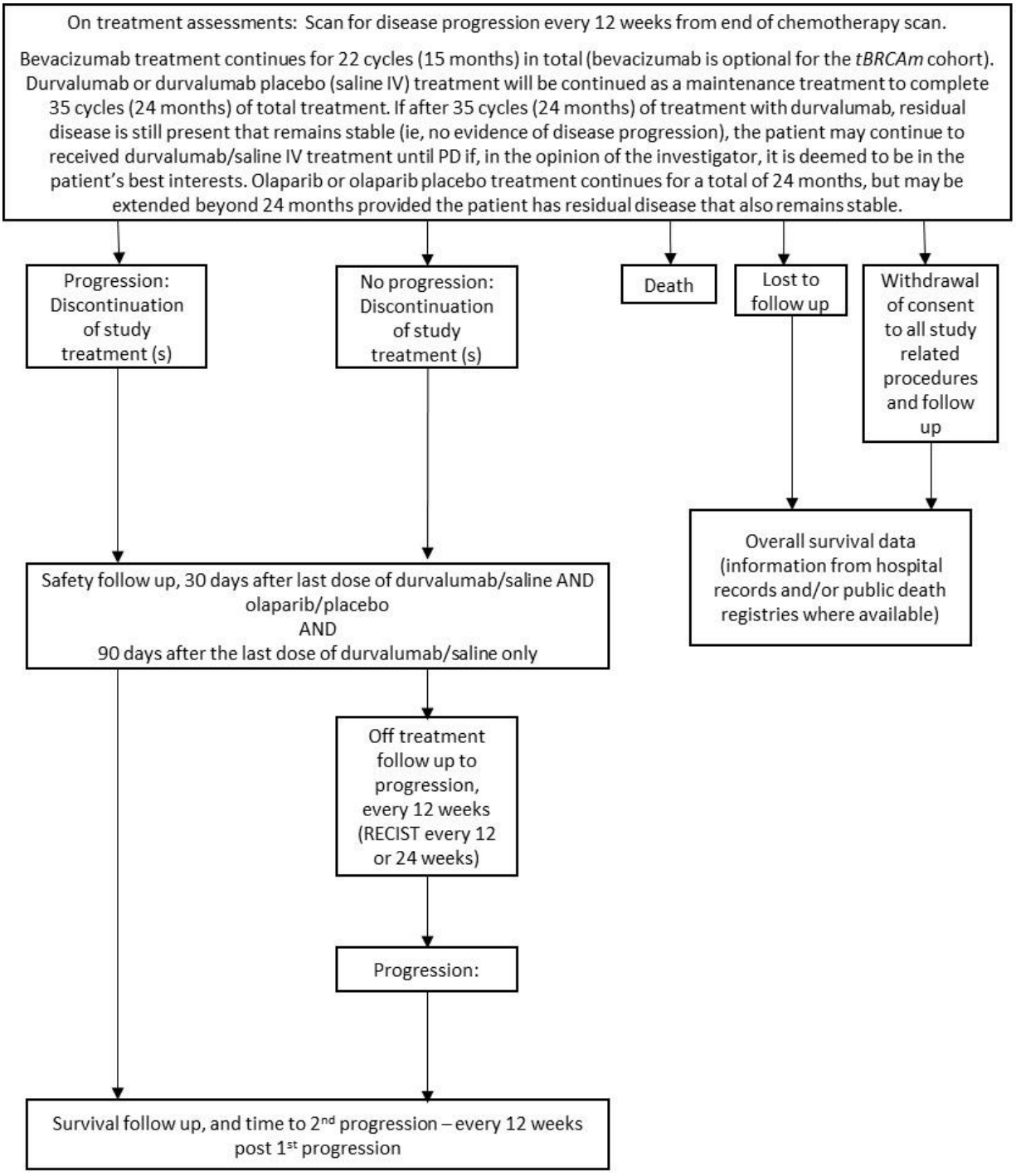


Abbreviations: *BRCA* = Breast cancer susceptibility gene; IDS = Interval debulking surgery; IV = intravenous

[a] Bevacizumab may be omitted from Cycle 1 (depending on extent of diagnostic surgery) but MUST be omitted from the treatment cycle immediately prior to IDS.

[b] Chemotherapy should be administered for a minimum of 4 cycles and a maximum of 6 cycles.

Figure 5 Study flowchart 2: Follow-up



Abbreviations: IV = Intravenous; RECIST = Response evaluation criteria in solid tumours.
In the event of an extended OS follow-up after the final OS analysis, survival follow-up will continue in the global non-*tBRCAm* cohort only.

2. INTRODUCTION

2.1 Background and rationale for conducting this study

2.1.1 Ovarian cancer

Ovarian cancer is the leading cause of death from gynaecological cancers in the United States of America (US), ranking as the fifth most common cause of cancer death in women (American Cancer Society 2017) and the fifth most common newly diagnosed cancer in females in the EU 27 (European Union) (Ferlay et al 2013). Ovarian cancer remains one of the most difficult cancers to diagnose at an early curable stage; 75% of patients present with advanced disease (Stage III or IV) (Hennessy et al 2009). The majority of patients die from their disease, with 5 year survival rates only 29% for advanced stages (Siegel et al 2017). Ovarian cancer is therefore an important public health issue.

2.1.1.1 Current standard of care

The current SoC for newly diagnosed advanced ovarian cancer consists of radical debulking surgery followed by post-operative platinum-based first line chemotherapy (NCCN Ovarian 2018). For patients for whom upfront surgery is unlikely to achieve a complete resection, treatment consists of neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy (NCCN Ovarian 2018). Cytoreductive therapy and platinum-based chemotherapy are considered the treatment of choice for patients with newly diagnosed advanced ovarian cancer.

First line chemotherapy is generally given for a maximum of 6 cycles. It cannot be continued until progression as it is associated with cumulative neurological, renal, and haematological toxicities. Moreover, clinical outcomes do not improve if chemotherapy is extended beyond 6 cycles (Ledermann et al 2013). Since chemotherapy is not a viable treatment option in the maintenance setting, there is a need for a well-tolerated maintenance treatment option in the first line setting.

The vascular endothelial growth factor inhibitor bevacizumab (Avastin®) in combination with carboplatin and paclitaxel followed by bevacizumab maintenance is approved in the first line maintenance ovarian cancer setting. The US approval was based on a 6.2 month improvement in median PFS (18.2 vs 12 months; hazard ratio 0.62 95% CI 0.52-0.75) for carboplatin and paclitaxel plus bevacizumab followed by bevacizumab maintenance vs chemotherapy alone in the GOG-218 study (Avastin USPI 2018). The EU approval of bevacizumab in the first line treatment of advanced ovarian cancer patients was based on a smaller magnitude of effect based on the primary analysis of GOG-218 (hazard ratio 0.71; 95% CI 0.61-0.83; p<0.0001) and ICON7 (hazard ratio 0.81; 95% CI 0.70-0.94; p=0.0041) (Perren et al 2011, Oza et al 2015) studies that demonstrated a 3.7 month and 1.7 month improvement in median PFS, respectively. Neither the final mature analysis of GOG-218 study nor the ICON 7 study

showed a difference in OS (Burger et al 2018). A recent exploratory analysis of the GOG-218 trial by HRD status (Norquist et al 2018) also suggested a possible modest effect of bevacizumab in patients with HRD tumours, including patients whose tumours had *BRCA* mutations. In patients with no HRR mutations (n = 581), bevacizumab significantly prolonged PFS (hazard ratio 0.71; 95% CI, 0.60–0.85; P < 0.0001), however in those with mutations (n = 228), the hazard ratio in favour of bevacizumab was 0.95 (95% CI, 0.71–1.26). In both the GOG-218 and ICON7 trials, bevacizumab treatment was shown to be associated with significant toxicity, including, but not limited to, hypertension, neutropenia, venous thromboembolic events, febrile neutropenia, wound healing complications, and gastrointestinal perforation/fistula/abscess (Gonzalez et al 2013).

On 14 September 2017, the FDA approved the first biosimilar for the treatment of cancer in the US. Mvasi (bevacizumab-awwb) was approved as a biosimilar to Avastin (bevacizumab) for the treatment of multiple types of cancer, including colorectal, non-small cell lung, renal cell and cervical cancers as well as glioblastoma multiforme. In approving Mvasi, FDA determined that there are no clinically meaningful differences between Mvasi and Avastin; however, the originator product and the biosimilar product are not interchangeable. As Avastin's indication for recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer that is platinum-resistant in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan is protected by orphan drug exclusivity, Mvasi was not approved for this indication at this time. However, following the end of data exclusivity (14 November 2021) it is anticipated that this indication would be included for the biosimilar. In addition, the European Medicines Agency (EMA) are currently assessing two biosimilar applications for bevacizumab for a number of oncology indications, including ovarian cancer, both of which have the potential to be approved in the near future.

Since bevacizumab biosimilars start to replace bevacizumab as standard of care, AstraZeneca allows patients to be treated with either bevacizumab or a single one of the FDA-, EMA- or PMDA-approved biosimilars in this study (for China only, a CDE-approved biosimilar also may be used). Where possible, patients should remain on the originator product Avastin® or a single one of the FDA-, EMA- or PMDA-approved biosimilars for the duration of their treatment. However, if the originator product is no longer available at the site, or if the patient is unable to tolerate it, individual patients are allowed to switch to Avastin or an approved bevacizumab biosimilar; once switched, it is recommended that the patient should then continue on that agent for the remaining duration of treatment unless this is not possible, for example the patient is unable to tolerate it, in which case a further switch would be permitted.

For the purposes of this CSP, the generic name bevacizumab is used throughout and taken to apply to either bevacizumab or an FDA-, EMA- or PMDA-approved biosimilar (for China only, a CDE-approved biosimilar also may be used).

2.1.1.2 Unmet medical need

Approximately 70% of patients relapse and experience disease progression, usually within 3 years of starting chemotherapy (Ledermann et al 2013). Once the disease comes back, it becomes largely incurable; therefore, there is a need for a well-tolerated first line treatment continuing as maintenance (following completion of chemotherapy) that extends PFS, leads to long-term remission, and potentially improves the cure rate.

The DUO-O study will investigate the role of two therapeutic targets: a DNA damage repair agent (olaparib) and a programmed death-ligand 1 (PD-L1) inhibitor (durvalumab) when used in combination with the SoC (chemotherapy plus bevacizumab). The clinical evidence that these agents, in combination with chemotherapy and anti-angiogenic therapy may provide a synergistic effect is outlined in Section 2.3.

2.1.1.3 Investigational products

Olaparib

A detailed description of the chemistry, pharmacology, efficacy, and safety of olaparib (AZD2281) is provided in the current Investigator Brochure (IB).

Olaparib (Lynparza®, AZD2281, KU-0059436) is a potent PARPi (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 anti-cancer agents.

Olaparib traps PARP at the sites of single-strand DNA damage and prevents their repair (Murai et al 2012). During replication the single-strand breaks with trapped PARP are converted to double -strand DNA breaks (DSBs). DSBs are normally repaired by a high fidelity process known as homologous recombination repair (HRR). In a cancer cell with a homologous recombination deficiency (HRD), the repair of DSBs cannot be effectively repaired resulting in preferential killing of cancer cells over normal cells. High-grade epithelial ovarian cancers have 2 principle phenotypic characteristics which may predict sensitivity to PARP inhibition. Firstly, epithelial ovarian cancers are highly responsive to platinum-based chemotherapy. Platinum agents induce DSBs, which require HRR for effective and accurate repair. Deficiencies in HRR may therefore result in the high degree of platinum sensitivity seen in high-grade serous ovarian cancer (Bowtell 2010). This is further supported by the evidence that sensitivity to platinum agents correlates with sensitivity to olaparib in ovarian cancer cell lines, as well as in cell lines of other tumour types where platinum-based chemotherapy is the SoC (Mason et al 2012). Secondly, high-grade serous ovarian cancer (HGSOC) is associated with the near universal presence of mutations in tumour protein 53 (TP53) and a pattern of genomic instability that is attributed to the absence of fully functional repair of DSBs (Bowtell 2010, Bowtell et al 2015).

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

The capsule formulation of olaparib is an approved maintenance treatment for *BRCA* mutated ovarian cancer in over 50 countries worldwide and as a monotherapy has been shown to produce significant improvements in PFS, compared with placebo in patients with platinum sensitive relapsed (PSR) *gBRCA* mutated ovarian cancer. Olaparib has also shown activity in advanced ovarian cancer patients who have been treated with ≥3 prior lines of chemotherapy. The tablet formulation of olaparib was first approved by the FDA in August 2017 for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. As of 01 August 2018, the tablet formulation of olaparib has received marketing approval in more than 30 countries (including the US, EU [via the centralised procedure], Japan and Canada) for the maintenance treatment of patients with PSR ovarian cancer. Furthermore, as of 01 August 2018, the olaparib tablet formulation is approved in the US, Japan and Canada for *gBRCAm* HER2-negative metastatic breast cancer.

Among studies of olaparib in patients with newly diagnosed advanced ovarian cancer, there are two large Phase III studies, both fully recruited and which investigated the role of olaparib maintenance treatment after first line chemotherapy in patients who carry *BRCA* mutation (SOLO1) and in combination with bevacizumab in patients who do or do not carry *BRCA* mutation (PAOLA-1).

Results from the SOLO1 study have shown a statistically significant and clinically meaningful improvement in PFS for olaparib monotherapy, compared with placebo in newly-diagnosed ovarian cancer patients who are *BRCAm* and is now approved for this indication in multiple regions including US and the EU. PAOLA-1 demonstrated significant benefit of olaparib maintenance in first-line ovarian cancer patients, with an improvement in mPFS of 22.1 months in the olaparib+bevacizumab arm compared with 16.6 months in the placebo+bevacizumab arm (hazard ratio = 0.59; CI 0.49-0.72, p<0.001).

Olaparib monotherapy is generally well tolerated; toxicity management guidelines for olaparib are provided in Section 8.4.6.1.

Durvalumab

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the current durvalumab IB/ Durvalumab (Imfinzi™) package insert.

Durvalumab (Imfinzi™) is a human monoclonal antibody (mAb) of the IgG 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with

programmed cell death protein 1 (PD-1) on T cells and cluster of differentiation 80 (CD80) on immune cells (IC). 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 mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumour elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (INF-γ) (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T cell dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's anti-tumour immune response by binding to PD-L1 and shifting the balance toward an anti-tumour 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 anti-cancer agents; toxicity management guidelines for durvalumab are provided in Annex to Protocol.

Durvalumab was approved in the US in February 2018 for the treatment of patients with Stage III non-small cell lung cancer (NSCLC) whose tumours are not able to be surgically removed (unresectable) and whose cancer has not progressed after treatment with chemotherapy and radiation (chemoradiation). In the EU, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for durvalumab for this NSCLC indication on 26 July 2018. European Medicines Agency (EMA) approved Durvalumab in NSCLC indication on 21 September 2018 through centralised procedure. As of 12 July 2019, durvalumab has been approved in 45 countries for NSCLC indication.

2.2 Study rationale

Poly (ADP-ribose) polymerase inhibitors (olaparib) and immune checkpoint inhibitors (durvalumab) are established cancer therapies and there is growing evidence that these therapies can be combined together and with the VEGF inhibitors (bevacizumab) to gain synergistic anti-tumour effects while minimising the potential for significant side-effects. The DUO-O study will assess the efficacy and safety of durvalumab and olaparib when added to SoC (platinum-based chemotherapy ± bevacizumab) in patients with newly diagnosed advanced ovarian cancer.

The SOLO1 study, investigating the efficacy and safety of maintenance treatment with olaparib vs placebo in patients with newly diagnosed *BRCAm* advanced ovarian cancer who

were in response to first line platinum based chemotherapy, has demonstrated a statistically significant and clinically meaningful improvement in PFS for olaparib compared with placebo. Given the results of SOLO1 and the subsequent approval of olaparib in patients with *BRCAm* newly-diagnosed ovarian cancer, this study has been redesigned to focus on the assessment of a potential clinical benefit in patients who do not carry a tumour *BRCA* mutation (non-*tBRCAm*).

The DUO-O study consists of 2 independent cohorts which are defined by the *tBRCAm* mutation status of the patients

The non-*tBRCAm* cohort

The proposed study design will allow non-*tBRCAm* patients to receive SoC platinum-based chemotherapy in combination with bevacizumab. Once chemotherapy is complete, patients will continue to receive bevacizumab in the maintenance setting for up to a total of 22 cycles (15 months), as per current SoC.

In addition to SoC, in order to improve clinical outcome, non-*tBRCAm* patients in this study will receive treatment with blinded durvalumab/placebo on a 3-weekly basis for the duration of the chemotherapy phase and as a maintenance treatment for up to a total of 35 cycles (24 months). Furthermore, these patients will receive oral olaparib/placebo as a maintenance therapy once they complete their chemotherapy phase.

The *tBRCAm* cohort (closed to recruitment November 2019)

Given the results of the SOLO1 study of olaparib as maintenance treatment in patients with newly-diagnosed advanced *BRCAm* ovarian cancer, to ensure that all patients who carry a *BRCA* mutation will receive optimal treatment, all *tBRCAm* patients in DUO-O will receive oral olaparib as a maintenance therapy once they complete their chemotherapy phase. These patients will be studied as a separate single arm, open-label cohort to investigate the potential benefit of adding durvalumab and olaparib treatment to current SoC platinum-based chemotherapy in combination with bevacizumab.

In the *tBRCAm* cohort, bevacizumab treatment is optional and can be administered per standard local practice; the rationale for this is based on the limited PFS improvement seen with bevacizumab in the subgroup of patients with HRRm patients in the GOG-218 study (Norquist et al 2018; see Section 2.1.1.1) and on data from subgroup analyses of Study NCI 8348 (see Section 2.3.2).

The clinical outcomes in the single arm cohort will be summarised descriptively and additional data will be provided from appropriate summaries of biomarker data.

2.2.1 Justification of study treatments

A detailed assessment of the clinical evidence of the combinations used in this study is provided in Section 2.3. The benefit of the combination of durvalumab and olaparib in patients with *gBRCA* mutated ovarian cancer shown by the MEDIOLA study (NCT02734004) suggests that the combination of olaparib and durvalumab when administered in the absence of chemotherapy in the treatment setting may be more effective than olaparib alone, suggesting synergistic activity.

The safety and efficacy of olaparib, durvalumab, and bevacizumab combination are being assessed in the MEDIOLA study, with no new safety signals being identified. This supports the use of the triplet combination of olaparib, durvalumab, and bevacizumab as a tolerable treatment option.

2.3 Background and clinical evidence to inform rational combinations in ovarian cancer

2.3.1 The combination of a PD-L1 inhibitor and chemotherapy

The presence and extent of CD8+ tumour infiltrating lymphocytes (TIL) or an immunoreactive gene expression profile (Hwang et al 2012; Cancer Genome Atlas Research Network 2011; Ovarian Tumor Tissue Analysis [OTTA] Consortium 2017) correlates with an improved prognosis in ovarian cancer, whereas immune evasion mechanisms such as T-regulatory cell infiltration and high PD-L1 expression are poor prognostic factors (Curiel et al 2004; Hamanishi et al 2015). As monotherapy, immune checkpoint inhibitors have demonstrated activity in ovarian cancer with response rates in the region of 10-15% for heavily pre-treated patients (Hamanishi et al 2015; Varga et al 2015) and therefore combining PD-L1 inhibitors with agents aimed at increasing the immunogenicity of tumours is a rational approach for the treatment of ovarian cancer. In a number of models, chemotherapy has been shown to alter the immune profile of tumours and their microenvironment, primarily through induction of immunogenic cell death, stimulator of interferon genes (STING) activation and resulting type I IFN production (Mouw et al 2017). These and other signalling pathways may also result in upregulation of PD-L1 expression, increasing antigen presentation and expansion of neoantigen repertoires (Mouw et al 2017), all of which have the potential to increase clinical responses to immune checkpoint inhibition.

In a first-in-human study of durvalumab monotherapy (Study 1108; NCT01693562), CCI patients with ovarian cancer were treated with durvalumab 10mg/kg every 2 weeks, which showed minimal activity. The ovarian patients recruited were late line and included platinum resistant patients.

Data from the CheckMate 153 trial in NSCLC suggests that longer duration of exposure to a PD-1/PD-L1 inhibitor is associated with greater efficacy without cumulative toxicities (Spigel

et al 2017). In addition, evidence from the durvalumab PACIFIC study (NCT02125461) suggests that in adjuvant setting post chemo-radiotherapy, NSCLC patients gain benefit beyond their treatment duration and no new safety signals were observed with durvalumab after 6 months of treatment. As such, no new safety signals are expected beyond 1 year of treatment with durvalumab. Given the aggressive nature and poor prognosis of patient presenting with advanced stage ovarian cancer, in order to maximise the benefit to patients, the durvalumab treatment is set to up to 35 cycles (24 months). This is in line with the approved treatment duration of other PD-1/PD-L1 inhibitors in a metastatic setting which is either up to 24 months or until disease progression (Keytruda USPI 2018; Opdivo USPI 2017; Imfinzi USPI 2018). In addition, patients with macroscopic residual stable disease at the end of 24 months, will have the option to continue durvalumab until disease progression at the discretion of the Investigator.

A Phase I/II study of carboplatin and paclitaxel in combination with durvalumab (NCT02726997) is ongoing in patients with ovarian cancer; for the majority of patients, the side effects have been primarily due to the chemotherapy (neutropenia, anaemia). There are several studies of other PD-1 or PD-L1 inhibitors in combination with carboplatin and paclitaxel that are either published or currently recruiting. A Phase III trial of avelumab in combination with carboplatin and paclitaxel for the first line treatment of ovarian cancer (JAVELIN100; NCT02718417) terminated early following results from a planned interim analysis for futility (Ledermann et al 2020). The Phase III trial of atezolizumab in combination with carboplatin, paclitaxel and bevacizumab has completed recruitment and is in follow-up (IMagyn050; NCT03038100). The primary PFS analysis was recently reported and did not reach statistical significance, however the study remains in follow-up in order to assess the dual primary endpoint of OS (Moore et al 2020).

In a Phase Ib study in non small-cell lung cancer (NSCLC), nivolumab 10 mg/kg, carboplatin AUC6, paclitaxel 200 mg/m^2 and bevacizumab 15 mg/m^2 Q3W has been demonstrated to be safe and tolerable with no dose-limiting toxicities observed (Kanda et al 2016; Japanese Pharmaceutical Information Center Clinical Trials Information [JapicCTI]-132071). In addition, the Phase III study of atezolizumab in combination with carboplatin, paclitaxel and bevacizumab is reported to show improved PFS benefit over carboplatin, paclitaxel and bevacizumab alone as first line treatment for NSCLC, with safety of the combination appearing consistent with the known safety profile of the individual medicines and no new safety signals identified (Reck et al 2017; NCT02366143).

2.3.2 The combination of a PARP inhibitor and an anti-angiogenic agent

The combination of PARPi with anti-angiogenic treatment such as bevacizumab also has the potential for a synergistic effect by tumour induced hypoxia which may lower the expression of DNA damage response genes and induce a synthetic “HRD phenotype” thereby increasing

sensitivity to PARP inhibitors (Hegan et al 2010). An increase in metabolic stress as caused by hypoxia would also restrict the potential to generate nucleotides and co-factors to drive DNA repair. Subsequently the combination of VEGF inhibitors with olaparib would further impair the ability of the tumour cell to tolerate an increase in DNA damage. In addition, preclinical studies have shown that PARP inhibition reduces angiogenesis in vivo and VEGF mediated cell migration in vitro (Tentori et al 2007), suggesting that combined PARP and VEGF inhibition could significantly impair tumour angiogenesis.

A Phase I study of the combination of olaparib and bevacizumab has been conducted in patients with advanced solid tumours, not amenable to surgery or radiation therapy with curative intent (Dean et al 2012; NCT00710268).

There were insufficient data to assess the potential for bevacizumab to alter the steady state exposure to olaparib 100 mg bd as PK sampling to determine the effect of olaparib on exposure to bevacizumab was not included in the study. However, whilst patient numbers were small, exposure appeared to be unaffected by the co-administration of bevacizumab for both 200 mg and 400 mg bd. There was no evidence to suggest that a PK interaction occurred when olaparib was administered in combination with bevacizumab.

No DLTs were observed with olaparib at 100, 200 or 400 mg bd. No unusual or unexpected AEs were observed following treatment with olaparib and bevacizumab, with no evidence to suggest that either drug had increased the severity or intensity of AEs commonly associated with the other.

As described in Section 2.1.1.1, the efficacy of bevacizumab in ovarian cancer patients may be affected by the *BRCAm* status of the patient. The PFS benefit of bevacizumab plus chemotherapy in the GOG218 was higher for the non-HRRm subgroup compared with the HRRm subgroup (Norquist et al 2018). A subgroup analysis from the NCI 8348 study showed no significant improvement in PFS when cediranib (a vascular endothelial growth factor receptor [VEGFR] tyrosine kinase inhibitor [TKI]) was added to olaparib compared with olaparib alone in patients with *BRCAm* platinum sensitive relapsed (PSR) ovarian cancer, in contrast to the effect seen with the combination of the 2 agents in patients with non-*BRCAm* ovarian cancer (Liu et al 2014).

A Phase III trial of the combination of olaparib and bevacizumab in patients with ovarian cancer (PAOLA-1; GINECO-OV125b, ENGOT-ov25, NCT02477644 investigated olaparib (300 mg bd) in combination with bevacizumab (15 mg/kg Q3W), as maintenance treatment after response to first line chemotherapy in patients with newly diagnosed advanced ovarian cancer. PAOLA-1 met its primary objective, demonstrating an improvement in PFS by investigator assessment in the ITT population treated with olaparib/bevacizumab compared with placebo/bevacizumab. The PFS improvement was statistically significant and clinically

relevant, as evidenced by the magnitude of effect: a 41% reduction (hazard ratio = 0.59; 95% CI, 0.49, 0.72, p < 0.0001; median PFS 22.1 months olaparib vs 16.6 months placebo), in the risk of disease progression or death for olaparib vs placebo, when added to standard of care bevacizumab first-line maintenance treatment (Ray-Coquard et al 2019). The safety profile of the study was consistent with the known toxicities of olaparib and bevacizumab with no safety signals identified. Pre-specified exploratory subgroup analyses of PFS by HRD subgroups identified that the greatest PFS benefit was observed in patients with HRD-positive status, defined as GIS ≥ 42 and/or *tBRCAm* using the Myriad myChoice® HRD test (HRD-positive: hazard ratio = 0.33; 95% CI: 0.25, 0.45). Similarly, a comparable, clinically meaningful benefit was also observed in the HRD-positive status patients excluding the *tBRCAm* subgroup, indicating that the effect was not driven by the *tBRCAm* population (hazard ratio = 0.43; 95% CI: 0.28 to 0.66).

The results from PAOLA-1 have led to the recent approval in the US and EU of the combination of olaparib and bevacizumab in patients with HRD-positive newly-diagnosed ovarian cancer in the maintenance treatment setting, and established HRD status as an important and clinically relevant biomarker in first-line, advanced ovarian cancer patients treated with carboplatin/paclitaxel and bevacizumab.

Olaparib has also been studied in combination with another anti-angiogenic agent, cediranib (a potent small molecule VEGF receptor tyrosine kinase inhibitor of all three VEGF receptors [VEGFR-1, -2 and -3]) in ovarian cancer.

The results of the randomised, Phase II study (NCT01116648) of olaparib in combination of cediranib vs olaparib alone for patients with PSR ovarian cancer regardless of their *BRCA* status demonstrated:

- Median PFS was 17.7 months for the women treated with cediranib plus olaparib compared with 9.0 months for those treated with olaparib monotherapy (hazard ratio= 0.42, 95% CI 0.23, 0.76; p=0.005).
- Subgroup analyses from this study have shown that non-*gBRCA* mutated patients showed the greatest benefit with the addition of cediranib to olaparib.
- Subgroup analysis of PFS showed a greater benefit for the combination of cediranib plus olaparib vs olaparib alone in patients without *gBRCA* mutations (combination versus monotherapy: 16.5 versus 5.7 months; p=0.008) compared with patients with *gBRCA* mutations (combination versus monotherapy: 19.4 versus 16.5 months, p=0.16) (Liu et al 2014). This was confirmed in a later analysis; in patients without *gBRCA* mutations the combination showed significant improvement versus olaparib monotherapy (23.7 versus 5.7 months; p=0.002; Liu et al 2017).
- The safety profile for the combination was consistent with what would be expected with either drug with no new safety signals identified.

- The OS in women both with, and without *gBRCA* mutations with the combination was numerically greater compared to olaparib monotherapy (for non-*gBRCA* mutated: 37.8 versus 23.0 months, p=0.074; for *gBRCA* mutated: 44.2 versus 40.1 months, p=0.55; Liu et al 2017).

A Phase III trial is currently ongoing to confirm the benefit of the combination of cediranib plus olaparib vs SoC platinum based chemotherapy in patients with PSR ovarian cancer (NCT02446600; NRG-GY004).

2.3.3 The combination of a PD-L1 inhibitor and an anti-angiogenic agent

Given the importance of angiogenesis for immune cell trafficking and maintenance of the tumour microenvironment it is plausible that the mechanisms that control angiogenesis could impact the immune system. In addition to its role in angiogenesis, VEGF modulates anti-tumour immunity on multiple levels including promotion and expansion of inhibitory immune cell subsets, such as regulatory T cells and myeloid-derived suppressor cells, suppression of dendritic cell maturation, mitigation of effector T cell responses, and alteration of lymphocyte development and trafficking (Ott et al, 2015; Motz and Coukos, 2013).

Preclinical data suggest that simultaneous blockade of PD-1 and VEGFR-2 has a synergistic effect on reducing tumour growth in vivo (Yasuda et al 2013). Another study has shown that VEGF-A produced in the tumour microenvironment enhances expression of PD-1 and other inhibitory checkpoints involved in CD8+ T cell exhaustion, which could be reverted by anti-angiogenic agents targeting VEGF-A (Voron et al 2015). It has also been shown that PD-L1 expression is upregulated under hypoxia in some cancer cell lines, through a hypoxia-inducible factor dependent mechanism (Barsoum et al 2014).

While the interplay of PD-L1 and VEGF pathways are to be fully elucidated, these studies support that a synergistic anti-tumour effect on dual blockade of PD-L1 and VEGF pathways is possible (Wallin et al 2016). Modulating both the immunosuppressive microenvironment with PD-L1 blockade (eg, mAbs such as durvalumab and atezolizumab) in combination with VEGFR inhibitors may provide a unique therapeutic strategy, particularly in targeting aggressive tumours. Several studies are already underway in evaluating the combination of bevacizumab (VEGFR mAb) with atezolizumab (PD-L1 mAb) in patients with ovarian cancer (NCT02839707, NCT02659384, NCT02891824, and NCT03038100).

The combination of durvalumab and bevacizumab is currently being evaluated in 2 clinical studies. The first is a Phase II study in glioblastoma (NCT02336165) where the combination of bevacizumab and durvalumab is being administered with and without concurrent radiation. The second is a Phase 1 study in advanced human epidermal growth factor receptor 2 (HER2) breast cancer (NCT02802098). Both studies are currently ongoing, no safety concerns are reported for the combination.

2.3.4 The combination of a PARP inhibitor and a PD-L1 inhibitor

The potential synergism of combining PARP inhibitor and PD-L1 is based on the hypothesis that pharmacological inhibition of PARP by olaparib will result in enhanced immunogenicity which can be further enhanced with an immune checkpoint inhibitor such as durvalumab. This could occur through a number of mechanisms, such as increased production of cytokines and chemokines that have the potential to promote antitumour immunity, upregulation of surface receptors which render tumour cells more visible to detection by cytotoxic T cells and death of tumour cells and release of antigen, that may help to promote antigen presentation and immune priming (Chatzinikolaou et al 2014; Kroemer et al 2013). This hypothesis is supported by preclinical studies in mouse models of cancer, demonstrating that administration of a PARP inhibitors to sensitive tumour types resulted in increased T cell infiltration and immune activation within tumours (Higuchi et al 2015). This is the basis for the ongoing MEDIOLA study (NCT02734004). As of March 2018, nearly 200 patients have been treated with olaparib and durvalumab in the Phase I and Phase II components of the MEDIOLA and National Cancer Institute (NCI) studies described in the following sections (77 of whom had ovarian cancer).

Ongoing Phase I/II study (MEDIOLA Study; Study D081KC00001; NCT02734004)

MEDIOLA is an ongoing Phase I/II open-label, multicentre study to evaluate the safety, tolerability, PK, and anti-tumour activity of durvalumab in combination with olaparib in patients with advanced solid tumours, including ovarian, breast, small cell lung and gastric cancers. Patients are PARPi and immunotherapy-naïve. Patients were enrolled concurrently into 4 exploratory cohorts, which included patients with relapsed small-cell lung cancer (SCLC), *gBRCA* mutated metastatic HER2 negative breast cancer, *gBRCA* mutated PSR ovarian cancer, and gastric cancer.

The olaparib plus durvalumab dose is olaparib tablet 300 mg bd and durvalumab 1500 mg every 4 weeks (Q4W).

As of March 2018, a total of 148 patients have been treated with olaparib plus durvalumab (34 with ovarian cancer [*gBRCA*]; 34 with HER2 negative breast cancer; 40 with small cell lung cancer and 40 with gastric cancer) in the Phase II component of the study.

Preliminary efficacy data in the ovarian cohort for the olaparib/durvalumab combination is presented in Table 5 (Drew et al 2018). With the caveat of small numbers, the ORR of 72% with the olaparib plus durvalumab in PSR *gBRCA* mutated ovarian cancer patients compares favourably with data reported for olaparib alone for which an ORR of 48% is reported in a similar patient population of PSR *gBRCA* mutated ovarian cancer patients (from a pooled analysis based on 6 olaparib monotherapy trials [Matulonis et al 2016]).

Table 5 Best ORR MEDIOLA Ovarian Cohort by prior line of chemotherapy (n=32)

RECIST Response	1 prior (Second line)	2 prior (Third line)	3 + prior (Fourth line)	All lines
ORR	77% (10/13)	67% (6/9)	70% (7/10)	72% (23/32)
95%CI	(46%, 95%)	(30%, 93%)	(35%, 93%)	(53%, 86%)

Note: Based on preliminary data

Abbreviations: CI = Confidence interval; ORR = Objective response rate; RECIST = Response Evaluation Criteria in Solid Tumours

The safety for the combination has been consistent with what would be expected for either drug, with no unexpected safety signals identified. The only death in this cohort has been attributed to disease progression. Safety of the combination in patients with ovarian cancer has been consistent with that observed in the other cohorts in the study.

Two new cohorts for patients with PSR *gBRCAwt* ovarian cancer are now added to the MEDIOLA trial. One cohort is testing the triplet combination of olaparib plus durvalumab plus bevacizumab in 30 PSR *gBRCAwt* ovarian cancer patients. The safety and tolerability of the triplet combination was assessed after 10 patients were enrolled and followed for at least 4 weeks. The data were reviewed by the DUO-O IDMC prior to patients starting the triplet maintenance treatment in this Phase III study. The IDMC did not identify any safety concerns impacting the conduct of the DUO-O study. Recently reported results for MEDIOLA (Drew et al 2020) in patients with PSR *gBRCAwt* ovarian cancer showed that at the data cut-off (13 February 2020), 22% of patients in the olaparib plus durvalumab (doublet) arm and 42% of patients in the olaparib plus durvalumab plus bevacizumab (triplet) arm remained on treatment. In the triplet arm, DCR at 24 weeks was 77.4% (90% CI: 61.7%, 88.9%), with a median PFS of 14.7 months (95% CI: 10.0 months, 18.1 months). Confirmed ORR was 77.4% (95% CI: 58.9%, 90.4%), and median DOR was 11.1 months (inter-quartile range [IQR]: 7.4 months to 16.4 months). In the doublet arm, DCR at 24 weeks was 28.1% (90% CI: 15.5%, 43.9%), with a median PFS of 5.5 months (95% CI: 3.6 months, 7.5 months). Confirmed ORR was 31.3% (95% CI: 16.1%, 50.0%), and median DOR was 6.9 months (IQR: 5.4 months to 11.1 months).

Ongoing Phase I/II NCI Study (Study 15-C-0145; NCI-2015-01401, 344406, P141726; NCT02484404: NCI study; olaparib plus durvalumab) has several arms; including olaparib plus durvalumab, durvalumab plus cediranib, and the triplet combination. Part 1 was a dose-escalation that evaluated the safety and tolerability of each combination. Part 2 will evaluate the anti-tumour activity of the recommended Phase II dose of each combination. As of 8 November, 2017, a total of [redacted] patients have been treated with olaparib plus durvalumab

([redacted] with female cancers [[redacted] ovarian and [redacted] breast cancer]; [redacted] with prostate cancer; [redacted] with small cell lung cancer and [redacted] with NSCLC).

This section presents information on the olaparib plus durvalumab arm. The patient population included predominantly heavily pre-treated patients with various gynaecological cancers, most of whom did not carry a *BRCA* mutation. For the combination with olaparib, Part 1 evaluated the safety and tolerability of 3 dose schedules. The recommended dose for the olaparib plus durvalumab combination from Part 1 has been determined as durvalumab 1500 mg fixed dose Q4W with olaparib 300 mg bd continuous dosing. This dose was based on data from a total of [redacted] patients treated with the olaparib plus durvalumab combination ([redacted] patients with HGSOC and [redacted] patients with triple negative breast cancer). This dose level is being taken forward in a larger cohort (dose expansion) to confirm activity (ORR).

Two of 12 patients in Part 1 who received durvalumab plus olaparib had durable partial responses (PRs: ≥15 months and ≥11 months). Eight patients had SD (Lee et al, 2017). Response to therapy was independent of *BRCA* mutation status and PD-L1 expression. No dose-limiting toxicities were recorded with durvalumab plus olaparib. The AEs reported were generally mild to moderate in severity and consistent with the known profiles of olaparib and/or durvalumab.

2.3.5 Clinical evidence for the triplet therapy (a PD-L1 inhibitor, an anti-angiogenic and a PARP inhibitor)

PARP inhibitors, immune checkpoint inhibitors, and VEGF inhibitors have an established role as cancer therapies, and there is growing evidence that these therapies can be combined to gain synergistic anti-tumour effects while minimizing the potential for significant side-effects. To further improve the efficacy seen with the olaparib plus durvalumab combination in the MEDIOLA study and expand the patient population to non-*BRCA* carriers, the addition of a VEGF-inhibitor is warranted. Recently reported results from MEDIOLA for triplet therapy is described in Section 2.3.4 (Drew et al 2020).

The triplet combination of olaparib plus durvalumab plus cediranib is currently also being tested in the ongoing Phase I/II NCI sponsored study (NCT02484404) in patients with variety of heavily pre-treated gynaecological cancers, described in Section 2.3.4. Preliminary data have shown partial responses in 3 of 9 patients, with a further 4 patients having SD; safety data that were generally consistent with the known profiles of the 3 agents (Lee et al, 2017).

The Phase II expansion study of the triplet therapy (olaparib plus durvalumab plus cediranib) in ovarian cancer is ongoing.

2.4 Benefit/risk assessment

Based upon the available non-clinical, clinical efficacy and safety data, and the limited long-term efficacy provided by the currently available treatment options to patients, the investigation of the potential therapeutic efficacy of the combination of the current SoC treatments in combination with durvalumab or durvalumab plus olaparib in patients with newly diagnosed advanced high grade epithelial ovarian cancer is acceptable, and the overall benefit/risk assessment supports the proposed study design.

All three targeted agents olaparib, durvalumab and bevacizumab have regulatory approvals and well characterised safety profiles. All three agents have been extensively studied in ovarian cancer and other tumour types, and in combination regimens. No major overlapping toxicities are expected from this triplet regimen.

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 of olaparib are non-overlapping; olaparib has also previously been combined with bevacizumab without significant drug-drug interaction. Pneumonitis is considered to be the most important potential exception. The management guidelines for pneumonitis (see Section 8.2.5.3) integrate the guidance provided for these two agents.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of durvalumab and olaparib may be found in the respective and current IBs. More detailed information about the known and expected benefits and risks of the SoC chemotherapies and bevacizumab can be found in the respective Package Inserts/Summaries of Product Characteristics.

See Section 9.5.1 and Appendix A for information regarding the Data Monitoring Committee.

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

3. OBJECTIVES AND ENDPOINTS

3.1 Primary objective

Primary objective:	Endpoint/variable:
To determine the efficacy of durvalumab and olaparib assessed by PFS in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	PFS by investigator assessment using modified RECIST 1.1 – time from randomisation to first progression or death. This will be assessed via: • Determining the efficacy of durvalumab in combination with platinum based chemotherapy and bevacizumab and continued as maintenance in combination with bevacizumab and olaparib versus SoC platinum based chemotherapy in combination with bevacizumab in the following populations: ° non-*tBRCAm* HRD positive population ° non-*tBRCAm* ITT population.

Abbreviations: HRD = homologous recombination deficiency; ITT = intention to treat; *tBRCAm* = Presence of a deleterious or suspected deleterious mutation in tumour breast cancer sensitivity gene; PFS = Progression free survival; RECIST = Response Evaluation Criteria In Solid Tumours; SoC = Standard of care

3.2 Secondary objectives

Secondary objectives:	Endpoint/variable:
To determine the efficacy of durvalumab assessed by PFS in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	PFS by investigator assessment using modified RECIST 1.1 – time from randomisation to first progression or death. This will be assessed via: • Determining the efficacy of durvalumab in combination with platinum-based chemotherapy and bevacizumab and continued as maintenance in combination with bevacizumab versus SoC platinum-based chemotherapy in combination with bevacizumab in the non-*tBRCAm* ITT population
To determine the efficacy of durvalumab and olaparib assessed by OS in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	OS – time from date of randomisation to death This will be assessed via: ° Arm 3 vs Arm 1 in non-*tBRCAm* HRD positive population ° Arm 3 vs Arm 1 in non-*tBRCAm* ITT population ° Arm 2 vs Arm 1 in non-*tBRCAm* ITT population.

Secondary objectives:	**Endpoint/variable:**
To assess the efficacy of durvalumab and olaparib in terms of PFS2, ORR, ORR pre-surgery in IDS group, duration of response, TFST, TSST and TDT in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	• Time from date of randomisation to second progression by investigator assessment of radiological, clinical or CA125 progression or death (PFS2) • ORR (CR + PR) by investigator assessment by modified RECIST 1.1 ° in all patients with evaluable disease at baseline ° prior to surgery in those patients planned to have IDS with evaluable disease at baseline. • Duration of response • TFST • TSST • TDT All endpoints will be assessed in the populations described for PFS and OS.
To determine the effects on HRQoL, global health status and ovarian cancer symptoms of the combination of durvalumab and olaparib in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	• Changes in the subscales from baseline of the EORTC-QLQ-C30; and EORTC-QLQ-OV28 questionnaires • Health state utility derived from the HRQoL instrument, the EuroQOL EQ5D-5L • Q-TwiST • QAPFS All endpoints will be assessed in the populations described for PFS and OS.
To determine the effects on pCR for the combination of durvalumab with platinum-based chemotherapy and bevacizumab in the first line treatment of non-*tBRCAm* patients with newly diagnosed advanced ovarian cancer.	• Proportion of patients with pCR in patients undergoing IDS

Secondary objectives:	Endpoint/variable:
• To characterize the PK and immunogenicity of durvalumab in combination with bevacizumab and olaparib • To determine olaparib plasma concentrations via sparse sampling for population PK analyses.	Only in non-*tBRCAm* patients with primary cytoreductive surgery • Serum concentrations of durvalumab and plasma concentrations of olaparib (samples to be taken in the non-*tBRCAm* cohort only) • ADA to durvalumab
• To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of *tBRCAm* patients with newly diagnosed advanced ovarian cancer.	OS, PFS, PFS2, ORR, ORR pre-surgery in IDS group, duration of response, TFST, TSST, TDT EORTC-QLQ-C30 and EORTC-QLQ-OV28, EQ5D-5L, Q-TwiST, QAPFS, proportion of patients with pCR in patients undergoing IDS

Abbreviations: ADA = Anti-drug antibody; CA125 = Cancer antigen 125; CR = Complete response; EORTC-QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ5D-5L = EuroQoL five dimensions, five level health state utility index; HRQoL = health-related quality of life; IDS = Interval debulking surgery; ORR = Objective response rate; OS = Overall Survival; pCR = Pathological complete response; PFS = Progression free survival; PFS2 = Time to second progression; PK = Pharmacokinetic; PR = Partial response; QAPFS = Quality-adjusted progression-free survival; Q-TwiST = Quality-adjusted time without symptoms of disease or toxicity; RECIST = Response Evaluation Criteria In Solid Tumours; SoC = Standard of care; *tBRCAm* = Presence of a deleterious or suspected deleterious mutation in tumour breast cancer sensitivity gene; TDT = Time to discontinuation or death; TFST = Time to first subsequent therapy; TSST = Time to second subsequent therapy.

3.3 Safety objectives (applicable to all patients)

Safety objectives:	Endpoint/variable: All patients
• To evaluate the safety and tolerability of the combination of durvalumab and bevacizumab given in combination with platinum based chemotherapy and continued as maintenance in patients with newly diagnosed advanced ovarian cancer • To evaluate the safety and tolerability of durvalumab in combination with platinum based chemotherapy+/- bevacizumab and continued as maintenance in combination with olaparib +/-bevacizumab in patients with newly diagnosed advanced ovarian cancer	• AEs / SAEs, physical examination, vital signs including BP, pulse, ECG and laboratory findings including clinical chemistry / haematology parameters • imAEs – given the intended mechanisms of action of durvalumab, particular attention will be given to AEs that may follow enhanced T-cell activation, or other imAE

Abbreviations: AE = Adverse event; BP = blood pressure; ECG = Electrocardiogram; imAEs = Immune-mediated adverse events; SAEs = Serious adverse events.

3.4 Exploratory objectives (applicable to all patients)

Exploratory objectives:	Endpoint/variable: All patients
• To determine the efficacy of olaparib and durvalumab in newly diagnosed advanced ovarian cancer by assessment of relapse free survival in patients who have NED/CR at the end of chemotherapy CT scan.	Relapse free survival for patients who have NED/CR at the end of chemotherapy: time from allocation/randomisation to disease progression
• To determine the efficacy of olaparib and durvalumab in newly diagnosed advanced ovarian cancer by assessment of the proportion of patients who have NED at 15, 24 and 48 months after initiation of treatment.	Proportion of patients who have NED at 15, 24 and 48 months after allocation/randomisation
To explore the impact of treatment and disease state on health state utility and to explore the impact of treatment and disease on resource use	Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay
To assess patient reported treatment-related side effects of olaparib, durvalumab and bevacizumab	Items selected from the PRO-CTCAE item bank (see Section 8.1.2.2)
To assess patients' overall impression of the severity of their cancer symptoms	PGIS
To further evaluate tumour HR deficiency status as candidate predictive biomarkers of olaparib and durvalumab in newly diagnosed advanced ovarian cancer patients[a].	May include, but is not limited to the following measurements within the tumour: • Mutation status of HRR genes, HRD status CCI [redacted]
To evaluate additional candidate predictive biomarkers of olaparib and durvalumab in newly diagnosed advanced ovarian cancer patients[a].	May include, but is not limited to: • PD-L1, CCI [redacted] • CCI [redacted]
To further assess the efficacy of treatment through longitudinal analysis of blood samples collected at regular intervals on study[a].	May include but is not limited to • CCI [redacted] response to treatment.
To explore whether resistance mechanisms to treatment can be identified through analysis of tumour and blood samples – archival tumour sample and blood samples at baseline and on progression (tumour sample optional on progression) [a].	Analysis and outcome variables yet to be defined but may include molecular analysis of CCI [redacted].
Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored blood or	Analysis and outcome variables yet to be defined.

Exploratory objectives:	**Endpoint/variable: All patients**
archival tumour samples that were mandatory for entry onto the study or on optional blood or tumour biopsy samples collected during the course of the study[a].	
To collect and store DNA according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional) [a].	To identify pharmacogenetic correlates for the response to treatment through the retrospective analysis of DNA extracted from an optional blood sample.

Abbreviations: CCI [redacted]; CD = Cluster of differentiation; CR = complete response; CT = Computed tomography; HR = Homologous recombination; HRR = Homologous recombination repair; HRD = homologous recombination deficiency; NED = No evaluable disease; PD L1 = Programmed death ligand-1; PGIS = Patient global impression of severity of cancer symptoms; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; TIL = Tumour-infiltrating lymphocytes.

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

4. STUDY DESIGN

4.1 Overall design

The DUO-O study will assess the efficacy and safety of durvalumab and olaparib when added to SoC in patients with newly diagnosed advanced ovarian cancer. The study consists of 2 independent cohorts which are defined by the breast cancer sensitivity gene mutation status, based on testing of tumour tissue (*tBRCAm* status*)* of the patients:

- **Non-*tBRCA*m cohort**: Patients who do not have a *tBRCA* mutation will be allocated to the non-*tBRCAm* cohort and be further randomised to 1 of 3 double-blind, placebo-controlled treatment arms to receive SoC plus investigational treatments as described in Section 1.1.3.
- ***tBRCAm* cohort**: Patients who have a *tBRCA* mutation will be allocated to a single arm cohort to assess the safety and potential additional clinical benefit of durvalumab added to SoC and olaparib.
  Note: The *tBRCAm* cohort was closed to recruitment as of November 2019 as the 150 patient allocation was reached.

This study will allocate/randomise approximately 1254 patients with newly-diagnosed advanced ovarian cancer patients. In addition, a China cohort of approximately 120 non-*tBRCAm* patients with newly-diagnosed advanced ovarian cancer patients will be randomised. If necessary, the China cohort will continue recruiting non-*tBRCAm* patients after recruitment to the Global population closes at approximately 1104 patients in the non-*tBRCAm* cohort. All patients must sign the (Pre-screen) informed consent form (ICF). The Pre-screen ICF provides consent for provision of tumour tissue sample and for prospective *tBRCAm* status analysis. If a patient has completed screening and meets all eligibility criteria, she will then receive Cycle 1 of platinum-based chemotherapy (carboplatin area under the plasma concentration-time curve [AUC] 5 or 6 and paclitaxel 175mg/m^2 Q3W), while the determination of central *tBRCAm* status is ongoing. This is the study 'run-in' period.

- Patients who have had primary upfront surgery must receive Cycle 1 of chemotherapy within a maximum of 8 weeks of upfront primary surgery; it is recommended that Cycle 1 starts a minimum 3 weeks after the surgery, however, Cycle 1 can also start as soon as their surgical wound is fully healed.
- Cycle 1 of chemotherapy may also include bevacizumab, according to local practice. In line with the European Summary of Product Characteristics (SmPC) and the US prescribing information it is recommended that bevacizumab should not be administered within the first 28 days following major surgery. If bevacizumab is not routinely used by the site, then bevacizumab should be started at Cycle 2.
- Once a patient's *tBRCAm* status is known, based on central *tBRCA* testing (and prior to Day 1 of Cycle 2), patients will be allocated to either the *tBRCAm* cohort or the

non-*tBRCAm* cohort (provided the patient continues to meet the study inclusion and exclusion criteria listed in Sections 5.1 and 5.2).

- Should the central *tBRCA* assay fail to determine the presence or absence of a deleterious/suspected deleterious mutation prior to the start of Cycle 2, due to technical failure or delay in testing the patient cannot continue on the study, even if she fulfils all other eligibility criteria: these patients will be withdrawn and receive SoC treatment outside the study.

Patients should have completed the first cycle of chemotherapy as part of the study run-in period as described in Section 1.1.2.1. Prior to Day 1 of Cycle 2 of platinum-based chemotherapy, patients with a valid central *tBRCAm* test result will be treated as follows:

Non-*tBRCAm* cohort

Approximately 1104 patients with no deleterious/suspected deleterious mutations in *BRCA1*, and *BRCA2* will be randomised 1:1:1 to receive a further 5 cycles of platinum-based chemotherapy (in combination with bevacizumab followed by bevacizumab maintenance for up to a total of 22 cycles [15 months] of treatment). For the China cohort, approximately 120 non-*tBRCAm* patients randomised (1:1:1) from sites in China will be required. If necessary, the China cohort will continue recruiting patients after recruitment to the Global population closes at approximately 1104 patients. Investigational treatments will be given as specified below:

(i) Arm 1 (SoC): Patients in Arm 1 will receive saline IV Q3W as a placebo for durvalumab from Day 1 of Cycle 2 for up to a total of 35 cycles (24 months) of treatment. At the end of chemotherapy, patients will also receive placebo tablets, matched to olaparib for up to a total of 24 months.

(ii) Arm 2: Patients in Arm 2 will receive durvalumab 1120 mg Q3W from Day 1 of Cycle 2 for up to a total of 35 cycles (24 months) of treatment. At the end of chemotherapy, patients will also receive placebo tablets, matched to olaparib for up to a total of 24 months.

(iii) Arm 3: Patients in Arm 3 will receive durvalumab 1120 mg Q3W from Day 1 of Cycle 2 for up to a total of 35 cycles (24 months) of treatment. At the end of chemotherapy, patients will also receive olaparib tablets, 300 mg twice daily (bd) for up to a total of 24 months.

NOTE: Patients who have completed 22 cycles of durvalumab/placebo, are permitted to restart durvalumab/placebo in order to receive up to a total of 35 cycles, providing no more than 12 weeks have elapsed between the last durvalumab/placebo dose and treatment restart, and only if deemed appropriate by the Investigator.

The randomisation scheme will be stratified according to:

- Timing and outcome of cytoreductive surgery: no macroscopic residual disease after upfront primary surgery vs all others (macroscopic residual disease after upfront primary surgery OR planned IDS).
- Geographic region: North America vs Europe vs RoW.

***tBRCAm* cohort**
Note: The *tBRCAm* cohort was closed to recruitment as of November 2019 as the 150 patient allocation was reached.

Approximately 150 patients with deleterious/suspected deleterious mutations in *BRCA1* or *BRCA2* as identified by central *tBRCA* testing will be allocated to a single arm cohort. Once olaparib becomes available as part of clinical practice for first-line maintenance treatment of ovarian cancer in a country, then this cohort may be closed to further recruitment within that country. Patients will receive a further 5 cycles of platinum-based chemotherapy (and optional bevacizumab for up to a total of 22 cycles [15 months] of treatment according to standard local practice). Investigational treatments will be given as specified below:

(i) Durvalumab 1120 mg Q3W from Day 1 of Cycle 2 for up to a total 35 cycles (24 months) of treatment. At the end of chemotherapy, patients will also receive olaparib tablets, 300 mg twice daily (bd) for up to a total of 24 months

NOTE: Patients who have completed 22 cycles of durvalumab, are permitted to restart durvalumab in order to receive up to a total of 35 cycles, providing no more than 12 weeks have elapsed between the last durvalumab dose and treatment restart, and only if deemed appropriate by the Investigator.

Note applicable to all patients: bevacizumab dosing may be achieved via use of the originator product (Avastin®) or a single one of the FDA-, EMA- or PMDA-approved biosimilars. For the purposes of this CSP, the generic name bevacizumab is used throughout and taken to apply to either Avastin or a single one of the FDA-, EMA- or PMDA-approved biosimilars (for China only, a CDE-approved biosimilar also may be used).

Once patients have been discontinued from all study treatment(s), other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. No cross over to olaparib or durvalumab is permitted within the study setting.

The study will continue until the last OS analysis (Section 9.5). This will be the end of the study, and after database lock all patients in the non-*tBRCAm* cohort will be unblinded.

Patients who are receiving active treatment can either choose to discontinue treatment or where the investigator believes patients are gaining clinical benefit; patients may continue to receive active treatment, but outside of the study setting. All patients will receive follow up care in accordance with standard local clinical practice.

For patients who do continue to receive treatment beyond the time of this data cut-off, Investigators will continue to report all SAEs to AstraZeneca Patient Safety until the end of the follow-up period, post treatment discontinuation, in accordance with Section 8.4.1 (Reporting of SAEs). If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the one or more of the products used in this study, the Investigator should notify AstraZeneca, Patient Safety. Additionally as stated in Section 8.3.3 (Follow-up of Aes and SAEs), any SAE or non-serious AE that is ongoing at the time of this data cut-off, must be followed up by the Investigator for as long as medically indicated.

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

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

4.2 Scientific rationale for study design

The scientific rationale for the 2 cohort design and the choice of study treatments is provided in Section 2.2. The prospective, placebo-controlled, double-blind design used in the non-*tBRCAm* cohort was selected to provide a rigorous assessment of a potential clinical benefit in patients who do not carry *BRCAm* (both in the non-*tBRCAm* HRD positive population and in the non-*tBRCAm* ITT population). The single arm open-label design for the *tBRCAm* cohort was selected to ensure that all *tBRCAm* patients will receive optimal treatment (ie, olaparib as a maintenance therapy, based on data from the SOLO1 study) once they complete their chemotherapy phase and to investigate the potential benefit of adding durvalumab to olaparib treatment.

4.3 Justification for dose

The dose of olaparib used in this study is 300 mg bd which is the currently approved dose for the tablet formulation (in markets where approval has been obtained).

For ease of use and convenience to Investigators and patients in this study, it is intended to administer durvalumab Q3W to align with the treatment intervals of bevacizumab and chemotherapy and use a fixed dose of 1120 mg (based on an average body weight of 75 kg, this is equivalent to a weight based dose of 15 mg/kg Q3W). A population PK analysis based on a PK study (Study D4190C00001) study indicated that body weight has a minor impact on

the PK of durvalumab and subsequent modelling demonstrated that body weight based and fixed dosing regimens yield similar median steady-state PK concentrations.

4.4 End of study definition

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

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

A patient is considered to have completed the study when she has completed her last scheduled visit shown in the SoA. Extended OS follow-up data for the global non-*tBRCAm* cohort may be collected in EDC up to 5 years after randomisation of the last patient in the non-*tBRCAm* cohort, as outlined in Section 8.10. At the time of DCO for the last OS analysis, the clinical study database will close to new data and post the database lock, all non-*tBRCAm* patients will be unblinded. See Appendix A 6 for guidelines for the dissemination of study results.

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

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

In the event that a roll-over or safety extension study is available at the time of the last DCO and database closure, patients currently receiving treatment with durvalumab plus placebo or

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

See Section 6.7 for details on participant management following the last DCO, as well as following study completion.

4.5 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS CoV-2 (COVID-19) or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with GCP, and minimise risks to study integrity. Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

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

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

5. STUDY POPULATION

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

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study in order to receive Cycle 1 of chemotherapy. Eligibility must be confirmed prior to treatment allocation/randomisation at Cycle 2 Day 1 when patients must meet all inclusion criteria except for criteria 7, 8 and 9 and meet none of the exclusion criteria except for criteria 24.

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 the Pre-screen informed consent. Cohort allocation is defined when a patient has known *tBRCAm* status as determined by central test and has been allocated to the non-*tBRCAm* or *tBRCAm* cohort. "Randomised" patients are patients in the non-*tBRCAm* cohort who undergo randomisation into 1 of the 3 treatment arms.

For procedures for withdrawal of incorrectly enrolled patients see Section 6.3.1.1 and Section 7.3.

5.1 Inclusion criteria

The study inclusion criteria marked with an asterisk (*) MUST be fulfilled prior to the patient signing the Pre-screen consent form.

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent forms (ICFs) and in this protocol. All patients must sign both the Pre-screen ICF and main ICF:
   (i) The separate (Pre-screen) ICF will be provided for the mandatory *tBRCA* testing.
   (ii) The main ICF for participation in the study. The main consent form includes a separate consent for the optional Genomics Initiative research component of the study (if a patient declines to participate in this research, there will be no penalty or loss of benefit to the patient and the patient will not be excluded from other aspects of the study).

The ICF process is described in Appendix A 3. Note that all patients, regardless of whether or not they already know whether they have a deleterious or suspected deleterious *BRCA*

mutation present or absent based on local blood or tumour testing MUST sign the Pre-screen ICF to allow for central testing of *tBRCAm* status. Subject to meeting other eligibility criteria, patients can also sign the main ICF, be enrolled on the study and receive Cycle 1 of platinum-based chemotherapy. Patients will only be allocated to a *tBRCAm* cohort at the start of Cycle 2, once their *tBRCAm* status is confirmed by central testing. Patients who do not have a valid central test result available prior to Day 1 of Cycle 2 will be withdrawn from the study and considered as screen failures.

***tBRCA* mutation status**

Patients MUST meet the following criteria to be enrolled in the study

2 Patients must provide sufficient formalin fixed, paraffin embedded (FFPE) tumour sample suitable for the Myriad myChoice HRD Plus test

Determination of *tBRCAm* status: Subject to local regulations, all patients must provide an FFPE tumour specimen sample for tissue-based *BRCA1/2* gene testing using the clinical trial assay (CTA) known as the myChoice HRD Plus assay. The results of this test MUST be available prior to Day 1 of Cycle 2.

- If the test results indicate that the patient has deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2*, the patient may (subject to fulfilling all other selection criteria) be eligible for allocation to the *tBRCAm* single arm cohort of the study.
- If the test results indicate that the patient has no detected deleterious or suspected deleterious mutation in *BRCA1* and *BRCA2* the patient may (subject to fulfilling all other selection criteria) be eligible for randomisation in one of 3 non-*tBRCAm* arms.
- If a valid *tBRCAm* test result is not obtained prior to Day 1 of Cycle 2, the patient will be withdrawn from the study and considered as a screen failure.

The cohort allocation and randomisation procedures are provided in Section 6.3.1.

Patients MUST meet the following criteria prior to receiving Cycle 1 of chemotherapy. Patients MUST meet the following criteria prior to allocation/randomisation except for criteria 7, 8, and 9.

In addition, non-*tBRCAm* patients must be able to receive bevacizumab at Day 1 of Cycle 2 to be randomised and continue on study (any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure).

Age

3 Patients must be aged ≥18 years of age. For patients enrolled in Japan that are aged <20 year, a written informed consent should be obtained from the patient and her legally acceptable representative*.

Type of patient and disease characteristics

4 Female patients with newly diagnosed, histologically confirmed, advanced (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] Stage III or IV) high grade epithelial ovarian cancer including high grade serous, high grade endometriod, clear cell ovarian cancer or carcinosarcoma (malignant mixed Mullerian tumour [MMMT] of the ovary, provided high grade epithelial component is present); ovarian cancer = ovarian, primary peritoneal cancer and / or fallopian-tube cancer.

5 All patients must have had either*:

- Upfront primary surgery
- OR, plan to undergo chemotherapy with interval debulking surgery

6 Patients must have a life expectancy of at least 12 months*.

7 Patients must have normal organ and bone marrow function measured within 28 days prior to administration of Day 1 of Cycle 1 as defined below:

- Haemoglobin (Hb) ≥10.0 g/dL
- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Total bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed to participate in the study, in consultation with their physician.
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤2.5 × institutional ULN unless liver metastases are present in which case they must be ≤5 × ULN.

8 Patients must within 28 days prior to administration of Day 1 of Cycle 1 have creatinine clearance (CrCL) of ≥51 mL/minute estimated using either the Cockcroft-Gault equation, a 24 hour urine test or another validated test as per local practice:

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

9 Adequately controlled blood pressure (BP) (systolic blood pressure [SBP] ≤150 mmHg; diastolic blood pressure [DBP] ≤ 100 mmHg). Patients must have a BP of ≤150/100 mmHg taken in the clinic setting by a medical professional within 2 weeks prior to starting study.

10 Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (see Appendix G).

11 Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations*.

Weight

12 Patients' body weight must be >30kg*

Reproduction

13 Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of Day 1 of Cycle 1 and confirmed prior to treatment on Day 1.

Postmenopausal is defined as any of the following:

- Surgical sterilisation (bilateral oophorectomy or hysterectomy).
- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments and age ≥50 years
- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments and luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post menopausal range for women <50 years old
- Radiation-induced oophorectomy with last menses >1 year ago.
- Chemotherapy-induced menopause with >1-year interval since last menses.

5.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled. Patients MUST not sign the Pre-screen consent if any of the exclusion criteria marked with an asterisk (*) are fulfilled.

Patients MUST NOT meet the following criteria prior to receiving Cycle 1 of chemotherapy. Patients MUST NOT meet the following criteria prior to allocation/randomisation except for criteria 24.

Medical conditions

1 Non-epithelial ovarian cancer, borderline tumours, low grade epithelial tumours or mucinous histology.

2 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 5 years may be included but only after consultation with AstraZeneca.
- Patients with coeliac disease controlled by diet alone may be included.

3 History of another primary malignancy except for*

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of Day 1 of Cycle 1 and of low potential risk for recurrence (patients who have received prior adjuvant chemotherapy for early stage breast cancer may be eligible, provided that it was completed ≥3 years prior to registration, and that the patient remains free of recurrent or metastatic disease)
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease
- Endometrial cancer FIGO Stage IA, Grade 1 or Grade 2

4 Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML*.

5 Patients with known brain metastases.

6 History of leptomeningeal carcinomatosis*

7 History of active primary immunodeficiency*

8 Active infection including tuberculosis (TB) (clinical evaluation that includes clinical history of TB, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive hepatitis B virus [HBV] surface antigen [HBsAg] result), hepatitis C (HCV), or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc], followed by a negative hepatitis B virus DNA test and absence of HBsAg) are eligible provided these tests are confirmed as negative prior to Cycle 2 Day 1. Patients positive for HCV antibody are eligible only if the polymerase chain reaction is confirmed as negative for HCV RNA prior to Cycle 2 Day 1.

9 Prior history of hypertensive crisis (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4) or hypertensive encephalopathy*.

10 Clinically significant (eg, active) cardiovascular disease*, including:
   - Myocardial infarction or unstable angina within ≤6 months of allocation/randomisation,
   - New York Heart Association (NYHA) Grade ≥2 congestive heart failure (CHF)
   - Poorly controlled cardiac arrhythmia despite medication (patient with rate controlled atrial fibrillation are eligible), or any clinically significant abnormal finding on resting electrocardiogram (ECG),
   - Peripheral vascular disease Grade ≥3 (eg, symptomatic and interfering with activities of daily living [ADL] requiring repair or revision).
11 Previous cerebrovascular accident (CVA), transient ischemic attack (TIA) or intracranial bleeds (ie, intra-cerebral haemorrhage, sub-arachnoid haemorrhage or subdural haemorrhage) within 6 months prior to randomisation*.
12 Clinically significant ECG abnormality.
13 Non-healing wound, active ulcer or bone fracture*.
14 Persistent toxicities CTCAE Grade >2 caused by previous cancer therapy*.
15 Pre-existing sensory or motor neuropathy Grade ≥2*.
16 Evidence of bleeding diathesis or significant coagulopathy (in the absence of coagulation).
17 History of abdominal fistula or gastrointestinal perforation or active gastrointestinal bleeding within 6 months prior to allocation/randomisation.
18 Current signs or symptoms of bowel obstruction, including sub-occlusive disease, related to underlying disease.
19 Patient with evidence of abdominal free air not explained by paracentesis or recent surgical procedure.
20 History of allogenic organ transplantation including previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)*.
21 Patients considered a poor medical risk due to a serious, uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure (CHF), uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent*.
22 Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication*.
23 Patients with a history of or current Nephrotic syndrome*.

Prior/concomitant therapy

24 Prior systemic anti-cancer therapy for ovarian cancer*.

25 Prior treatment with PARP inhibitor or prior exposure to immune-mediated therapy, including but not limited to, anti- cytotoxic T lymphocyte-associated (CTLA-4), anti- programmed cell death protein 1 (PD-1), anti- programmed death-ligand 2 (PD-L1), or anti-programmed death-ligand 2 (PD-L2) antibodies, including therapeutic anticancer vaccines*.

26 Planned intraperitoneal cytotoxic chemotherapy*.

27 Other concurrent systemic anticancer therapy apart from the protocol specified. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) or bisphosphonates, if indicated, is acceptable*.

28 Current or prior use of immunosuppressive medication within 14 days before allocation/randomisation. 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, computed tomography [CT] scan premedication or as a premedication for paclitaxel) or as prophylaxis for CINE (chemotherapy-induced nausea or vomiting).

29 Receipt of live attenuated vaccine within 30 days prior to Day 1 of Cycle 1*.

Note: Patients, if enrolled, should not receive live vaccine whilst receiving study treatment and up to 30 days after the last dose of study treatment.

Prior/concurrent clinical study experience

30 Participation in another clinical study with an investigational product administered in the last 12 months.

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

32 Patients with a known hypersensitivity to the combination/comparator agents.

Other exclusions

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

34 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.

35 Previous allocation/randomisation in the present study.

36 Breast feeding women.

See Section 6.3.1.1 and Section 7.3 for procedures for withdrawal of incorrectly enrolled, allocated or randomised patients.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

The consumption of grapefruit juice while on olaparib therapy is prohibited.

On the PK sampling day for olaparib, patients should try to fast for 1 hour before olaparib dosing, and for 2 hours after olaparib dosing.

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

5.3.2 Contraception

Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective form of contraception and their partners must use a male condom (as described in Appendix F). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix F).

For details of acceptable methods of contraception refer to Appendix F Acceptable Birth Control Methods.

5.3.3 Other

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

5.4 Screen failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently allocated to either the *tBRCAm* or non-*tBRCAm* cohort, or randomly assigned to study treatment(s). A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from

regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. Rescreening will be allowed if the patient fails on any eligibility criteria, which subsequently resolves. Retesting of eligibility blood samples will be permitted within the 28-day screening window, if the patient has a blood sample abnormality that subsequently improves, without the need to rescreen the patient. Rescreened patients will be assigned a new enrolment number; however, the interactive response technology system (IRT) report will identify the old enrolment number and the reasons for rescreening will be documented in the eCRF, so that the effect on study results, if any, can be assessed. If the first tumour sample submitted for *tBRCAm* status testing is inconclusive due to technical test failure, a further tumour sample may be submitted for testing (see Section 8.8.1.1). Patients who do not have a valid *tBRCAm* test result determined by central *BRCA* testing before Day 1 of Cycle 2 will be withdrawn from the study and considered as screen failures. Data for these patients collected up to this time will be databased.

All screen failure patients should have the reason for study ineligibility recorded in the eCRF.

Patients who fail to meet the eligibility criteria should not, under any circumstances, be allocated to either cohort, randomised or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study. These patients should have the reason for study withdrawal recorded in the eCRF.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to chemotherapy, bevacizumab, durvalumab/saline and olaparib/placebo (see Figure 1 for an illustration of treatment scheduling and durations). For carboplatin dosing recommendations please refer to NCCN guidelines:

https://www.nccn.org/professionals/OrderTemplates/PDF/appendix_B.pdf

All patients will receive platinum based chemotherapy (and optional bevacizumab, according to local practice) for the first cycle (Cycle 1) before commencing durvalumab/saline from Day1 of Cycle 2. Patients will be allocated to either the *tBRCAm* or non-*tBRCAm* cohort by Cycle 2 provided the patient continues to meet the study selection criteria specified in Sections 5.1 and 5.2. Patients in the non-*tBRCAm* cohort will also be randomised to 1 of the 3 treatment arms by Day 1 of Cycle 2 and will receive mandatory bevacizumab from Day 1 of Cycle 2 (any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure). In the *tBRCAm* cohort, all patients will receive treatment with durvalumab and olaparib (bevacizumab is optional, as defined by standard local practice).

The intravenous study treatments ideally should be administered on the same day and in the following order:

- **Durvalumab/saline**
  - Durvalumab dose of 1120 mg should be administered for 1 hour; if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours.
- **Bevacizumab**
  - Dose of 15 mg/kg body weight by IV infusion over 90 minutes as first infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
- **Paclitaxel**
  - 175 mg/m^2 by IV infusion over 3 hours.
- **Carboplatin**
  - AUC 5 or AUC 6 by IV infusion over 1 hour or as according to local practice

    Note: As per NCCN guidance, to avoid overestimation of CrCl and subsequent overestimation of carboplatin dose, in patients with low serum creatinine, the

creatinine clearance MUST be estimated using a minimum value of 0.7 mg/dl (equivalent to 62 µmol/L).

– The Calvert Formula should be used to calculate the dose of carboplatin as shown:

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

Note: the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.
The maximum recommended doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

– For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance.
– For patients from Asian sites, it is recommended to use AUC5 for the carboplatin dose calculation.

6.1 Treatments administered

6.1.1 Investigational products

Refer to Table 6 for information on investigational study treatments.

Patients will receive durvalumab or saline (placebo) treatment from Cycle 2 for a period of up to 35 cycles (24 months). Patients who have evidence of macroscopic residual disease that remains stable (ie, no evidence of disease progression) after completing the maintenance phase of treatment may continue to receive blinded durvalumab or placebo treatment (or unblinded durvalumab for patients in the *tBRCAm* cohort) until PD if, in the opinion of the investigator, it is in patient's best interest.

For operational consistency and to maintain the study blind, patients in the open-label *tBRCAm* cohort will receive durvalumab solutions that are covered with a translucent coloured or opaque sleeve after preparation, this unifies the method of preparing and dispensing infusions in both cohorts and all treatment arms, so that correct preparation of blinded durvalumab/saline infusions becomes a pharmacist's routine. Durvalumab infusions will be labelled in a way that provides all relevant information regarding the treatment given to the patient and allows the investigator to distinguish blinded treatment arms from the open-label. Patients and Investigators are fully informed of treatment given in open-label arm (by means of infusion label/IRT), however blinding of infusion bag itself will remain.

Patients will also receive olaparib or placebo treatment after chemotherapy has completed (treatment will commence a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion) for a period of up to 2 years.

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

- Patients must have normal organ and bone marrow function as defined below:
  - Haemoglobin (Hb) ≥10.0 g/dL
  - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
  - Platelet count ≥100 x 10^9/L
  - Total bilirubin ≤1.5 × institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed to participate in the study, in consultation with their physician.
  - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤2.5 × institutional ULN unless liver metastases are present in which case they must be ≤5 × ULN.
- Patients must have creatinine clearance (CrCL) of ≥51 mL/minute estimated using either the Cockcroft-Gault equation, a 24 hour urine test or another validated test as per local practice:

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

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

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

NOTE: Patients who have already completed 22 cycles of durvalumab (*tBRCAm* positive cohort) or durvalumab/placebo (non-*tBRCAm* cohort) can restart durvalumab/placebo to receive up to a total of 35 cycles, providing no more than 12 weeks have elapsed between the last durvalumab/placebo dose and treatment restart, and only if deemed appropriate by the Investigator.

Patients may also continue with olaparib or placebo until objective disease progression (determined by RECIST 1.1) if they have evidence of macroscopic residual disease that remains stable (ie, no evidence of disease progression) and in the opinion of the investigator, it is in the patient's best interest.

Once patients have been discontinued from all study treatments, other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. No cross over to olaparib or durvalumab is permitted whilst participating in the study.

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

Table 6 Investigational study treatments

	Olaparib	**Durvalumab**
Study treatment name:	olaparib/placebo	Durvalumab (MEDI4736)/saline
Dosage formulation:	300 mg olaparib/placebo (2 x 150 mg/placebo tablets) bd 100 mg olaparib/placebo tablet available if dose reductions are required	1120 mg every 3 weeks 500-mg vial containing a 50 mg/mL solution for IV infusion after dilution Placebo for durvalumab is a sterile solution of 0.9% (w/v) sodium chloride for injection (saline infusion provided by unblinded study pharmacists)
Route of administration	Oral	IV
Dosing instructions:	Two x 150 mg Olaparib/placebo tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food except for the day on which PK samples are taken when olaparib should be given fasted: patients should take olaparib at least one hour after food, and should refrain from eating for 2 hours afterwards. If vomiting occurs shortly after the study treatment 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	A study centre pharmacist will be unblinded to study drug and will prepare durvalumab or saline as a placebo for a patient as specified by the randomisation scheme and IRT (only the unblinded pharmacist will know the randomisation/treatment allocation details for the non-*tBRCAm* patients). Pharmacists will be given specific instructions for study drug preparation and will note if the double-blind conditions have been compromised or the blind broken. Durvalumab/saline should be administered prior to dosing with bevacizumab and chemotherapy. Lot numbers of durvalumab dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. Other

Table 6 Investigational study treatments

	Olaparib	Durvalumab
	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.	study centre staff and monitors will not be given access to lot number information. The dose of durvalumab for administration must be prepared using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed: • 24 hours at 2°C to 8°C (36°F to 46°F) • 4 hours at room temperature Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration. A dose of 1120 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 22.4 mL of durvalumab (ie, 1120 mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. The IV bag should be covered with a translucent colored or opaque sleeve, after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover should be secured (eg, using stapling, heat-sealing), to maintain double-blind conditions. An IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose (approximately) matching the IV bag volume containing active drug will be used for placebo. The IV bag should be covered with a translucent colored or opaque sleeve, after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover should be secured (eg, using stapling, heat-sealing) to maintain double-blind conditions. Infusion time is 1 hour and should be delivered through an IV

Table 6 Investigational study treatments

	Olaparib	Durvalumab
		administration set with a 0.2- or 0.22-µm filter. Standard infusion time is 1 hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. Do not co-administer other drugs through the same infusion line. The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.
Packaging and labelling	Study treatment will be provided in HDPE bottles with child-resistant closures. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Durvalumab is supplied 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. Vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.
Provider	AstraZeneca	AstraZeneca

Abbreviations: GMP = Good manufacturing practice; HDPE = High-density polyethylene IV = Intravenous; IRT = Interactive response technology system; PK = Pharmacokinetic.

6.1.2 Non-investigational products

Bevacizumab and chemotherapy (carboplatin/paclitaxel) will be administered in accordance with recommendation of this treatment combination in international guidelines (NCCN

Ovarian 2018; for carboplatin dosing recommendations **please also refer to NCCN guidelines https://www.nccn.org/professionals/OrderTemplates/PDF/appendix_B.pdf**), at the doses described in their marketing authorisation/approved drug labelling. Bevacizumab, carboplatin and paclitaxel will be supplied locally by sites and used in accordance with the relevant local prescribing information. In the EU, bevacizumab and carboplatin and paclitaxel are considered Auxiliary Medicinal Products (AxMPs) according to EU clinical trials guidance (EU Guidance 2017).

Bevacizumab

For all arms bevacizumab will be locally sourced and will be administered according to prescribing information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally source the drug which will be labelled with text translated to local language in accordance with regulatory guidelines.

Bevacizumab or a single one of the FDA-, EMA- or PMDA-approved biosimilars will be administered at a dose of 15 mg/kg body weight by IV infusion Q3W. In the *tBRCAm* cohort ONLY (ie, in the single arm cohort) where the use of bevacizumab is optional, the dose of bevacizumab that is standard local practice may be administered. Where possible, patients should remain on the originator product Avastin® or a single one of the FDA-, EMA- or PMDA-approved biosimilars for the duration of their treatment (for China only, a CDE-approved biosimilar also may be used). However, if the originator product is no longer available at the site or if the patient is unable to tolerate it, individual patients are allowed to switch to Avastin or an approved bevacizumab biosimilar; once switched, it is recommended that the patient should then continue on that agent for the remaining duration of treatment unless this is not possible, for example the patient is unable to tolerate it, in which case a further switch would be permitted.

Bevacizumab should be administered in combination with carboplatin and paclitaxel, followed by continued use as a maintenance treatment until disease progression or for up to a maximum of 22 cycles (15 months) or until unacceptable toxicity, whichever occurs earlier.

Bevacizumab is optional in Cycle 1 of platinum-based chemotherapy, depending on standard local practice. In line with the European Summary of Product Characteristics (SmPC) and the US prescribing information it is recommended that bevacizumab should not be administered within the first 28 days following major surgery. If bevacizumab is not routinely used by the site, then bevacizumab should be started at Cycle 2. For patients scheduled to undergo IDS, bevacizumab MUST be omitted from the treatment cycle immediately prior to IDS. If chemotherapy is started within 4 weeks after IDS then bevacizumab must also be omitted from the first cycle post IDS.

Platinum-based chemotherapy

SoC chemotherapy will be locally sourced and will be administered according to prescribing information or treatment guidance in general use by the investigating site, including any required premedication. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally source the drug which will be labelled with text translated to local language in accordance with regulatory guidelines.

For all arms chemotherapy will be a "non-investigational drug" as it is a recommended SoC in international guidelines. Chemotherapy, as SoC therapy, will be administered in all arms in line with NCCN guidelines. For carboplatin dosing recommendations, please also refer to NCCN guidelines: https://www.nccn.org/professionals/OrderTemplates/PDF/appendix_B.pdf

Chemotherapy, as SoC therapy, will be administered in all arms:

For a minimum of 4 and a maximum of 6 treatment cycles of paclitaxel 175 mg/m^2 Q3W and carboplatin AUC 5 or AUC 6

- For **Carboplatin** dose:

– As per NCCN guidance, to avoid overestimation of CrCl and subsequent overestimation of carboplatin dose, in patients with low serum creatinine, the creatinine clearance MUST be estimated using a minimum value of 0.7 mg/dl (equivalent to 62 µmol/L). The Calvert Formula should be used to calculate the dose of carboplatin as shown:

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

NOTE: It is recommended that the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.
The maximum recommended doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

– For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance.

– For patients from Asian sites, it is recommended to use AUC5 for the carboplatin dose calculation.

Platinum-based chemotherapy will be administered in Cycle 1 before cohort allocation and randomisation at Cycle 2. The first cycle of chemotherapy will be included in the maximum and minimum number of treatment cycles of chemotherapy. If platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of 4 cycles of the platinum regimen for the patient to be able to continue into the maintenance treatment phase.

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

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

6.2 Preparation/handling/storage/accountability

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

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

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

Further guidance and information for the final disposition of unused study treatment are provided in the laboratory manual.

6.3 Measures to minimise bias: randomisation and blinding

All non-*tBRCAm* patients will be centrally assigned to randomised study treatment using an interactive response technology system (IRT). Before the study is initiated the log-in information and directions for the IRT will be provided to each site.

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

6.3.1 Procedures for enrolment and randomisation

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

All patients must sign the Pre-screen informed consent form (ICF). The Pre-screen ICF provides consent for provision of tumour tissue sample and for prospective *tBRCAm* status analysis. Also the study inclusion and exclusion criteria marked with an asterisk in Sections 5.1 and 5.2 MUST be met prior to the patient signing the Pre-screen ICF. If a patient is assigned to primary upfront cytoreductive surgery, a sample from the primary cytoreductive surgery should be provided, or, if not available, a biopsy tumour sample previously obtained at diagnosis may be provided. Provided the patient has signed the Pre-screen ICF, and a suitable tumour sample has been provided, the screening process can continue.

At Pre-screening/baseline (diagnosis to Day 0), for enrolment into study run in phase:

- Obtain signed informed consent before any study specific procedures are performed.
- Obtain a unique 7-digit enrolment number (E-code) during Pre-screening, through the IRT in the format PPD PPD This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
- Determine patient eligibility (see Sections 5.1 and 5.2).

For all patients who have provided an FFPE tumour sample for central tissue-based *BRCA* mutation testing using the Myriad Genetics myChoice HRD Plus assay:

- If the patient meets all of the study inclusion and exclusion criteria (Sections 5.1 and 5.2), she can also sign the main consent form, and will then receive 1 cycle of platinum-based chemotherapy, while the determination of central *tBRCAm* status is ongoing. Cycle 1 of chemotherapy may also include bevacizumab, according to local practice. If bevacizumab is not routinely used by the site, then bevacizumab should be started at Cycle 2.
- Once a patient's *tBRCAm* status is known, based on central *tBRCA* testing (and prior to Cycle 2), patients will be allocated to either the *tBRCAm* cohort or the non-*tBRCAm* cohort (provided the patient continues to meet of the eligibility criteria listed in

Section 5.1 and 5.2). All patients in the *tBRCAm* cohort will enter the single arm part of the study; patients in the non-*tBRCAm* cohort will enter the double-blind randomised part of the study and will be randomised to 1 of 3 treatment arms by Day 1 of Cycle 2 and will receive mandatory bevacizumab from Day 1 of Cycle 2 (any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure).

- Should the central *tBRCA* assay fail to determine the presence or absence of a deleterious/suspected deleterious mutation prior to the start of Cycle 2, due to technical failure or delay in testing the patient cannot continue on the study, even if she fulfils all other eligibility criteria: these patients should continue SoC treatment outside the study.

The actual treatment given to individual patients will be determined by cohort allocation and, if in the non-*tBRCAm* cohort, by a randomisation scheme that has been loaded into the (IRT) database. The randomisation scheme will be produced by a computer software program called AZRand (AZ Global Randomisation System) that incorporates a standard procedure for generating randomisation schemes in order to assign subjects to treatment groups within a clinical trial.

A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of non-*tBRCAm* patients assigned to each treatment group.

The randomisation scheme will be stratified based on:

- Timing and outcome of cytoreductive surgery: no macroscopic residual disease after upfront primary surgery vs all others (macroscopic residual disease after upfront primary surgery OR planned IDS)
- Geographic region: North America vs Europe vs RoW.

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

Patients will be identified to the Centralised Randomisation Centre using Ecode and date of birth.

Randomisation codes will be assigned strictly sequentially within each strata as patients become eligible for randomisation.

For the *tBRCAm* cohort, the IRT will be set up in such a way that will allow the closing of recruitment to a particular country once olaparib becomes available as part of clinical practice for first line maintenance treatment of ovarian cancer.

It is recommended that patients commence Day 1 of Cycle 1 as soon as possible after completion of all screening tests (with the exception the central *tBRCAm* test result which is only required by Day 1 of Cycle 2), and ideally within 3 days.

The IRT will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the dispensing visit.

To ensure that there is no significant over recruitment beyond the planned non *BRCAm* randomisation target, the AstraZeneca Study Team will actively manage study enrolment. The AstraZeneca Study Team will close the global study enrolment to all sites apart from sites in China at an appropriate time to ensure an appropriate number of patients from sites in China are randomised. Enrolment of patients from sites in China will be actively managed by the AstraZeneca Study Team to ensure there is no significant over recruitment of patients from sites in China.

6.3.1.1 Procedures for handling incorrectly enrolled or randomised patients

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

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

6.3.2 Methods for ensuring blinding

The olaparib and durvalumab treatments will both be blinded to patients and investigators for the non-*tBRCAm* patients and durvalumab treatment will also be prepared and administered in a blinded state for the *tBRCAm* patients (see Section 6.2). Patients in the *tBRCAm* cohort will know they are receiving treatment with olaparib, however as olaparib and placebo for olaparib treatment are visually indistinguishable, blinding in the non-*tBRCAm* cohort will not be compromised.

Each study medication will be labelled using unique Kit ID numbers, and linked to the randomisation scheme.

- The olaparib and placebo tablets will be presented in the same packaging to ensure blinding of the study medication.

- Durvalumab and saline placebo solutions will be prepared by an unblinded pharmacist who is independent of the study (3rd party); the solutions for IV administration will be covered with a translucent colored or opaque sleeve, after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover should be secured (eg, using stapling, heat-sealing*),* to maintain double-blind conditions.

The IRT will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Blinded and unblinded access and notifications will be controlled using the IRT. Investigators will remain blinded to each non-*tBRCAm* patient's assigned study treatment throughout the course of the study. To maintain this blind, an otherwise uninvolved 3rd party (unblinded pharmacist) will be unblinded and responsible for the reconstitution and dispensation of durvalumab and will endeavour to ensure that there are no differences in time taken to dispense following randomisation. The unblinded pharmacists will be monitored by unblinded study monitors all of whom will have no further role in the management of study patients or data collection and will not have access to the study database. All other site personnel will be blinded for the dispensation of durvalumab and olaparib.

The study staff administering the treatment and the patient should avoid discussing the appearance of the study treatment with the investigator.

In the event that the treatment allocation for a patient becomes known to the investigator or other study staff involved in the management of study patients, the sponsor must be immediately notified without revealing treatment allocation. If the treatment allocation needs to be known to treat an individual patient for an AE, the sponsor must be notified promptly by the investigator and if possible, before unblinding.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. Once unblinding has occurred, the unblinded IMP treatment must be discontinued but the patient should continue to follow all other protocol procedures and assessments. The Investigator documents and reports the action to AstraZeneca, without revealing to the AstraZeneca staff, the treatment given to patient.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to one or more of the investigational products in this study 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 and the database locked.

The IRT will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the patient's best interest for the investigator to know

the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (eg, antidote available). In this case, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF (electronic), as applicable. Study unblinding by the study team should not occur until database lock and all decisions on the evaluability of the data from each individual patient have been made and documented.

The exception to the above is for those personnel analysing the PK samples. The randomisation code will be provided to ensure that only samples from patients who were on active study treatments are analysed. These personnel will have no role in the management of study patients or data collection and will not have access to the study database.

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

If a patient is continuing to derive benefit from olaparib at the end of the study, then they may continue to receive treatment as open labelled drug via manual supply outside of the study setting once the IRT has been closed.

6.4 Treatment compliance

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

For all study arms, study site staff will administer chemotherapy, bevacizumab and durvalumab/durvalumab placebo.

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

6.4.1 Accountability

The study drug provided for this study will be used only as directed in the CSP.

The study site staff will account for all study drugs dispensed to and returned from the patient.

Study site staff will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed.

For sites in Japan, study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The Investigator(s) is responsible for ensuring that the patient has returned all unused study drug.

6.5 Concomitant therapy

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

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

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

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

Anti-emetics/Anti-diarrhoeals

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

Medications that may NOT be administered

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

Other medication other than that described in Table 7 and Table 8, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

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

Table 7 Prohibited medications

Prohibited medication/class of drug:	**Study treatments for which concomitant use is prohibited:**	
Other anticancer therapy: Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy* for cancer treatment other than those under investigation in this study Radiotherapy (except palliative) Biological therapy mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study Other novel agents	Durvalumab/saline AND olaparib/placebo	Not permitted while the patient is receiving study medication.
Live virus vaccines Live bacterial vaccines	Durvalumab/saline AND olaparib/placebo	Not permitted while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with study medications are unknown.

Table 7 Prohibited medications

Prohibited medication/class of drug:	Study treatments for which concomitant use is prohibited:	
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Durvalumab/saline ONLY	Should not be given concomitantly, or used for premedication prior to the durvalumab/saline infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study medication related AEs, • short-term premedication for patients receiving platinum-based chemotherapy where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions or for prophylaxis of chemotherapy-induced nausea and vomiting • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)	Durvalumab/saline AND olaparib/placebo	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab and should only be used more than 30 days after the last dose of olaparib/placebo treatment. Increased incidences of pneumonitis (with third generation EGFR-TKIs) and increased incidence of transaminase increases (with 1st generation EGFR-TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Durvalumab/saline ONLY	Should not be given concomitantly unless agreed by the Sponsor

Abbreviations: AE = Adverse event; bd = twice daily; EGFR-TKI = Epidermal growth factor receptor tyrosine kinase inhibitors; mAb = Monoclonal antibody; CTLA-4 = cytotoxic T lymphocyte-associated-4; PD-1 = Programmed cell death protein-1; PD-L1 = Programmed death-ligand 1;

*Hormone Replacement Therapy (HRT) is acceptable

Table 8 Restricted concomitant medications

Medication/class of drug	Study treatments for which concomitant use is restricted:	Usage (including limits for duration permitted and special situations in which the medication is allowed)
Strong CYP3A inhibitors: eg • itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, and telaprevir Moderate CYP3A inhibitors: eg ciprofloxacin, erythromycin, diltiazem, fluconazole, and verapamil	Olaparib/placebo treatment ONLY	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. • Moderate CYP3A inhibitors – reduce the dose of olaparib to 150 mg bd for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards. • After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.
Strong CYP3A inducers: eg, • phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers: eg, bosentan, efavirenz and modafinil	Olaparib/placebo treatment ONLY	Strong or moderate CYP3A inducers 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 8 Restricted concomitant medications

Medication/class of drug	Study treatments for which concomitant use is restricted:	Usage (including limits for duration permitted and special situations in which the medication is allowed)
CYP3A4 substrates with narrow therapeutic margin: eg, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and warfarin. Sensitive CYP3A4 substrates: eg, buspirone, felodipine, fluticasone, lovastatin, quetiapine, saquinavir, sildenafil and simvastatin. CYP2B6 substrates: eg bupropion, efavirenz OATP1B1substrates: eg bosentan, glibenclamide, repaglinide, statins and valsartan OCT1, OCT2, MATE1 and MATE2K substrates: eg metformin OCT2 substrates: eg cimetidine and metformin OAT3 substrates: eg furosemide, methotrexate BCRP substrates: eg,. methotrexate and rosuvastatin. P-gp substrates: eg, simvastatin, pravastatin, dabigatran, digoxin and colchicine.	Olaparib/placebo treatment ONLY	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP2B6 (and potentially substrates of CYP2C9, CYP2C19 and P-gp). The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Caution should be observed if statins or sensitive CYP3A4 substrates are co-administered. Appropriate clinical monitoring is recommended for patients receiving P-gp substrates or CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Table 8 Restricted concomitant medications

Medication/class of drug	Study treatments for which concomitant use is restricted:	Usage (including limits for duration permitted and special situations in which the medication is allowed)
Anticoagulant therapy	Olaparib/placebo treatment	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (eg, apixaban and rivaroxaban) if possible.
Anticoagulant therapy	Bevacizumab	Note that patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage. There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients and their INR should be carefully monitored. Sites should follow local standard practice and prescribing guidance.

Table 8 Restricted concomitant medications

Medication/class of drug	Study treatments for which concomitant use is restricted:	Usage (including limits for duration permitted and special situations in which the medication is allowed)
Palliative radiotherapy	Durvalumab/saline AND olaparib/placebo	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Administration of other anti-cancer agents	Durvalumab/saline AND olaparib/placebo	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease provided these were started at least 4 weeks prior to beginning study treatment.

Abbreviations: bd = twice daily; CRF = case report form; CYP = cytochrome P450; INR = international normalised ratio; MATE = Multidrug and toxin extrusion; OAT = Organic anion transporter; OATP1B1 = Organic anion transporting polypeptide 1B1; OCT = Organic cation transporter.

Subsequent therapies for cancer

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

Rescue medication

As a result of immune-mediated adverse events (im-AEs) that could potentially be experienced by patients on durvalumab, steroids and other immunosuppressants, rescue medication has to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for

hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy related toxicities. These rescue medications must be receipted, controlled, and administered by the unblinded pharmacist and stored according to the labelled storage conditions, with temperature excursions reported accordingly by the unblinded pharmacist. If required for use as a result of an im-AE, then the IRT will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the time. Blinded and unblinded access and notifications will be controlled using the IRT.

6.6 Dose modification

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

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

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

Abbreviations: bd = twice daily.

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

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

Abbreviations: bd = twice daily.

Table 11 Dose reductions for olaparib/placebo if patient has to start taking a strong or moderate CYP3A inhibitor

Initial Dose	Strong CYP3A inhibitor	Moderate CYP3A inhibitor
300 mg bd	100 mg bd	150 mg bd

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

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Section 6.5.

When dose reduction is necessary patients will take one 150 mg tablet and one 100 mg tablet bd or 2 x 100 mg tablet bd or 1 x 150 mg tablet bd or 1 x 100 mg tablet bd. For durvalumab, dose reductions are not permitted.

Dose delays are permitted for durvalumab (see Annex to Protocol). For guidance on dose modifications for management of AEs (including renal impairment) for olaparib and durvalumab, refer to Section 8.4.6. The durvalumab dose may be delayed for up to a maximum of 12 weeks. If the toxicity has not resolved by 12 weeks, durvalumab should be stopped permanently (as no dose adjustment is allowed). See the durvalumab toxicity management guidelines (TMGs) for guidance regarding the starting timepoint for the start of the 12-week period (see Section 8.4.6.2 for details on how to access the TMGs).

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

It is recommended that Investigators follow the ASCO guidelines regarding the use of Granulocyte colony-stimulating factor (G-CSF). Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, appropriate management including G-CSF should be given according to local hospital guidelines.

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

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

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

In cases of bevacizumab toxicity which have not resolved, the bevacizumab dose may be delayed and given 3 weeks later at the next scheduled visit. Dose delays are permitted for bevacizumab for up to a maximum of 12 weeks from the date of first delay of bevacizumab. If the toxicity has not resolved by 12 weeks, bevacizumab should be stopped permanently, as no dose adjustment is allowed (unless otherwise agreed with the Study Physician).

6.7 Treatment after the end of the study

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

After the last DCO, AstraZeneca will continue to supply durvalumab and/or olaparib to participants who were randomised/allocated to receive durvalumab and/or olaparib until PD occurs as judged by the investigator or until meeting any other discontinuation criteria, as defined in Section 7.1. Participants should be followed according to the institution's standard of care assessments. No further data collection is required, except for reporting of SAEs.

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

AstraZeneca will continue to supply olaparib and/or durvalumab in the continued access phase of this study and after completion of this study while, in the opinion of the Investigator, the participant is benefiting and has not met any of the discontinuation criteria (see Section 7.1).

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

In the event that a roll-over or safety extension study is available at the time of the last DCO and database closure, participant(s) currently receiving treatment with olaparib and/or durvalumab may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients must be discontinued from study treatments in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Note that any patient receiving combination treatment who has an AE that contraindicates further dosing and is considered to be attributable to 1 of the study treatments but not the others, may continue on study and continue to receive the therapies that have not been considered to be the cause of the AE (a discontinuation of 1 drug should not affect the dosing schedule of the other drugs) and continue following the on-treatment SoA (see Section 6.1.2 for guidance on permitted drug substitutions in the event of a hypersensitivity reaction to carboplatin or paclitaxel leading to discontinuation)
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Severe non-compliance with the CSP
- Bone marrow findings consistent with MDS/ AML
- Objective disease progression according to Modified RECIST 1.1 criteria
- Pregnancy or intent to become pregnant

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed. Note that patients can be discontinued from an individual study treatment if any discontinuation criteria are fulfilled but the treatment discontinuation visit will only occur when all treatments have been discontinued.

7.1.1 Procedures for discontinuation of study treatment

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

Any patient discontinuing study treatments should be seen at the appropriate follow-up visits, post discontinuation for the evaluations outlined in Table 4. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment.

After discontinuation of all study medications at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Section 7.2). All new AEs and SAEs occurring during the follow-up period after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 8.4.1) and followed to resolution as above. For guidance on reporting AEs after the follow up period see Section 8.3.2.1.

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

All patients must be followed for survival, up to the last OS analysis, provided they have not withdrawn consent to do so, as outlined in Section 8.10.

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

7.2 Lost to follow-up

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

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.

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

7.3 Withdrawal from the study

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Incorrectly enrolled patients ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Death

Note that patients who are enrolled into the study and receive Cycle 1 of chemotherapy but do not have a valid *tBRCAm* test result determined by central *BRCA* testing before Day 1 of Cycle 2 will be withdrawn from the study and considered as screen failures.

In addition, non-*tBRCAm* patients must be able to receive bevacizumab at Day 1 of Cycle 2 to be randomised and continue on study (any patient unable to receive bevacizumab at Day 1 of Cycle 2 should not be randomised and constitutes as a screen failure).

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

A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

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

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

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

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

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

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

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

See SoA, Table 4, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

See Section 6.3.1.1 for procedures for incorrectly allocated or randomised patients.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

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

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

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

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

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

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

8.1 Efficacy assessments

8.1.1 CT and MRI scans tumour assessments (modified RECIST 1.1)

The preferred methods of assessment are CT or magnetic resonance imaging (MRI) scans of chest, abdomen and pelvis. The use of positron emission tomography (PET) scans is described in Appendix H. The same methods of assessment of tumour burden must be used at baseline and at each subsequent follow-up assessment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

Baseline RECIST scan should occur within 28 days prior to or on Day 1 of Cycle 1 of chemotherapy. Patients with upfront cytoreductive surgery should have the baseline scan conducted post surgery. Following the baseline assessment, the first follow-up tumour assessment according to modified RECIST 1.1 (the end of chemotherapy assessment scan) will be performed within 3 weeks ±1 week after the last dose of chemotherapy and before the

start of the maintenance treatment. During the maintenance phase assessments will be performed every 12 weeks ±2 weeks for the first 3 years (156 weeks) and then every 24 weeks ± 2 weeks, relative to the date of end of chemotherapy assessment scan, according to the planned study schedule up to objective progression by modified RECIST 1.1. Patients requiring IDS including patients in whom primary surgery has been unsuccessful and further surgery is planned as IDS will have additional scans pre-surgery (after the last dose of neoadjuvant chemotherapy but prior to IDS surgery (see Table 12). It should be noted that for the statistical analysis, the scan performed during the screening period will be regarded as the baseline scan as patients planned for IDS may potentially receive durvalumab as an investigational product (and the impact of planned IDS will be managed by stratification on this factor).

Table 12 CT and MRI scan schedules from screening to progression

Timepoint	Patients with primary surgery at study entry	Patients requiring IDS
Within 28 days prior to or on Day 1 of Cycle 1	X	X
Prior to IDS (any time after the last dose of neoadjuvant chemotherapy but prior to IDS surgery)	NA	X
End of chemotherapy assessment scan (within 3 weeks ±1 week of the last dose of chemotherapy [ie. Day 1 of Cycle 6] but prior to the start of maintenance)	X	X
Post chemotherapy (≤3 years from end of chemotherapy assessment scan)	X (every 12 weeks ± 2 weeks)	X (every 12 weeks ± 2 weeks)
Post chemotherapy (>3 years from end of chemotherapy assessment scan)	X (every 24 weeks ± 2 weeks)	X (every 24 weeks ± 2 weeks)

Note: Post chemotherapy scans are scheduled from the date of the end of chemotherapy assessment scan, rather than from the date of allocation/randomisation.

Any patient unable to complete the minimum 4 cycles of platinum-based chemotherapy required to continue to the maintenance phase should have their 'End of Chemotherapy'imaging assessment performed at Week 15 (or as soon as possible after Week 15 in the case of IDS patients) relative to randomisation; subsequent scans will then be performed every 12 weeks ± 2 weeks for the first 3 years (156 weeks) and then every 24 weeks ± 2 weeks relative to this End of Chemotherapy assessment..

Abbreviations: CT = Computed tomography; IDS = Interval debulking surgery; MRI = Magnetic resonance imaging; NA = Not applicable.

Radiological examinations performed in the conduct of this study should be retained at site as source data.

Anonymised copies of the scans will be collected from all patients and will be sent to an AstraZeneca appointed Contract Research Organisation (CRO); scans from non-*tBRCAm* patients will undergo BICR assessment. Scans from *tBRCAm* patients may undergo a central review.

All treatment decisions will be based on site assessment of scans. After the primary PFS analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Ongoing collection of site review tumour assessment is required and must be recorded in the eCRF.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit ± 2 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST 1.1 as per the study schedule (see Table 2 and Table 3), and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

8.1.1.1 Tumour evaluation

Modified RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS times and ORR. The modified RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria (CR, PR, SD, PD, no evidence of disease [NED]) are presented in Appendix H.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. TL progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of a best response of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before allocation/randomisation. Patients with no disease at baseline will be assessed according to modified RECIST 1.1 criteria for new lesions with response of NED or PD.

For those patients with no evidence of disease at baseline, following a complete resection after surgery, progression is defined by the detection of new lesions on follow up radiological assessments (modified RECIST 1.1).

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

For patients requiring IDS, an additional scan is mandated pre-surgery. It should be noted that for the statistical analysis, the last scan prior to allocation/randomisation will be regarded as the baseline scan for all patients.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status with a new scan. If the repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Although CA125 is measured in this study it will not be used for assessing objective response or progression and patients should be continued on treatment until objective radiological disease progression as defined by modified RECIST 1.1.

8.1.1.2 Central reading of scans

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

A sensitivity analysis for this study will be based on the BICR analysis of the radiological scans for non-*tBRCAm* patients only. Retrospective central reading of the scans in the *tBRCAm* cohort is not planned, but may be conducted, if needed.

8.1.1.3 Patients having IDS

For those patients that have IDS during the study, information will be collected regarding the outcome of the IDS surgery (ie, whether there is any residual macroscopic disease post-surgery and also if there is any histological evidence of cancer in all surgical specimens, including the adnexa [residual microscopic disease]). This is to evaluate the pathological complete response (pCR) rate after 3 cycles of chemotherapy, bevacizumab (optional for *tBRCAm* patients) and durvalumab/placebo.

8.1.2 Patient reported outcome assessments

Patient Reported Outcomes (PROs), an umbrella term referring to all outcomes and symptoms, are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered using a handheld electronic device (ePRO): EORTC-QLQ-C30; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28 (EORTC QLQ-OV28); patient reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE); patient global impression of severity of cancer symptoms (PGIS);and EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index (see Appendix J). Each is described below.

8.1.2.1 EORTC-QLQ-C30 and EORTC-QLQ-OV28

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993; it consists of 30 items and measures cancer patients' functioning (Health-related quality of life [HRQoL]) and symptoms (Aaronson et al 1993) for all cancer types. Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, and nausea and vomiting); a 2-item global HRQoL scale; 5-single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea) and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

The ovarian cancer module EORTC-QLQ-OV28, is designed for patients with local or advanced disease who receive treatment by surgery with or without chemotherapy and was developed according to the EORTC Guidelines; it consists of 28 items assessing abdominal/GI symptoms (7 items), peripheral neuropathy (3 items), other chemotherapy side effects (7 items), hormonal symptoms (2 items), body image (2 items), attitudes to disease/treatment (3 items), and sexuality (2/4 items).

EORTC-QLQ-C30 and EORTC-QLQ-OV28 will be assessed at:

- baseline (prior to dosing on Day 1 of Cycle 1)
- then Q6W (±3 days) during the chemotherapy phase (until the start of the maintenance phase or discontinuation of all study treatments, whichever occurs first)
- at the start of maintenance (+3 days) then Q6W (±3 days) from the start of maintenance until discontinuation of all study treatments
- at the treatment discontinuation visit (discontinuation of all study treatment) and then 30 and 90 days post the treatment discontinuation visit followed by every 12 weeks (±14 days) from the 30 day post treatment discontinuation visit, up to a maximum of 36 months post Visit 2 (Cycle 1 Day 1) or primary data cut-off date [DCO], whichever comes first).

8.1.2.2 PRO-CTCAE

The PRO-CTCAE system has been developed by the NCI. The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The PRO version of the CTCAE is an item-bank of symptoms experienced by patients while undergoing treatment of their cancer. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Sprangers and Aaronson 1992; Litwin et al 1988; Basch et al 2009). To date, 81 symptoms of the CTCAE v4 have been identified to be amenable to patient reporting. These symptoms have been converted to patient terms (eg, CTCAE term "myalgia" converted to "aching muscles"). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. For other symptoms like rash, additional questions focus on the presence on the body. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. Using cognitive testing methods, these items and the additional questions for some of the symptoms have been extensively evaluated by cancer patients, so that symptoms of interest are clear, comprehendible, and measurable. Not all items are administered in any one clinical trial. The intention is to only ask patients to complete those items, which are considered relevant for the trial, site of cancer, and cancer treatment (See Appendix J). For this study, 9 items are considered relevant for this cancer treatment, (ie, nausea, vomiting, diarrhoea, decreased appetite, abdominal pain, itching, muscle pain, fatigue and chills). In addition to these items from the PRO-CTCAE item bank, the following additional items will be asked together with the PRO-CTCAE items: CCI

CCI

CCI

CCI

PRO-CTCAE will be assessed at:

- baseline (prior to dosing on Day 1 of Cycle 1)
- then weekly (±3 days) for the first 12 weeks of the chemotherapy phase, and thereafter Q6W (±3 days) (until the start of the maintenance phase or discontinuation of all study treatments, whichever occurs first)
- at the start of maintenance (+3 days) and then weekly (±3 days) for the first 6 weeks, and then Q6W (±3 days) until discontinuation of all study treatments
- at the treatment discontinuation visit (discontinuation of all study treatment) and then 30 and 90 days post the treatment discontinuation visit followed by every 12 weeks (±14 days) from the 30 day post treatment discontinuation visit, up to a maximum of

36 months post Visit 2 (Cycle 1 Day 1) or primary data cut-off date [DCO], whichever comes first).

8.1.2.3 Patient global impression of severity of cancer symptoms (PGIS)

The PGIS item is included to assess how a patient perceives her overall current severity of cancer symptoms. This is a single item questionnaire and patients will choose from response options ranging from “no symptoms” to “very severe”.

PGIS will be assessed at:

- baseline (prior to dosing on Day 1 of Cycle 1)
- then Q6W (±3 days) during the chemotherapy phase (until the start of the maintenance phase or discontinuation of all study treatments, whichever occurs first)
- at the start of maintenance (+3 days) and then Q6W (±3 days) from the start of maintenance until discontinuation of all study treatments
- at the treatment discontinuation visit (discontinuation of all study treatment) and then 30 and 90 days post the treatment discontinuation visit followed by every 12 weeks (±14 days) from the 30 day post treatment discontinuation visit, up to a maximum of 36 months post Visit 2 (Cycle 1 Day 1) or primary data cut-off date [DCO], whichever comes first).

8.1.2.4 EQ-5D-5L

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

EQ-5D-5Lwill be assessed at:

- baseline (prior to dosing on Day 1 of Cycle 1)
- then Q6W (±3 days) during the chemotherapy phase (until the start of the maintenance phase or discontinuation of all study treatments, whichever comes first)
- at the start of maintenance (+3 days) and then Q6W (±3 days) from the start of maintenance until discontinuation of all study treatments
- at the treatment discontinuation visit (discontinuation of all study treatment) and then 30 and 90 days post the treatment discontinuation visit followed by every 12 weeks (±14 days) from the 30 day post treatment discontinuation visit, up to a maximum of 36 months post Visit 2 (Cycle 1 Day 1) or primary data cut-off date [DCO], whichever comes first).

8.1.2.5 Administration of ePRO questionnaires

Patients will complete ePRO assessments at home, and sometimes at site, using the same handheld electronic device (ePRO). Patients will be issued with the ePRO device and given training on how to use it. For the baseline ePRO, this should be performed on C1D1 and before any study procedures are conducted (exception may be made for blood draws), however, it will be permitted for the patient to complete the ePRO before C1D1 as long as treatment is given within 3 days after ePRO completion. If a site wishes to perform both blood draws and ePRO before C1D1, then ideally the ePRO should be performed prior to the blood draws. In the event of ePRO device failure at site, paper questionnaires may be used during this site visit.

All assessments should be completed according to the following parameters:

- Without assistance from site staff or anyone else, and according to the study schedules (Table 2 and Table 3)
- Before any other study procedures are conducted at a given visit (with exception of blood draw)
- Before being seen by a study nurse or physician
- Each centre must allocate the responsibility for the administration of the ePROs to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent. Patients may complete some of the ePROs at study sites if the assessment time point coincides with a scheduled site visit; otherwise, patients should complete the ePROs at home. Similarly, during the post-progression visit period, patients should complete ePROs at home or at the study site if a scheduled visit coincides with the time point.

  The Investigator will arrange for relevant training in the set-up of the electronic device and training patients in how to self-administer the ePROs using the device. Patients should complete the PROs in accordance with the study schedule. The significance and relevance of the data should be explained carefully to patients so that they are motivated to comply with the data collection. Reminders should be sent to patients at home as needed to ensure compliance with the assessment schedule.

The following guidelines should be followed:

- When each instrument is due to be completed, the following order for completion should be ensured (and the ePRO device should be programmed accordingly): EORTC-QLQ-C30, EORTC-QLQ-OV28, PRO-CTCAE, PGIS, EQ-5D-5L
- ePRO completion must be done by the patient in private and when assessments occur on site, site staff should ensure that patients get a quiet place to do the assessments
- The research nurse or appointed site staff must explain to patients the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also

stress that the information is confidential. Therefore, if the patients have any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must train the patient on how to use the ePRO device, using the materials and training provided by the ePRO vendor, and provide guidance on whom to call if there are problems with the device when the patient is completing the ePROs at home.
- The research nurse or appointed site staff should remind patients that there are no right or wrong answers.
- The research nurse or appointed site staff must avoid clarifying items in order to avoid bias.
- The patient must not receive help from relatives, friends, or clinic staff to answer the ePRO questionnaires. If a patient uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when she attends the clinic, the patient should be asked to complete the ePROs at home instead, as long as within time window. Site staff must not read or complete the ePROs on behalf of the patient.
- If the patient is unable to read (eg, blind or illiterate), that patient is exempted from completing the ePROs and may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff.
- The research nurse or appointed site staff must monitor compliance to ensure all data is captured. Compliance must be checked at each study visit to identify problems early. If a patient's compliance drops below 85%, they will be flagged in the routine compliance report generated by the ePRO system and a check-in call from the site to ask the patient if she has any difficulties is highly recommended.

8.2 Safety assessments

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

Whenever 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 relevant schedule of activities.

8.2.1 Laboratory safety assessments

See Table 13 for the list of clinical safety laboratory tests to be performed and to the SoA tables (Table 2, Table 3 and Table 4) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

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

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

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

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

Table 13 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)	Urinalysis (dipstick)
B-Haemoglobin (Hb)	S/P-Creatinine	U-Hb/Erythrocytes/Blood
B-Total white cell count	S/P-Bilirubin, total[b]	U-Protein/Albumin
B-Absolute Lymphocyte count[a]	S/P-Alkaline phosphatase (ALP)[b]	U-Glucose
B-Absolute neutrophil count[a]	S/P-Aspartate transaminase (AST)[b]	Ketones[c]
B-Platelet count	S/P-Alanine transaminase (ALT)[b]	pH[c]
B-Mean cell volume (MCV)	S/P-Albumin	Specific gravity[c]
Reticulocyte count[g]	S/P-Potassium	Bilirubin[c]
Coombs test (direct)[g]	S/P-Calcium, total	
	S/P-Sodium	
	Glucose[d]	
	Lactate dehydrogenase[d,g]	
	Amylase/lipase[d,e]	
	Creatinine clearance[c]	
	Total protein	
	Thyroid function (TSH, T3 [reflex], T4 [reflex])[d,f]	
	Urea or blood urea nitrogen	
	Haptoglobin[g]	

Abbreviations: ALT = Alanine aminotransferase; ALP = alkaline phosphatase; ANC = Absolute neutrophil count; AST = Aspartate aminotransferase; B = Blood; CTCAE = Common Terminology Criteria for Adverse Events; Hb = Haemoglobin; MCV = Mean Cell volume; P = Plasma; S = Serum; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid Stimulating Hormone; ULN = upper limit of normal.

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by data management if entered as a percentage. Total white cell count therefore has to be provided.

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

[c] These tests should be performed, on Day 1, Cycle 2 and if clinically indicated.

[d] These tests should be performed from Cycle 2 and then every 6 weeks, rather than every 3 weeks and aligned with the treatment cycle. Glucose can be tested at fasting or fed state depending on local laboratory requirements. These assessments are not required beyond the 90-day durvalumab safety visit in patients who continue on other study treatments but have discontinued durvalumab.

[e] 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.

[f] If TSH is measured within 14 days prior to Day 1, Cycle 2 (first durvalumab/saline infusion day), it does not need to be repeated at Day 1, Cycle 2. 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. On treatment, TSH should be measured every 6 weeks and aligned with the treatment cycle; if there is an abnormality, follow-up should also occur at the next scheduled visit.

[g] If a transfusion is required for a CTCAE Grade ≥ 3 anaemia while the patient is receiving olaparib and durvalumab in combination (or is within 90 days of receiving the combination, if either drug has been discontinued), these tests should be performed, ideally prior to the transfusion, per Appendix I 1.

All patients should have further chemistry profiles performed during follow-up (see Table 4).

NB: In case a patient shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

8.2.1.1 Coagulation

- Activated partial thromboplastin time (APTT) and international normalised ratio (INR) will be performed at screening only for patients receiving anticoagulant therapy or when clinically indicated. On study, coagulation tests should only be performed if clinically indicated.
- Patients taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib. If NOACs are used, it is preferable to avoid CYP3A substrates (eg, apixaban and rivaroxaban) if possible.

Each coagulation test result will be recorded in eCRF.

8.2.1.2 Bone marrow or blood cytogenetic samples

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

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

8.2.1.3 Disease specific tumour marker samples (CA125)

As part of the routine safety blood samples, CA125 assessment will take place as described in the SoAs (Table 2, Table 3 and Table 4). It is important to follow the assessment schedule as closely as possible. If CA125 assessment is performed outside of scheduled visit ± 2 weeks window interval, every attempt should be made to assess the CA125 at the scheduled time

points. A rise in CA125 alone is not sufficient to declare progression, and discontinue treatment.

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

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

8.2.2 Physical examination

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems. For timing of individual measurement refer to study schedule (see Table 2, Table 3 and Table 4). Following the baseline assessment, it is not necessary to record the details on an eCRF. Any clinically significant changes should be recorded as AEs.

Targeted physical examinations are to be utilised by the Investigator on the basis of clinical observations and symptomatology. ECOG performance status should be assessed according to Appendix G.

8.2.3 Vital signs

Vital signs (BP, pulse and temperature) will be evaluated according to the SoAs (see Table 2, Table 3 and Table 4). Height will be assessed at screening only. Weight will be assessed at screening and as clinically indicated at any other time.

First infusion of durvalumab/saline placebo

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

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

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

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

Subsequent infusions

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

Any changes in vital signs should be recorded as an AE, if applicable.

- BP and pulse rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size after 10 minutes rest.
- The date of collection and measurement will be recorded on the appropriate eCRF.
- Body temperature will be measured in degrees Celsius according to local practice at screening, baseline and as clinically indicated.

Any changes in vital signs should be recorded as an AE, if applicable. For information on how AEs based on changes in vital signs should be recorded and reported, see Section 8.3.6.

8.2.4 ECG

8.2.4.1 Resting 12-lead ECG

ECGs are required at screening and when clinically indicated.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

8.2.5 Other safety assessments

8.2.5.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days of Day 1 of Cycle 1, on Day 1 of Cycle 1 of the study prior to commencing treatment, at the time points shown in Table 2, Table 3 and Table 4 during study treatment and at the 30 day follow up visit. Tests will be performed by the hospital's local

laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

8.2.5.2 Early patient review for safety

It is recommended that patients are contacted 2 weeks (±3 days) after receiving the first 3 cycles of treatment with durvalumab/saline therapy (Cycle 2 Day 14; Cycle 3 Day 14; and Cycle 4 Day 14) to ensure early identification and management of toxicities.

8.2.5.3 Pneumonitis (ILD) investigation

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the durvalumab toxicity management guidelines (see Section 8.4.6.2) will be applied. If pneumonitis/ILD is suspected,then prompt investigations should be initiated and olaparib treatment interrupted. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately; and for durvalumab the guidance in the toxicity management guidelines (TMGs) should be followed (Section 8.4.6.2).

The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

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

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

(ii) Tumour markers: Particular tumour markers which are related to disease progression.

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

8.3 Collection of adverse events

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

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

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

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

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

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

8.3.2.1 Adverse events after the safety follow up period

For Pharmacovigilance purposes and characterisation, any SAE of MDS/AML or new primary malignancy occurring after the follow up periods specified in Section 1.1.3.2 should be reported to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for OS if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

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

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

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAE and AEs of special interest (AESIs as defined in Section 8.3.13), will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up

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

Any SAE or non-serious AE that is ongoing at the time of the 30-day or 90-day follow up, whichever is later, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The dates when the AE started and stopped
- CTCAE grade and changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day); see Appendix B for CTCAE gradings
- Whether the AE is serious or not
- Investigator causality rating against the study treatments(s) (yes or no); if the causality rating is given as "yes", an assessment of which study treatment(s) the AE is considered causally related to should also be provided
- Action taken with regard to study treatment(s)
- Administration of treatment for the AE
- AE caused patient's withdrawal from study
- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Seriousness criteria
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'
- Description of AE

8.3.5 Causality collection

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

For SAEs, causal relationship will also be assessed for other medications, including all study medications, as well as any study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

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

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

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

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

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

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

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN will need to be reported as SAEs if criteria is met for a Potential Hy's Law. 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 study treatments are under investigation. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The

development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.10 New cancers

The development of a new primary cancer should be reported as an AE (see Section 8.3.13 Adverse Events of Special Interest) and would in most cases meet seriousness criteria (with the exception of some non-melanoma skin cancers). New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

8.3.11 Lack of efficacy

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

8.3.12 Deaths

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

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours (see Section 8.4.1 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the ‘death eCRF’.

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

8.3.13 Adverse events of special interest

AESIs are events of scientific and medical interest specific to the further understanding of the study treatments safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca.

AESIs for olaparib are the Important Identified Risk of MDS/AML, the Important Potential Risk of new primary malignancy (other than MDS/AML), and the Potential Risk of pneumonitis.

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

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 im-AE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an im-AE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the im-AE. If the Investigator has any questions in regards to an event being an im-AE, the Investigator should promptly contact the Study Physician.

AESI/im-AEs 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 (including pemphigoid), myocarditis, myositis/polymyositis, pancreatitis, immune thrombocytopenia, and rare/less frequent im-AEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

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

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology 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 Annex to Protocol). 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.

8.4 Safety reporting and medical management

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

8.4.1 Reporting of serious adverse events

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

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

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

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

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

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

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

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

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

8.4.2 Regulatory reporting requirements for SAEs

Please refer to Appendix A 1.

8.4.3 Pregnancy

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

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

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

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

8.4.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, study treatment(s) should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatments may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) occurring from the date of the first dose of study medication until 6 months after the last dose of study medication should be followed up and documented even if the patient was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

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

8.4.4 Overdose

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

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

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

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

If an overdose on an IMP (Section 6.1.1) or AstraZeneca NIMP (Section 6.1.2) occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, within one (1) calendar day but no later than 24 hours of when he or she becomes aware of it.

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

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

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

8.4.5 Medication error, drug abuse, and drug misuse

8.4.5.1 Timelines

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow up fatal/life-threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.3.2) and **within 30 days** for all other events.

8.4.5.2 Medication error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an investigational product (ie, olaparib or durvalumab) study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of a medication error can be found in Appendix B 4

8.4.5.3 Drug Abuse

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

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

8.4.5.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of investigational product for medicinal purposes outside of the authorised product information, or for unauthorised study interventions, outside the intended use as specified in the CSP and includes deliberate administration of the product by the wrong route.

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

8.4.6 Toxicity management guidelines

8.4.6.1 Management of olaparib-related toxicities

Potential olaparib-related toxicities during the course of the study could be managed by interruption of the dose of olaparib/placebo treatment or dose reductions (see Appendix I, Section I 1). Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. If the reduced dose of 200 mg bd is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 6.5).

8.4.6.2 Management of durvalumab toxicities

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). These guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (ie, antineoplastic chemotherapy,

targeted agents), as part of a protocol specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment (see Sections 8.4.6.1 and 8.4.6.4). The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

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

Toxicity management and dose modifications for durvalumab

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

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

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

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

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the im-AE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an im-AE 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 IP, subsequent administration of durvalumab can be modified based on toxicities observed as

described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the durvalumab regimen by the reporting Investigator.

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

8.4.6.3 Management of olaparib in combination with durvalumab-related toxicities

Pure red cell aplasia (PRCA) has been identified as a new adverse drug reaction, and auto-immune haemolytic anaemia (AIHA) has been identified as a new potential risk for the combination of olaparib with durvalumab. If PRCA and / or AIHA are diagnosed, treatment with both olaparib and durvalumab should be discontinued (see also Appendix I1).

8.4.6.4 Specific toxicity management and dose modification information – Standard of Care

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

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

In cases of bevacizumab toxicity which have not resolved, the bevacizumab dose may be delayed and given 3 weeks later at the next scheduled visit. Dose delays are permitted for bevacizumab for up to a maximum of 12 weeks. If the toxicity has not resolved by 12 weeks, bevacizumab should be stopped permanently, as no dose adjustment is allowed (unless otherwise agreed by the Study Physician).

It is recommended that Investigators follow the ASCO guidelines regarding the use of Granulocyte colony-stimulating factor (G-CSF). Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, appropriate management including G-CSF should be given according to local hospital guidelines.

Please note: It is recommended that G-CSF should only be administered at least 24 hours after the last dose of chemotherapy and should not be administered on the day before or on the day of chemotherapy. Therefore, G-CSF should not be used to enable chemotherapy dosing in the event of neutropenia and instead chemotherapy should be delayed until recovery of the neutrophil count. If a patient experiences an event of febrile neutropenia, then secondary

prophylaxis using G-CSF should be considered and, if necessary, dose reduction of chemotherapy should be implemented for subsequent treatment based on the investigator's clinical judgement.

8.5 Pharmacokinetics (collection in non-*tBRCAm* patients only)

8.5.1 Collection of samples

Blood samples for determination of durvalumab concentrations in serum and olaparib concentration in plasma will only be taken in a subset of approximately 100 non-*tBRCAm* patients (approximately 33 evaluable patients per arm) who have already had upfront primary cytoreductive surgery at those sites that are able to take PK assessment samples. On-treatment PK samples will be taken at the times presented in the study plan (see Table 2) and at the 90-day safety follow-up (see Table 4).

For the on-treatment PK samples in Cycle 2, Cycle 4, Cycle 6 and the third cycle of the maintenance phase, durvalumab (or placebo [saline IV]) and bevacizumab must be dosed on the same day; if one treatment is delayed, the other treatment must also be delayed, so that dosing is coincident.

PK sampling for durvalumab will be carried out at the timepoints shown in Table 14:

Table 14 Durvalumab PK sampling schedule

Cycle number	Pre-dose sample	Post-dose sample	Comments
Cycle 2		X	Post dose sample to be taken up to 1 hour after the end of infusion
Cycle 4	X		Pre dose sample only; to be taken within 6 hours prior to start of infusion
Cycle 6	X	X	Pre dose to be taken within 6 hours prior to start of infusion; Post dose sample to be taken up to 1 hour after the end of infusion
Third cycle of maintenance phase	X	X	Pre dose to be taken within 6 hours prior to start of infusion; Post dose sample to be taken up to 1 hour after the end of infusion. Patients should have received 2 cycles of the combination of bevacizumab plus durvalumab/saline plus olaparib/placebo.
Safety follow-up (90 days after the last dose of durvalumab)	X (at any time)		Sample may be taken at any time during the visit

PK sampling for determination of olaparib in plasma will be performed on Day 1 of the third cycle of olaparib as maintenance treatment (ie, patients should have received 2 cycles of the combination of bevacizumab plus durvalumab/saline plus olaparib/placebo and received all treatments as scheduled) and collected at the following times:

Table 15 Olaparib PK sampling schedule

Cycle number	Pre-dose sample	Post-dose samples	Comments
Third cycle of maintenance phase	X	X	Samples to be taken at: Pre-dose to be collected within 0.5 hour prior to dosing Post dose: 0.5 hour to 1 hour; 1 hour to 3 hours; 3 hours to 6 hours; 6 hours to 12 hours after dosing

All olaparib PK samples should be taken at least 1 hour apart.

The actual date and time of dosing of olaparib on the PK sampling day and the day prior to the PK sampling day must be recorded. The date of the dosing of olaparib should be recorded for the 3 days prior to the PK sampling day. The patient will be provided with a dosing diary to document this information to provide to the site. PK samples are to be taken as a blood sample for determination of olaparib concentrations.

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

Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual.

8.5.1.1 Anti-drug antibodies (ADAs) and anti-drug neutralising antibodies

Anti-drug antibodies (ADA) samples for durvalumab will only be taken in the subset of approximately 100 non-*tBRCAm* patients who have already had upfront primary cytoreductive surgery and who are also scheduled for PK sampling; samples will be taken at the times presented in the study plan (see Table 2). In upfront primary surgery patients, samples will be collected pre-infusion at Cycle 2, Cycle 4, Cycle 6 and the third cycle of the maintenance phase (Cycle 9; ie, patients should have received 2 cycles of the combination of bevacizumab plus durvalumab/saline plus olaparib/placebo). A sample will also be collected at the 90-day safety follow-up visit.

Samples will be measured for the presence of ADAs and ADA-neutralising antibodies for durvalumab using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titre assay components, and positive negative cut-points previously statistically determined from drug-naïve validation samples will be employed.

Full details of the analytical method used will be described in a separate bioanalytical report.

ADA or anti-drug neutralising antibody information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5.2 Determination of drug concentrations

Samples for determination of drug concentrations of durvalumab in serum, will be analysed by a bioanalytical laboratory on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report. Placebo samples will not be analysed.

Samples for determination of drug concentrations of olaparib in plasma will be analysed by a bioanalytical laboratory on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report. Placebo samples will not be analysed.

8.5.3 Storage and destruction of pharmacokinetic/ADA samples

ADA and durvalumab PK samples will be disposed of a maximum of 5 years after the study treatments are approved for marketing. Olaparib PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

PK samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses will 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 Report.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

8.7.1 Mandatory blood sample for retrospective *BRCA* analysis

A significant proportion of tumour mutations are reflective of pre-existing germline mutations. Patients with central tumour *BRCA* results (*tBRCAm* and non-*tBRCAm*) will be required to submit a blood sample at Day 1 of Cycle 2 or at later visits for retrospective central germline *BRCA1/2* analysis. This may also include the analysis of germline HRR genes. If testing is done, the results will be shared with investigators in accordance with local requirements.

8.7.2 Collection of optional Genomics Initiative blood samples

The patient's consent to participate in the genetic research component (optional Genomics Initiative sample) of the study is optional. Consent for this sample is a separate section of the main ICF (see Appendix A, Section A 3), this section must be signed by the patient, before the optional blood sample is taken at screening. More details on the potential use of the Genomics Initiative sample are provided in Appendix D.

8.7.3 Storage and destruction of genetic samples

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

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

8.8 Biomarkers

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual. For blood volumes, please refer to the Laboratory Manual.

8.8.1 Sample requirements

8.8.1.1 Mandatory tumour sample requirements and analyses

Myriad Genetics myChoice HRD Plus assay

The investigational Myriad myChoice HRD Plus assay used in this study is being developed for approval as a companion diagnostic (note: since October 2020 this assay has also become known as the "Myriad myChoice CDx Plus assay" in some regions). All patients must sign the Pre-screen ICF to provide a mandatory FFPE tumour sample that meets the tissue specifications outlined in the Laboratory Manual for the determination of *BRCA1* and *BRCA2*

status using the myChoice HRD Plus test. The patient's consent to the use of tumour samples is mandatory (subject to local regulations). Tumour *BRCA* testing on the myChoice HRD Plus test will be conducted centrally in a single laboratory using a sequencing assay based on DNA extracted from FFPE tumour tissue. The tumour sample will be used to test the following biomarkers simultaneously on the myChoice HRD Plus assay: (i) tumour *BRCA1/2* gene mutation status and variant classification, (ii) genomic instability score and (iii) gene mutation status and variant classification of 13 Homologous Recombination Repair (HRR) genes: *ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L.*

In patients randomised, HRD status will be defined on the basis of the GIS score only (as all of them are non-*tBRCAm*). A patient with a GIS ≥ 42 is defined as HRD-positive, GIS < 42 as HRD-negative or, if GIS testing fails, as HRD-unknown.

Collection, Analysis and Reporting of Tumour Samples

Mandatory FFPE tumour sample from the primary cancer or metastatic lesions must be provided for central *BRCA* testing, as detailed in the laboratory manual. FFPE tumour tissue blocks are required for each patient, but if not available, tissue sections are accepted. The tumour specimen submitted should be of sufficient quantity to allow determination of the *tBRCAm* status and other exploratory biomarker analyses. Please consult the laboratory manual for specific instructions and guidelines regarding sections. Collection of these samples is mandatory, subject to local regulations.

If the first tumour sample submitted for testing is inconclusive due to technical test failure, a further tumour sample may be submitted for testing provided there is sufficient time available to receive the result before *tBRCAm*/non-*tBRCAm* cohort allocation and randomisation on Day 1 of Cycle 2. Submission and testing of new samples can only be performed if the original testing failed due to technical failure. Please refer to the Laboratory manual for further details regarding retesting procedures. For each subject that passes tissue sample and sequencing quality control, Myriad will generate a report specifying presence or absence of deleterious or suspected deleterious *BRCA1/2* gene mutations. A mutation is regarded as deleterious if it results in protein truncation (which includes nonsense, frameshift, or consensus splice site mutations), or select missense mutations well-known to be deleterious in ClinVar/BIC databases in *BRCA1* and *BRCA2*. Furthermore, larger scale alterations such as genomic truncating rearrangements or homozygous deletions will also be classified as deleterious. Subjects without myChoice HRD Plus Assay results will not be eligible for the study.

The mandatory archival tumour sample can either be one of the following (as detailed in the laboratory manual):

- A tumour sample obtained from primary cytoreductive surgery in patients who have already undergone such surgery
- If a primary cytoreductive surgery sample is not available, a biopsy sample previously obtained at diagnosis may be provided. The tumour sample provided may be from either a primary or metastatic site. Use of new tumour sample (a *de novo* sample) for *BRCA* testing is permitted provided the sample is taken as part of routine clinical practice.
- Patients scheduled for IDS should also consent to provide a tumour sample to be obtained at the time of IDS (provided a tumour sample can be collected during IDS).

As described, the tumour sample will be used to test several biomarkers simultaneously (tumour *BRCA1/2* and HRR gene mutation status and variant classification, and HRD status). Further exploratory genomic profiling of the tumour may include but is not limited to CCI , CCI CCI Exploratory analyses to explore the impact of PD-L1 expression on treatment regimen in PD-L1 high, low and unknown patient subgroups of the non-*tBRCAm* (ITT) population will be conducted. Based on availability of tissue, additional biomarkers may be evaluated which may include, but are not limited to: CCI as well as CCI
CCI
CCI
CCI

CCI

Baseline measures will be correlated with outcomes. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with durvalumab and olaparib therapy versus SoC. Changes in biomarker status pre- and post- treatment with chemotherapy +/- durvalumab will be assessed in IDS patients where a tumour sample is available at the time of debulking surgery. These data may be reported separately to the CSR.

Residual tumour sample may be used for further research or to develop and validate future companion diagnostic tests. Consent for use of sample for future testing is optional.

8.8.1.2 Blood samples for exploratory biomarker analysis

Determining the molecular phenotype of a tumour from a peripheral blood sample has numerous advantages over relying on archival tumour samples or fresh biopsies, not least because these features may be tracked over time and genetic changes may inform tumour resistance mechanisms. CCI

CCI

CCI

CCI

CCI

CCI Samples may be used for CCI

CCI

CCI

CCI

CCI

CCI

Table 16 Biomarker sampling schedule

Timepoint	CCI	Patients with primary cytoreductive surgery	Patients requiring IDS	Notes
		CCI		
Main screen	CCI			Baseline samples
Cycle 1 Day 1				Baseline sample
Cycle 2 Day 1				During chemotherapy + bevacizumab + durvalumab/saline for IDS patients
Cycle 3 Day 1				During chemotherapy + bevacizumab + durvalumab/saline for IDS patients
Visit 8 (start of maintenance phase)				Chemotherapy completed. Start of maintenance treatment sample.
Maintenance Phase				Samples taken in alignment with imaging assessments (Q12W for 3 years then Q24W until disease progression).
Disease progression[b]				CCI

Table 16 Biomarker sampling schedule

Timepoint	CCI	Patients with primary cytoreductive surgery		Patients requiring IDS		Notes
	CCI		Plasma biomarkers (optional)	CCI	Plasma biomarkers (optional)	
Treatment discontinuation						Required from all patients at treatment discontinuation[b]
30-day follow-up						Required from all patients who have discontinued all treatment

a CCI

b

Abbreviations: CCI; IDS = Interval debulking surgery; Q12W = Every 12 weeks; Q24W = Every 24 weeks.

Please refer to Laboratory manual for further details of biomarker blood sample collection, shipping, and storage.

8.8.1.3 Optional tumour sample requirements and analyses

Optional on-study tumour samples should be collected as follows:

- A tumour sample obtained at disease progression.

Analyses for tumour specimens obtained on disease progression will focus on CCI CCI and may include, but are not limited to: CCI CCI

Optional tumour sample for academic research

If available, an additional tumour sample from the primary cytoreductive surgery or core biopsy at diagnosis should be collected at Pre-screening for exploratory predictive and prognostic analyses. Collection of these samples is optional, subject to local regulations.

If collected, this sample will be finally stored in the biobank nominated by Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Research GmbH.

Please refer to Laboratory manual for further details of tumour sample collection, shipping, and storage.

8.8.1.4 Optional blood samples for exploratory biomarker analysis

Circulating soluble factors

Optional pre-treatment plasma samples, will be obtained from all patients at time-points described in the SoAs (Table 2, Table 3, Table 4 and Table 16). Please refer to the laboratory manual for specific instruction on sample collection.

CCI

CCI part of the exploratory biomarker work. Comparisons will be made between baseline measures and changes in concentrations over time and with treatment, to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with durvalumab and olaparib therapy versus SoC.

CCI

CCI

CCI

CCI

CCI

CCI

Focus is likely to be given to the expression of CCI

CCI

CCI

CCI

CCI

CCI

CCI

8.8.2 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.9 Medical resource utilisation and health economics

Resource use data, including inpatient admissions, intensive care unit (ICU) and length of stay in hospital, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all patients throughout the study. The data may be

used as input to cost analyses for example cost utility analysis or cost effectiveness analysis. Protocol-mandated procedures, tests, and encounters are excluded.

8.10 Data collection during extended OS follow-up (Global *tBRCAm* and non-*tBRCAm* cohorts only)

8.10.1 Patients on treatment at final OS analysis (Global *tBRCAm*/non-*tBRCAm* cohorts)

Patients in the global cohorts who are on study treatment at the final OS analysis DCO should continue to receive their assigned treatment if, in the opinion of the Investigator, it is in the patient's best interest and in accordance with CSP requirements (see Section 6.1.1). For patients continuing to receive olaparib/placebo and/or durvalumab/placebp following the final OS analysis DCO, it is recommended that patients continue the scheduled site visits and safety assessments so Investigators can monitor safety associated with ongoing treatment.

8.10.2 Patients who have discontinued treatment by the final OS analysis (Global non-*tBRCAm* cohort only)

Patients in the non-*tBRCAm* cohort who have discontinued treatment by the final OS analysis DCO should continue survival assessment every 12 weeks (±2 weeks) during extended OS follow up, which may be performed via phone contact and does not require an in-person visit.

8.10.3 Data collected during extended OS follow-up

Post final OS analysis, limited data should be collected as outlined below.

- Global *tBRCAm* and non-*tBRCAm* cohorts: Olaparib and/or durvalumab administration must continue to be reported if patients continue study treatments during extended OS follow-up.

- Global *tBRCAm* and non-*tBRCAm* cohorts: All SAEs, AEs, and pregnancies occurring on treatment or within the safety follow-up periods, must continue to be reported to the Sponsor within the usual timelines (ie, for SAEs immediately, or no later than 24 hours of when the site become aware of the SAE) directly in the EDC. For patients who have completed treatment, AEs should be reported as described in Section 8.3.2.1.

- Global non-*tBRCAm* cohort only: Survival status will be collected for all patients in the non-*tBRCAm* cohort during extended OS follow-up, and information of subsequent anti-cancer therapy will be collected if patients started anti-cancer therapy during extended OS follow-up. Survival information may be obtained via telephone contact with the patient, patient's family, by contact with the patient's current physician, local death registries as described per local rules and regulations, and/or medical records.

- No sample collections, images or PFS2 data are required for any patients in the extended OS follow up.

9. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives. All personnel involved with the analysis of the study (except unblinded 3rd party pharmacists preparing durvalumab/saline and PK analysts, as detailed elsewhere in the CSP) will remain blinded to the randomised treatment in the non-*tBRCAm* cohort until after database lock and CSP deviations identified. Refer to the Statistical Analysis Plan (SAP) for details.

A comprehensive SAP will be prepared prior to first patient enrolled and any subsequent amendments will be documented, with final amendments completed prior to database lock.

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

9.1 Statistical hypotheses

The primary objective of the study is to compare PFS (per RECIST 1.1 as assessed by investigator) for Arm 3 vs Arm 1 in non-*tBRCAm* HRD positive population and in the non-*tBRCAm* ITT population. A key secondary comparison is to compare PFS (per RECIST 1.1 as assessed by investigator) for Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population.

The hypotheses of interest with regards to the efficacy in the non-*tBRCAm* cohort for each population of interest are as follows:

H_{031}: Arm 3 = Arm 1 vs H_{131}: Arm 3 ^= Arm 1

and

H_{021}: Arm 2 = Arm 1 vs H_{121}: Arm 2 ^= Arm 1

Where H_0 = the null hypothesis; H_1 = the alternate hypothesis and:

- Arm 1 = bevacizumab in combination with platinum-based chemotherapy
- Arm 2 = bevacizumab in combination with platinum-based chemotherapy + durvalumab
- Arm 3 = bevacizumab in combination with platinum-based chemotherapy + durvalumab + olaparib

In addition, an exploratory analysis comparing Arm 3 and Arm 2 will also be undertaken, where required. This will be further described in the SAP.

9.2 Sample size determination

Approximately 1104 eligible ovarian cancer patients will be randomised globally at a 1:1:1 ratio to the study treatments in the non-*tBRCAm* cohort. The sample size for the non-*tBRCAm* cohort was derived using a validated non-proportional hazards-based AstraZeneca R package for sample size calculations and was based on the following assumptions:

- The sample size is based on an assumed median PFS duration of 18 months for the chemotherapy + bevacizumab arm and is based on the results seen in the PAOLA-1 study (Ray-Coquard et al 2019) in addition to the expected average time for chemotherapy and the inclusion of the stable disease population in the DUO-O study. The original assumed median PFS for the control arm was 16 months and was based on the data reported in the GOG218, ICON7 and GOG262 clinical trials with bevacizumab in the first-line setting, including subgroup analysis from the GOG218 study based on *BRCA*/HRR wild type status (Perren et al 2011; Burger et al 2013; Norquist et al 2018).
- The sample size has been derived on the assumption of a 3 months delay in separation of the PFS curves between Arm 2 vs Arm 1 and between Arm 3 vs Arm 1. The assumed average hazard ratio for PFS for the chemotherapy, bevacizumab, durvalumab + olaparib arm in the non-*tBRCAm* HRD positive population is 0.49 (approximately 39 months median PFS), in the non-*tBRCAm* ITT population is 0.61 (approximately 30 months median PFS) and for the chemotherapy, bevacizumab and durvalumab arm in the non-*tBRCAm* ITT population it is 0.74 (approximately 24 months median PFS).
- In addition the sample size has been derived on the assumption that 15% of patients will drop out.

The data cut off for the primary analysis of PFS for the two comparisons of interest (Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population) will be undertaken at the same calendar time when approximately 149 PFS events have occurred (58% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and approximately 453 PFS events (62% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population. At the time of the PFS primary analysis approximately 480 PFS events (65% maturity) are expected to have occurred for the comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population. Assuming a non-linear recruitment period of 26 months, the data cut off for the analysis of PFS will take place at approximately 52 months after the first patient has been randomised.

The PFS comparisons are adequately powered, under the assumed effect sizes, for each comparison of the experimental arms vs chemotherapy and bevacizumab combination. A hierarchical testing procedure will be applied to strongly control the type I error at the 5% two-sided level (see Section 9.4.4 for more information).

For the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population, if the average true PFS hazard ratio is 0.49, the study will have >90% power to demonstrate a

statistically significant difference at a two-sided alpha level of 5%. The smallest treatment difference that would be statistically significant is an average hazard ratio of 0.72.

For the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population, if the average true PFS hazard ratio is 0.61, the study will have >90% power to demonstrate a statistically significant difference at a two-sided alpha level of 5% overall. The smallest treatment difference that would be statistically significant is an average hazard ratio of 0.83.

For the comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population, if the average true PFS hazard ratio is 0.74, the study will have >80% power to demonstrate a statistically significant difference at a two-sided alpha level of 2.5%. The smallest treatment difference that would be statistically significant is an average hazard ratio of 0.81.

An interim PFS analysis is planned and is described in detail within Section 9.5.

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

- A 3 month delay in the separation of the OS curves between Arm 2 vs Arm 1 and between Arm 3 vs Arm 1
- Median OS of 55 months for Arm 1
- An average hazard ratio of 0.79 for OS for Arm 3 vs Arm 1 comparison in both the non-*tBRCAm* HRD-positive population and the non-*tBRCAm* ITT population (hazard ratio 0.78 from 3 months onwards [approximately 70 months median OS])
- An average hazard ratio of 0.86 for OS for Arm 2 vs Arm 1 comparison in the non-*tBRCAm* ITT population (hazard ratio 0.85 from 3 months onwards [approximately 65 months median OS]).

At the time of the primary analysis of PFS, the interim analysis of OS will also be performed. For the comparison of Arm 3 vs Arm 1 it is anticipated that the maturity will be approximately 31% in both the non-*tBRCAm* HRD-positive population and the non-*tBRCAm* ITT population and for the comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population, it is anticipated that the maturity will be approximately 32%.

A final analysis of OS may be performed at approximately 50% maturity across the 3 treatment arms in the non-*tBRCAm* ITT population or 5 years following randomisation of the last *non-tBRCAm* patient, whichever occurs sooner. The power to detect a difference between Arm 3 and Arm 1 will be approximately 17% in the non-*tBRCAm* HRD-positive population and approximately 48% in the non-*tBRCAm* ITT population at the 2.5% level (using a two-sided test). The power to detect a difference between Arm 2 and Arm 1 in the non-*tBRCAm* ITT population will be approximately 21% at the 2.5% level (using a two-sided test). Note that these estimates are based on the assumption that no confounding will occur.

AstraZeneca anticipates potential confounding of OS data due to availability of PARP inhibitors for ovarian cancer patients.

In the event final analysis of OS occurs when approximately 50% maturity has occurred across the 3 treatment arms in the non-*tBRCAm* ITT population, an extended OS descriptive analysis (non-*tBRCAm* cohort only) may also be performed 5 years after the last non-*tBRCAm* patient is randomised to treatment.

9.3 Populations for analyses

For the non-*tBRCAm* cohort, 4 analysis sets will be defined for analysis of: safety, PK, efficacy and ADA. Similar definitions will be used for the *tBRCAm* cohort (Full Analysis Set and Safety Analysis Set).

Note, Global recruitment to the study will close when approximately 1104 non-t*BRCA*m patients are randomised. If necessary, enrolment in China will continue after global recruitment is closed (ie, last subject randomised from a non-Chinese site) to allow inclusion of a China cohort consisting of approximately 120 non-*tBRCAm* randomised patients. The China cohort will support standalone safety and efficacy analyses of the non-t*BRCA*m patients from sites in China (please see Section 9.4.6 for details).

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

9.3.1 Full analysis set

The Full Analysis Set (FAS) comprises all patients who are randomised in to the study regardless of whether they receive treatment or not. All efficacy and HRQoL data will be summarised and analysed using the FAS on an intention to treat (ITT) basis.

There are two primary efficacy populations in the non-*tBRCAm* cohort: the non-*tBRCAm* HRD-positive population and the non-*tBRCAm* ITT population.

- The non-*tBRCAm* HRD-positive population includes all non-*tBRCAm* patients who are randomised into the study and identified as HRD positive (GIS ≥ 42).
- The non-*tBRCAm* ITT population includes all non-*tBRCAm* patients who are randomised into the study.

9.3.2 Safety analysis sets

The safety analysis set will comprise all patients who received at least one dose of any of the investigational treatments (ie, durvalumab/olaparib), including placebo, in either cohort, (regardless of whether that was the randomised therapy intended or indeed whether, in rare cases, they received therapy without being randomised).

For the non-*tBRCAm* cohort, patients who initially received a dose of durvalumab/durvalumab placebo will be summarised according to the arm they are randomised to. This is in order to provide a summary of the underlying safety profile that patients should expect when initially prescribed to treatment (i.e. SoC, SoC + durvalumab, or SoC + durvalumab + olaparib).

9.3.3 Pharmacokinetic analysis set (non-*tBRCAm* patients only)

Each PK analysis set will comprise of all evaluable patients dosed with the relevant study drug and having any sample collection of blood with evaluable and measurable concentration of that drug in plasma or serum.

9.3.4 ADA analysis set (non-*tBRCAm* patients only)

The ADA evaluable subjects are patients in the Safety Analysis Set who received at least 1 dose of durvalumab and have non-missing baseline ADA and at least 1 post-baseline ADA result.

9.4 Statistical analyses

A comprehensive SAP will be developed and finalised before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR. An independent statistical analysis will be done by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group, but will be described and reported separately.

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

9.4.1 Efficacy analyses

9.4.1.1 Calculation or derivation of tumour response variables

At each visit patients will be programmatically assigned a modified RECIST Version 1.1 overall visit response of CR, PR, SD, PD or non-evaluable (NE) depending on the status of

their disease compared with baseline and previous visit assessments. For the statistical analysis, the last scan prior to randomisation will be regarded as the baseline scan.

The following tumour response variables will then be derived:

- PFS
- ORR
- Duration of response

Tumour response

Please refer to Appendix H for tumour response analysis details.

Progression free survival

PFS is defined as the time from allocation to the *tBRCAm* cohort, or randomisation to the non-*tBRCAm* cohort until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from assigned therapy or receives another anticancer therapy prior to progression. 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 RECIST Version 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest RECIST Version 1.1 assessment prior to the two missed visits. If the patient has no RECIST visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline.

Objective response rate

ORR is defined as the number (percentage) of patients with at least one investigator-assessed visit response of CR or PR as assessed by the investigator as per RECIST Version 1.1 and who have evaluable disease at baseline. Data obtained up until progression, or the last RECIST assessment in the absence of progression, will be included in the assessment of ORR.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), no evidence of disease (NED) and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of a best response of progression, tumour response (CR, PR, SD) will be calculated in comparison with the baseline tumour measurements obtained before randomisation. For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PD and Non CR/Non PD. Patients with no disease at baseline will be assessed according to RECIST 1.1 criteria for new lesions with responses of NED or PD.

A patient will be classified as a responder if the RECIST 1.1 criteria for a CR or PR are satisfied at any time up to and including the defined analysis cut-off point. For each treatment group, the ORR is the number of CR and PR divided by the number of patients in the group in the FAS with evaluable disease at baseline.

Duration of response

Duration of response will be defined as the time from the date of first documented response (CR/PR) as per RECIST Version 1.1 as assessed by the investigator until the date of documented progression or death in the absence of disease progression, the end of response will coincide with the date of progression or death from any cause. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

9.4.1.2 Analysis of the non-*tBRCAm* Cohort

Analysis of the primary variable

PFS will be analysed using a log rank test stratified by timing and outcome of cytoreductive surgery (no macroscopic residual disease after upfront primary surgery vs all others [macroscopic residual disease after upfront primary surgery or planned IDS]), and geographic region (North America vs Europe vs RoW). The hazard ratio together with its 95% CI and p-value will be presented (a hazard ratio less than 1 will favour the comparator arm). The hazard ratio and confidence interval will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron and the stratification variables as strata) and the CI will be calculated using a profile likelihood approach. The primary analyses will be based on investigator-recorded assessment of disease progression by RECIST 1.1.

Stratification variables will be defined according to data from the interactive response system (IRT). If there are any patients who are mis-stratified, a sensitivity analysis will be carried out using the baseline data collected in the eCRF.

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

The assumption of proportionality will be assessed. Note that in the presence of non-proportionality, the hazard ratio will be interpreted as an average hazard ratio over the observed extent of follow-up. Proportionality will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation.

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

The proportion of patients alive and progression free at 6 monthly intervals from randomisation will be summarised (using the KM curve) and presented by treatment group.

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

Analysis of the secondary variable(s)

The analyses of PFS2, OS, TFST, TSST and TDT will use the same methodology as specified for PFS.

ORR will be analysed using logistic regression stratified by timing and outcome of cytoreductive surgery and geographic region. The odds ratio (OR) together with its 95% CI and p value will be presented (an OR less than 1 will favour the comparator arm). ORR will be analysed across the entire period of the study (ie, chemotherapy phase and maintenance phase) and for the two phases separately, for all patients with evaluable disease at baseline. In addition, ORR will be analysed prior to surgery in those patients planned to have IDS with evaluable disease at baseline. Duration of response will also be summarised across the entire period of the study (ie, chemotherapy phase and maintenance phase) and for the two phases separately.

At the time of the final analysis of PFS an interim analysis of OS will be performed. A final analysis of OS may be performed when approximately 552/1104 OS events (~50% maturity) have occurred across the 3 non-*tBRCAm* treatment arms or 5 years following randomisation of the last non-*tBRCAm* patient, whichever occurs sooner. *(Note, In the event final analysis of OS occurs when approximately 552/1104 OS events [~50% maturity] have occurred across the 3 treatment arms in the non-*tBRCAm *ITT population, an extended OS descriptive analysis [non-*tBRCAm *cohort only] may also be performed 5 years after the last non-tBRCAm patient is randomised to treatment.)*

Subgroup analyses

Subgroup analyses will be conducted for PFS to assess consistency of treatment effect across potential or expected prognostic factors including:

- Timing and outcome of cytoreductive surgery (no macroscopic residual disease after upfront primary surgery vs all others [macroscopic residual disease after upfront primary surgery OR planned IDS]),
- Geographic region (North America vs Europe vs RoW);
- Age (<65 years vs ≥65 years);
- ECOG performance status (PS0 vs PS1);
- Stage of disease at diagnosis (Stage III vs Stage IV);
- CR/PR/NED vs non CR/PR/NED at the end of chemotherapy;
- HRD status (HRD positive vs HRD negative vs HRD unknown), as required;
- Homologous recombination repair related gene mutation (HRRm) status (HRRm vs non HRRm);
- PD-L1 expression (high vs low vs unknown).

Other biomarker subgroups can be added prior to database lock based on emerging clinical trial evidence. An analysis will not be performed if there are too few events available for a meaningful analysis of a particular subgroup (ie, if there are less than 5 events in a stratum). Other subgroups of exploratory interest will be defined in the SAP.

The subgroup analyses for the stratification factors will be based on the values entered into the IRT, all other factors will be based on values recorded on the eCRF, or from the third party vendor data.

For each subgroup factor, the hazard ratio and 95% profile likelihood CI will be calculated from an un-stratified Cox proportional hazards model that only contains treatment as a term. The Cox models will be fitted with the Efron method to control for ties.

Sensitivity Analyses

Sensitivity analyses will be performed, including using the BICR analysis of disease progression.

Summary statistics for the number of weeks between the time of progression and the last RECIST 1.1 assessment prior to progression will be presented.

(a) Evaluation-Time bias

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous RECIST 1.1 assessment will be analysed using a stratified log rank test, as described for the primary analysis of PFS. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010). This approach will use the investigator RECIST 1.1 assessments.

(b) Attrition bias

Attrition bias will be assessed by repeating the primary 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 two, or more, missed RECIST tumour assessments will be included. In addition, patients who take subsequent therapy prior to their last RECIST assessment or progression or death will be censored at their last RECIST assessment prior to taking the subsequent therapy.

Additionally, a KM plot of the time to censoring where the censoring indicator of the primary PFS analysis is reversed will be presented.

(c) Ascertainment bias

A stratified log-rank test will be repeated using the BICR assessed RECIST 1.1 data to programmatically derive PFS. The hazard ratio and 95% CI will be presented.

If there is an important discrepancy between the primary analysis using investigator assessments and this sensitivity analysis using BICR assessments, then the proportion of patients with site but no central confirmation of progression will be summarised. The approach of imputing an event at the next visit in the central review analysis may help inform the most likely hazard ratio value, but only if an important discrepancy exists.

(d) Deviation bias (if meaningful to do)

As a sensitivity to the primary endpoint of PFS, an analysis excluding patients with selected important deviations (to be defined in the SAP) that may affect the efficacy of the trial study treatment will be performed if >10% of patients have such deviations.

A stratified log-rank test will be repeated using the investigator RECIST 1.1 data, using the same ties and stratification factor as described for the primary analysis of PFS. The hazard ratio and 95% CI will be presented.

9.4.2 Safety analyses

Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, SAEs, AEs leading to treatment discontinuation, laboratory data, vital signs, ECG changes, and physical examinations. These will be collected for all patients from Day 1 of Cycle 1 (SAEs will also be collected from signing of the Main ICF). Appropriate summaries of these data will be presented by treatment and by treatment phase.

Creatinine clearance

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

For creatinine values in µmol/L:

- Females: [(140-age)×weight (kg)×1.04)]/serum creatinine (µmol/L)]

For creatinine values in mg/dL:

- Females: 0.85×[(140-age)×weight (kg)/[72×serum creatinine (mg/dL)]

Other significant adverse events

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

All safety analyses will be performed on the Safety Population.

9.4.3 Other analyses

The following exploratory endpoints will be examined (note; some or all of these may be reported in a separate document to the CSR):

- The proportion of patients with NED at 15, 24 and 48 months after initiation of treatment will be summarised descriptively.
- Duration of relapse free survival for patients who have NED/CR at the end of chemotherapy will be summarised descriptively.
- Resource use will be summarised descriptively.
- Biomarkers will be analysed using appropriate summaries of the exploratory outcome variables and data listings will be produced and compared across the treatment arms. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.
- For the serum concentrations of durvalumab and olaparib, the maximum plasma concentration at steady state and the area under the curve at steady state will be summarised appropriately.
- The presence of ADAs for durvalumab will be summarised as appropriate.

Analysis of PRO Endpoints

Change from baseline in the physical functioning subscale of the EORTC-QLQ-C30 will be regarded as the main analysis of interest and will be analysed using a piecewise linear modelling analysis of the change from baseline (defined as prior to first dose) in scores for each visit.

The main analysis will be to compare the average treatment effect from the point of randomisation for the first 24 months.

The other scores of the EORTC-QLQ-C30 and EORTC-QLQ-OV28 will be analysed in a similar manner. The data from both EORTC questionnaires, the PGIS and the PRO-CTCAE will be summarised descriptively.

For the EQ-5D descriptive statistics, graphs and listings will be reported for health state utility values and visual analogue scale by visits as well as change in these scores from baseline.

Quality adjusted progression free survival (QAPFS), will be calculated using a mixed model for repeated measures analysis. The model will include all EQ-5D measures up to the measurement closest to progression as well as treatment, patient, baseline score, visit and a treatment by visit interaction.

Quality-adjusted time without symptoms of disease or toxicity (QTWiST) will be performed to assess duration of 'good quality of life' in which the survival time will be partitioned into three health states; toxicity, time without symptoms and relapse.

Additional PRO analyses will be described in a separate data analysis plan.

9.4.4 Methods for multiplicity control

In order to strongly control the type I error at the 5% two-sided level, a multiple testing procedure will be employed (see Figure 6). The overall 5% type I error rate will be allocated to the primary PFS comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population.

- If the PFS analysis for this comparison is statistically significant at the time of either the interim analysis or the final analysis, 5% alpha (two-sided) will be allocated to the next level in a pre-defined order:
  - 5% alpha will be assigned to PFS comparison of Arm 3 vs Arm 1 non-*tBRCAm* ITT population. If statistical significance for PFS comparison of Arm 3 vs Arm 1 non-*tBRCAm* ITT population is met, the 2.5% (two-sided) test mass is recycled to test the PFS comparison of Arm 2 vs Arm 1 non-*tBRCAm* ITT population and the other

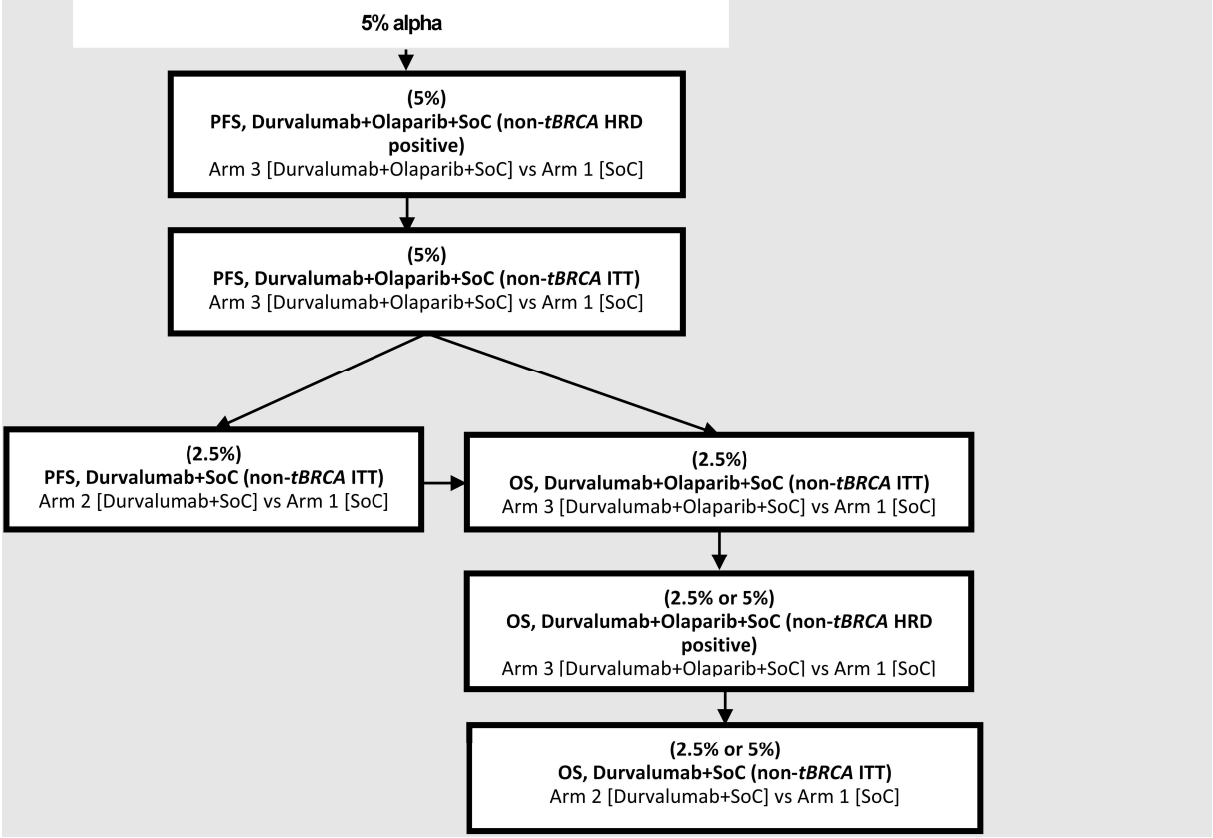
2.5% alpha (two-sided) assigned to the OS comparison of Arm 3 vs Arm 1 non-*tBRCAm* ITT population.

- If statistical significance for PFS comparison of Arm 2 vs Arm 1 non-*tBRCAm* ITT population is met, the 2.5% (two-sided) test mass is recycled to test the OS comparison of Arm 3 vs Arm 1 non-*tBRCAm* ITT population and this will be tested at 5% alpha.
- If statistical significance for OS comparison of Arm 3 vs Arm 1 non-*tBRCAm* ITT population is met, the test mass (2.5% or 5% [two-sided]) is recycled to test the OS comparison of Arm 3 vs Arm 1 non-*tBRCAm* HRD-positive population.
- If statistical significance for OS comparison of Arm 3 vs Arm 1 non-*tBRCAm* HRD-positive population is met, the test mass (2.5% or 5% [two-sided]) is recycled to test the OS comparison of Arm 2 vs Arm 1 non-*tBRCAm* ITT population.

A PFS interim analysis and an OS interim analysis is planned (see Section 9.5 for details). Note: If any interim analysis or primary analysis is statistically significant, the overall 2.5% or 5% (two-sided) alpha will be allocated to the next level[1]. If the interim results do not meet the criterion of stopping for superiority for a given hypothesis, then follow-up will continue until the final target number of PFS/OS events for that comparison has been observed, following which the hypothesis will be retested. If the hypothesis is then rejected, subsequent testing will continue hierarchically. The above testing procedure will ensure strong control of the family-wise error rate (Glimm et al 2009).

[1] The 5% alpha (two-sided) allocation for the primary and secondary PFS endpoints will be controlled at the interim and the final analysis timepoints separately for each PFS comparison by using a bespoke spending function, where a fixed significance level will be assigned at the interim and the remaining significance level assigned to the final analysis, taking account of correlation (Stone 2010). For OS, the 2.5%/5% alpha (two-sided) would be controlled at the interim and the final analysis timepoints separately for each comparison by using Lan De Mets O'Brien-Fleming spending function, where the significance level applied at the interim analysis depends upon the proportion of information (ie, information fraction) available.

Figure 6 Multiple Testing Procedure in the Randomised non-*tBRCAm* Cohort



HRD = homologous recombination deficiency; OS = overall survival; PFS = progression free survival; SoC = standard of care; *tBRCA* = tumour breast cancer susceptibility gene.

In order to describe the nature of the benefits of durvalumab and durvalumab + olaparib compared with the comparator arm, ORR, PFS2, TFST, TSST, TDT and change from baseline score in the physical functioning subscale of the EORTC-QLQ-C30 will be tested at a two-sided significance level of [redacted]%.

9.4.5 Analysis of the *tBRCAm* cohort

At the time of the DCO and unblinding for the PFS analysis in the non-*tBRCAm* cohort, the PFS data from the *tBRCAm* cohort will be appropriately summarised.

PFS, PFS2, TDT, TFST, TSST and OS will be derived as described above. Kaplan-Meier plots will be presented and summaries of the number and percentage of patients experiencing the respective endpoints will be provided along with the estimate of the median, if achieved. ORR and duration of response to treatment will be summarised across the entire period of the study. Tumour samples will be analysed retrospectively for biomarkers of response to durvalumab, in a similar manner to the non-*tBRCAm* cohort.

Safety data will be appropriately summarised in a similar manner to the non-*tBRCAm* cohort. PRO data will be summarised using appropriate descriptive statistics. Other data including exploratory research endpoints will also be described using appropriate summary statistics.

Full details of the analyses for the *tBRCAm* cohort will be provided in the Statistical Analysis plan.

9.4.6 China Cohort (non-*tBRCAm* patients only)

The global recruitment into the non-*tBRCAm* cohort of this study will close to all sites apart from China when approximately 1104 patients have been randomised. Any patient from China, randomised before the global recruitment is closed (ie, last subject randomised from a non-Chinese site) will be included in both the global ITT population and the China cohort ITT population. A patient randomised in China after the global recruitment closure will be included only in the China cohort ITT population.

Approximately 120 patients from sites in China will be recruited and randomised in a 1:1:1 ratio to the study treatments in the non-*tBRCAm* cohort and will follow the same study plan and procedures as patients recruited to the global study. The safety and efficacy data collected will be summarised and analysed separately to the global study safety and ITT analysis sets (as defined in Section 9.3.1).

The primary analysis of efficacy for the China cohort will be an assessment of programmatically derived PFS based on investigator assessments (RECIST 1.1) in the China cohort ITT population (China FAS). The China FAS comprises all patients from sites in China who are randomised regardless of whether they receive treatment or not. The data cut off for the analysis of PFS in the China cohort for the two comparisons of interest (Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population) will be undertaken at the same calendar time when approximately 17 PFS events have occurred (61% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and approximately 51 PFS events (64% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population. At this time approximately 54 PFS events (68% maturity) are expected to have occured for the comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population.

Where data permit, summaries and analysis of secondary supportive efficacy endpoints (including at least but not limited to OS) will be performed for the China cohort. The detailed analysis plan will be documented in the China supplementary SAP.

When assessing safety and tolerability, summaries will be produced separately for the China cohort based on the China safety analysis set. The China safety analysis set includes all subjects from sites in China who receive at least one dose of randomised investigational

treatment (ie, durvalumab/olaparib), including placebo. The China safety data will be summarised descriptively and will not be formally analysed.

9.5 Interim analyses

One interim analysis will be performed for PFS and one interim analysis will be performed for OS:

- The first DCO, an interim PFS analysis, will occur when approximately 86% of the target number of PFS events is expected to be reached for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population **and** non-*tBRCAm* ITT population (ie, approximately 128 of 149 PFS events across Arm 3 and Arm 1 in non-*tBRCAm* HRD-positive population and 390 of 453 PFS events in the non-*tBRCAm* ITT population). It is anticipated that approximately 86% of the target number of PFS events (ie, approximately 414 of 480 PFS events) will be available for the comparison of Arm 2 vs Arm 1 in the non-*tBRCAm* ITT population at that time. In addition, a descriptive analysis of OS will also occur at this time. This interim will occur approximately 43.5 months after the first patient is randomised
- The second DCO, primary analysis of PFS and an interim OS analysis, will occur when approximately 149 PFS events have occurred (58% maturity) for the comparison of Arm 3 vs Arm 1 in non-*tBRCAm* HRD-positive population **and** approximately 453 PFS events have occurred (62% maturity) for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* ITT population (approximately 52 months after the first patient is randomised). It is anticipated that 480 PFS events will have occurred (65% maturity) for the comparison of Arm 2 vs Arm 1 in the non *tBRCAm* ITT population at that time.
- The third DCO, the final OS analysis, is planned to occur at approximately 50% OS maturity across the 3 treatment arms in the non-*tBRCAm* ITT population or 5 years following randomization of the last non-*tBRCAm* patient (approximately 86 months after the first patient is randomised), whichever occurs sooner. *(Note, in the event the final OS analysis occurs when approximately 50% maturity has occurred across the 3 treatment arms in the global non*-tBRCAm *ITT population, an extended OS descriptive analysis [non*-tBRCAm *cohort only] may also be performed 5 years after the last non*-tBRCAm *patient is randomised to treatment.)*

For PFS, the 2.5%/5% alpha (two-sided) for the secondary PFS endpoints will be controlled at the interim and the final analysis timepoints separately for each PFS comparison by using a bespoke spending function (Stone 2010), where a fixed significance level will be assigned at the interim and the remaining significance level assigned to the final analysis, taking account of correlation as shown in Table 17.

Table 17 Details of two-sided Significance Levels for each PFS Comparison

Comparison	Population	Total Alpha Assigned	Interim	Final [a]
Arm 3 vs. Arm 1	non-*tBRCAm* HRD-positive	5%	0.0022	~0.05
Arm 3 vs. Arm 1	non-*tBRCAm* ITT	5%	0.0080	0.0497
Arm 2 vs. Arm 1	non-*tBRCAm* ITT	2.5%	0.0050	0.0246

[a] Actual significance level for final analysis dependent on actual number of events at interim and final analysis. Assumes 86% of target events at the time of the interim analysis for each respective treatment comparison/population.

BRCA = breast cancer susceptibility gene; HRD = homologous recombination deficiency; ITT = intention to treat; PFS = progression free survival.

Note, both the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD positive population and in the non-*tBRCAm* ITT population will be required to have met their respective statistical threshold in order for the study to be unblinded at the time of the interim analysis of PFS.

For OS, the 2.5%/5% alpha (two-sided) would be controlled at the interim and the final OS analysis timepoints separately for each comparison by using Lan De Mets O'Brien-Fleming spending function (Lan and DeMets 1983), where the significance level applied at the interim analysis depends upon the proportion of information (ie, information fraction) available.

With an alpha level of 2.5%, if 63% of the target events are available at the time of the interim OS analysis (ie, 81 of 129 OS events have occurred), then the two-sided significance levels of 0.00324, and 0.02396 will be applied to the interim and final analysis for OS for the Arm 3 vs Arm 1 non-*tBRCAm* HRD-positive population, respectively.

With an alpha level of 2.5%, if 63% of the target events are available at the time of the interim OS analysis (ie, 231 of 369 OS events have occurred), then the two-sided significance levels of 0.00319, and 0.02397 will be applied to the interim and final analysis for OS for the Arm 3 vs Arm 1 non-*tBRCAm* ITT population, respectively.

With an alpha level of 2.5%, if 63% of the target events are available at the time of the OS interim analysis (ie, 237 of 379 OS events have occurred), then the two-sided significance levels of 0.00317, and 0.02398 will be applied to the interim and final analysis for OS for the Arm 2 vs Arm 1 non-*tBRCAm* ITT population, respectively.

The final PFS and the interim/final OS analysis boundaries will ultimately be derived based on the actual number of events observed in the study; those referenced above are provided as examples only. The SAP will describe the planned interim analyses in greater detail.

Additional analyses of PFS and/or OS may also be performed to meet Regulatory Agency requests, as required.

9.5.1 Data monitoring committee

A data monitoring committee will be utilized for this study. The IDMC will meet to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. In addition, the IDMC will meet for the interim PFS analysis, which will occur when approximately 86% of the target number of PFS events for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and non-*tBRCAm* ITT population have been reached (approximately 43.5 months after the first patient has been randomised).

For the interim analysis, the IDMC will review unblinded interim data and inform the sponsor whether the interim boundaries specified in Section 9.5 are met.

The IDMC will not reveal the results of the analyses when they make recommendations. The final decision to modify or stop the study will however rest with AstraZeneca.

Appendix A, Section A 5 provides more details on the rationale for and the remit of the committee. Full details of the IDMC procedures and communication process concerning all safety reviews and the PFS interim analysis can be found in the IDMC Charter.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

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

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

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

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

AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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

Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

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

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA Clinical Trials Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach

– A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 Financial disclosure

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

A 3 Informed consent process

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

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign 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 centre.

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

Patients must be re-consented to the most current version of the 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 authorised representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study (ie, the Genomics Initiative research component), 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.

Rescreening will be allowed if the patient fails on any eligibility criteria, which subsequently resolves, including a failed *BRCA* test result. Rescreening may occur a single time only. Rescreened patients will be assigned a new enrolment number; however, the IRT report will identify the old enrolment number and the reasons for rescreening will be documented in the eCRF, so that the effect on study results, if any, can be assessed. Patients who are rescreened will be required to sign a new ICF.

The main ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give agreement to allow any remaining specimens to be used for exploratory research within a separate section of the main ICF. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each patient will be assigned a unique identifier by the sponsor. Any patient records or data sets transferred to the sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

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

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

The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

The participant must be informed that in some cases their data may be pseudonymised. The general data protection regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal data breaches

A ‘personal data breach’ means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[2] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to participants:

- notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach

[2] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.

- If a personal data breach involving an AstraZeneca's representative device (i.e Study Monitor laptop), AstraZeneca representative will provide will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees structure

This study will use an external Independent Data Monitoring Committee (IDMC) to perform interim reviews of accumulating study safety data, including data from other relevant studies, as appropriate. This committee will be composed of therapeutic area experts and a statistician, who are not employed by the Sponsor, and do not have any major conflict of interest. Following the review, the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. The IDMC will not reveal the results of the analyses when they make recommendations. The final decision to modify or stop the study will however rest with AstraZeneca.

The IDMC will meet regularly to review accumulated study safety data, by cohort and treatment arm, with the initial review planned to take place prior to dosing with the combination of bevacizumab, durvalumab/saline, and olaparib/placebo to examine available safety data. During regular data reviews, the IDMC will also separately assess the safety of the combination therapy in Japanese patients as well as safety data for patients in the China cohort. Further details are in the IDMC charter.

In addition, the IDMC will meet for the PFS interim analysis, which will occur when approximately 86% of the target number of PFS events for the comparison of Arm 3 vs Arm 1 in the non-*tBRCAm* HRD-positive population and non-*tBRCAm* ITT population have been reached (approximately 43.5 months after the first patient has been randomised). For the

interim analysis, the IDMC will review unblinded interim data and inform the sponsor whether the interim boundaries specified in Section 9.5 are met.

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

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com [http://www.clinicaltrials.gov and https://euclinicaltrials.eu/] as will the summary of the main study results when they are available. The clinical trial 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. Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A 7 Data quality assurance

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

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan(s).

AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Study Level Medical Oversight Plan.

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

AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study completion unless local regulations or institutional policies require a longer retention period, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Study and site closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

A 9 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 entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the Clinical Study Agreement (CSA).

A 10 Publication policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

Life threatening

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

Hospitalisation

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

Important medical event or medical treatment

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

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

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity rating scale:

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the 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.

For each episode of an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

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

B 3 A guide to interpreting the causality question

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

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

The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative aetiology present in the patient's medical record.
- Not protocol related: The event is related to an aetiology other than the procedure or intervention that was described in the protocol. The alternative aetiology must be documented in the study patient's medical record.

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

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

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

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

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

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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

Medication error includes situations where an error:

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

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT errors)
- Wrong drug administered to participant (excluding IRT errors)

Examples of events that do not require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or SoC medication in open label studies, even if an AstraZeneca product

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of an investigational product for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of an investigational product for medicinal purposes outside of the authorised product information, or for unauthorised study interventions, outside the intended use as specified in the clinical study protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes

- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

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

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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 keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered during the entire life cycle.

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 analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

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

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

C 3 International Airline Transportation Association (IATA) 6.2 guidance document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (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 either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

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

D 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

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

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

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

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

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

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in the Genomics Initiative 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:

- 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 7.3 of the main Clinical Study Protocol.

Collection of samples for genetic research

Although DNA variants are stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the Genomics Initiative sample is not drawn at the main screening visit, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study.

Coding and storage of DNA samples

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

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

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

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

The Genomics Initiative component of this study is optional and the patient may participate in other components of the main study without participating in the Genomics Initiative component. To participate in the Genomics Initiative component of the study the patient must sign and date the Genomics Initiative subsection of the main consent form for the study. Copies of the signed and dated main consent form must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. In addition, Regulatory authorities may

require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

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

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

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

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

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

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 ×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to Day 1 of Cycle 1 (See Section 8.4 Safety Reporting)
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change* in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
    - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
    - Complete the three Liver CRF Modules as information becomes available

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

E 5 Review and assessment of potential Hy's Law cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

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

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determine.

E 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

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

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

- If there is no significant change, no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2

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

E 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease), or did the patient meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix E 6

If **No**: Follow the process described in Appendix E 4.1 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant* change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Appendix E 4.2 for reporting PHL as an SAE.

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

Appendix F Acceptable birth control methods

All treatments used in this study have a medium/high foetal risk.

- Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective form of contraception and their partners must use a male condom [as listed below]. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

F 1 Acceptable non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 6 months after the last dose of study drug. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD (provided coils are copper-banded) PLUS male condom.

F 2 Acceptable hormonal methods:

- Mini pill PLUS male condom: Progesterone-based oral contraceptive pill using desogestrel. Cerazette (Merck, Sharp & Dohme) is currently the only highly efficacious progesterone based pill available.
- Combined pill PLUS male condom: Normal and low-dose combined oral pills
- Injection PLUS male condom: Medroxyprogesterone injection (eg., Depo-Provera [Pfizer])
- Implants PLUS male condom: Etonogestrel-releasing implants (eg, Nexplanon [Merck, Sharp & Dohme])
- Patch PLUS male condom: Norelgestromin / EE transdermal system (eg, Xulane)
- Intravaginal device (eg, EE-etonogestrel-releasing intravaginal devices such as NuvaRing [Merck, Sharp & Dohme]) PLUS male condom
- Levonorgestrel releasing intrauterine system (eg, Mirena [Bayer]) PLUS male condom

Appendix G ECOG performance status

Example of performance status (ECOG scale)

Description	ECOG grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework, office work.	1
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Appendix H RECIST v1.1

H 1 Introduction

This appendix details the implementation of Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D081RC00001 study with regards to the Investigator assessment of tumour burden including protocol-specific requirements for this study.

H 2 Definition of measurable, non-measurable, target and non-target lesions

Patients with measurable disease and/or non measurable and/or no evidence of disease assessed at baseline by CT/MRI will be entered in this study. RECIST 1.1. has been **modified** to allow the assessment of progression due to new lesions in patients with no evidence of disease at baseline.

Measurable:

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

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline[3]).
- Truly non-measurable lesions include 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[4]
- Skin lesions assessed by clinical examination
- Brain metastasis.

[3] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

[4] Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected 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 target lesions (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.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

H 3 Methods of assessment

The same method of assessment and the same technique should be used to characterise each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided in Table 18 and those excluded from tumour 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 X-ray, Chest X-ray	CT (preferred) MRI X-ray, Chest X-ray Bone scan FDG-PET

CT Computed tomography; FDG-PET 18-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D081RC00001 study it is recommended that CT examinations of the chest and abdomen (including liver and adrenal glands) and pelvis will be used to assess tumour burden at baseline. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contraindicated. For brain lesion assessment, MRI is the preferred method.

Clinical examination

In the D081RC00001 study, clinical examination will not be used for assessment. Clinically detected lesions should be confirmed by CT or MRI for the RECIST assessment.

Chest X-ray

In the D081RC00001 study, chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

In the D081RC00001 study 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 assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and new lesions are observed on an ultrasound scan, then these should be confirmed by CT or MRI.

Endoscopy and laparoscopy

In the D081RC00001 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Tumour markers

In the D081RC00001 study tumour markers (CA125) will not be used for tumour response assessments as per RECIST 1.1.

Cytology and histology

In the D081RC00001 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or

stable disease. In such circumstances, the cytology is necessary to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

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 the baseline assessment.

In the D081RC00001 study 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 will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

FDG-PET scan

In the D081RC00001 study, 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive 18-Fluoro-deoxyglucose uptake[5] not present on an FDG-PET scan from a previous visit or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no FDG-PET scan available from a previous visit, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

H 4 Tumour response evaluation

Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed within the 28 days prior to or on Day 1 of Cycle 1 of chemotherapy and ideally as close as possible before the

[5] A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

start of chemotherapy. Follow-up assessments will be performed at the times specified in the study plans (see Table 2, Table 3, and Table 4). In patients who have had upfront primary cytoreductive surgery, the baseline scan must be performed following primary cytoreductive surgery; the first follow-up scan for these patients will be performed at the end of chemotherapy within 3 weeks ±1 week of the last dose of chemotherapy but prior to the start of maintenance. Patients who are scheduled to have IDS should have a baseline scan as close as possible to study treatment. For patients who have undergone partial or unsuccessful primary surgery and are also planned for IDS, a baseline scan must be done after the unsuccessful upfront surgery but prior to Day1 of Cycle 1. The first follow-up scan for IDS patients will take place prior to IDS and the second follow-up scan will be performed at the end of chemotherapy within 3 weeks ±1 week of the last dose of chemotherapy but prior to the start of maintenance. During the maintenance phase, follow-up assessments will be performed every 12 weeks (± 2 weeks), up to 156 weeks, then every 24 weeks (±2 weeks) relative to end of chemotherapy assessment scan until objective disease progression as defined by modified RECIST 1.1.

Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), 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 for lymph nodes). All measurements should be recorded in millimetres. 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 lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- 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, radiotherapy, embolisation, surgery, during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour 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
Progressive 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 were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

CR = Complete response; PR = Partial response; PD = Progression of disease; NE = Not evaluable; SD = Stable disease; TL = Target lesion.

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 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.
Progressive Disease (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 1 or some of the NTLs were not assessed or had a lesion intervention and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR = Complete response; PR = Partial response; PD = Progression of disease; NE = Not evaluable; NTL = Non-target lesion; TL = Target lesion.

To achieve ‘unequivocal progression’ on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of 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 one 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.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

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
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NA	NA	No	NED

CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progression of disease, NE = Not evaluable, NED = no evidence of disease; NA = Not applicable (only relevant if there were no target lesions/non-target lesions at baseline).

H 5 Central Review

The Contract Research Organisation (CRO) appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

H 6 REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009 Jan;45(2):228-47.

Appendix I Toxicity management instructions

I 1 Olaparib toxicity management instructions

Management of haematological toxicity

Management of anaemia

Table 22 Management of anaemia

Haemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	First occurrence Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to >9g/dl. Subsequent occurrences: If repeat Hb <10 g/dl *but* ≥9 g/dl, investigator judgement to continue olaparib with supportive treatment (eg, transfusion) or dose interrupt (for a maximum of 4 weeks) and upon recovery dose reduction may be considered (to **250** mg bd as a first step and to **200** mg bd as a second step). If Hb <9 but ≥8 g/dl, dose interrupt (for a maximum of 4 weeks) until Hb ≥9 g/dl and upon recovery dose reduction may be considered (to **250** mg bd as a first step and to **200** mg bd as a second step).
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks, until improved to Hb ≥9 g/dl. Upon recovery dose reduce to **250** mg bd as a first step and to **200** mg bd as a second step in the case of repeat Hb decrease. If transfusion is required (when the patient is receiving olaparib and durvalumab in combination, or is within 90 days of receiving the combination, if either drug has been discontinued), the following should be undertaken ideally prior to transfusion: direct Coombs test, reticulocyte count, haptoglobin, and LDH.

Abbreviations: bd = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; Hb = haemoglobin; LDH=lactate dehydrogenase.

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to guidance later in this section for the management of this.

Management of neutropenia, leukopenia and thrombocytopenia

Table 23 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to 250 mg bd as a first step and 200 mg bd as a second step

Abbreviations: bd = twice daily; CTCAE = Common Terminology Criteria for Adverse Events.

AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTCAE Grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within 24 hours of the last dose of study treatment unless absolutely necessary. Study treatment can be restarted at the same dose if the AE of neutropenia or leucopenia has recovered to CTCAE Grade ≤1 (ANC > 1.5 x 10^9/L). Growth factor support should be stopped at least 24 hours before restarting study drug (7 days for pegylated G-CSF).

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

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or worse), refer to guidance later in this section for the management of this.

Management of prolonged haematological toxicities while on study treatment

If a patient develops prolonged haematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTCAE Grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to Common Toxicity Criteria (CTC) Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

PRCA and/or AIHA have been reported when olaparib has been used in combination with durvalumab.

If PRCA or AIHA are confirmed, treatment with olaparib and durvalumab should be discontinued.

Management of non-haematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

Management of new or worsening pulmonary symptom

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis. Please also refer to the durvalumab toxicity management guidelines in (see Section 8.4.6.2 and Appendix I 2).

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

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (European Society for Medical Oncology [ESMO], National Comprehensive Cancer Network [NCCN]), generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines or dexamethasone.

Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AstraZeneca Study Physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

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

Olaparib treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Olaparib treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Table 24 Dose reductions for study treatment

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

Abbreviations: bd = twice daily

Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCL falls below the threshold for study inclusion (≥51 mL/minute), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated CrCL either by Cockcroft-Gault equation, a 24 hour urine test or another clinically validated test) of between 31 and 50 mL/minute for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg bd (see Table 10).

Because the CrCL determination is only an estimate of renal function, in instances where the CrCL falls to between 31 and 50 mL/minute, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (≤ 30 mL/minute) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

I 2 Durvalumab toxicity management instructions

Comprehensive toxicity management guidelines (TMG) have been developed to assist investigators with the recognition and for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions toxicities associated with the use of the immune-checkpoint inhibitors for durvalumab. 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. The most current version of these guidelines the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is also maintained within the Site Master File. Note: The durvalumab dose may be delayed for up to a maximum of

12 weeks. If the toxicity has not resolved by 12 weeks, durvalumab should be stopped permanently (as no dose adjustment is allowed).

Appendix J Patient reported outcomes

This appendix includes example copies of the following PRO questionnaires:

- EORTC-QLQ-C30;
- EORTC QLQ-OV28;
- PRO-CTCAE;
- PGIS
- EQ-5D-5L

J 1 CCI

Patient Reported Outcomes questionnaires EORTC QLQ-C30 removed due to copyrights.

Patient Reported Outcomes questionnaires EORTC QLQ-C30 removed due to copyrights.

J 2 CCI [redacted]

Patient Reported Outcomes questionnaires EORTC QLQ-OV28 removed due to copyrights.

Patient Reported Outcomes questionnaires EORTC QLQ-OV28 removed due to copyrights.

J 3 CCI [redacted]

Patient Reported Outcomes questionnaires PRO-CTCAE removed due to copyrights.

Patient Reported Outcomes questionnaires PRO-CTCAE removed due to copyrights.

J 4 PGIS

Patient Global Impression of Severity for Cancer Symptoms

Overall, how would you rate the severity of your cancer symptoms today?

- ☐ No symptoms
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

J 5 CCI

Patient Reported Outcomes questionnaires EQ-5D-5L removed due to copyrights.

Patient Reported Outcomes questionnaires EQ-5D-5L removed due to copyrights.

Appendix K Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 [COVID-19] or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the Sponsor.

Study sites may continue to recruit new patients into ongoing studies provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enroll and manage new subjects effectively and in compliance with the protocol
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

K 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Section 1.1.2.1 to Section 1.1.2.3. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

K 2 Rescreening of Study Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The investigator should confirm this with the designated AstraZeneca study physician. In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with study treatment. If this delay is outside the screening window specified in Section 1.1.1, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in

addition to that detailed in Section 5.4. The procedures detailed in Section 1.1.1 must be undertaken to confirm eligibility.

K 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified health care professional from the study site or third party vendor service may visit a the patients home/ or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified health care professional will be expected to collect information per the clinical study protocol (CSP).

K 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication and other relevant data to be collected according to study requirements to be reported and documented.

K 5 At-home or Remote Location Study Treatment Administration Instructions

If a site visit is not possible, at-home or remote location administration of study treatment may be performed, where available on a case by case basis by a qualified health care professional, provided this is acceptable within local regulation/guidance. Please contact your monitor. The option of at-home or remote location study treatment administration ensures patients safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimise interruption of study treatment administration during other study disruptions, eg, site closures due to natural disaster.

K 5.1 At-home or Remote Location Study Treatment Administration by a Qualified Health Care Professional or Third Party Vendor Service

A qualified health care professional from the study site or third party vendor service may administer the study treatment at the patient's home or a remote location according to the CSP. All necessary supplies and instructions for administration and documentation of study treatment administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

K 6 At-home or Remote Delivery of Olaparib/Placebo

Alternative secure delivery methods for oral drug supply (olaparib/placebo) may be permitted if the patient is unable to attend the site, but only provided the critical safety assessments have been performed and the delivery methods are in line with local regulatory requirements.

K 7 Data Capture During Telemedicine or Remote Visits

Data collected during telemedicine or remote visits will be captured in the source documents by the qualified health care professional from the study site or third party vendor service, or from the patient themselves.

Appendix L Guidance during the COVID-19 Outbreak

L 1 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section L 4). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also EMA 2020).

Notably, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see Section 5.2, Exclusion Criteria 8 and 21).

L 2 Potential Risks during COVID-19

Every effort should be made to follow the CSP. This appendix provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention durvalumab/placebo and/or olaparib/placebo.

The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

L 3 New Participant Enrolment

Study sites may continue to recruit new participants into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new participants effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criteria 8 and 21 (see Section 5.2), participants with active infection or considered a poor medical risk due to a serious, uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such participants (including those who have confirmed COVID 19) should not be included for study participation.

Per Exclusion Criterion 34 (see Section 5.2), patients who have circumstances that could limit compliance with study requirements should also be excluded. Please consider this criterion carefully considering evolving circumstances, travel restrictions and health care delivery in your local area that may impact the continued treatment in the study.

The Study Physician should be contacted if any additional guidance or clarification is needed via the local monitor or directly.

L 4 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

Adverse events, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

L 5 Vaccination against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of intravenous study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

L 6 Durvalumab/Placebo: Product Specific Guidance in Relation to the Ongoing and Emerging Novel Coronavirus (COVID-19) Pandemic

L 6.1 Ongoing Participants Receiving Durvalumab/Placebo

Participants receiving treatment with durvalumab/placebo should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, treatment with durvalumab/placebo should be interrupted until such assessments can be completed.

L 6.1.1 Participants with an Event Suspected to be COVID-19

Delay or omit treatment with durvalumab/placebo as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, treatment with durvalumab/placebo may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

L 6.1.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have treatment with durvalumab/placebo withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

L 6.2 Restarting Treatment with Durvalumab/Placebo

Treatment with durvalumab/placebo must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, laboratory testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance. The study clinical lead should be contacted if any additional guidance or clarification is needed.

L 7 Olaparib/Placebo: Product Specific Guidance In Relation To The Ongoing And Emerging Novel Coronavirus (COVID-19) Pandemic

For Ongoing Patients:

- Patients must continue to have safety blood tests as per protocol schedule. Alternative methods for safety assessments include using local laboratories and follow up by phone contact, virtual visits can be used (see Appendix K for mitigation procedures)
- If it becomes unfeasible to perform the required safety blood tests for a patient, then study treatment should be interrupted until this can resumed and the reason clearly documented, with reference to COVID-19.
- If a patient tests positive for the COVID-19 virus, interrupting olaparib/placebo treatment for 14 days or until symptoms resolve should be considered. Factors that should be taken into consideration might include:
  - Severity of COVID-19 symptoms
  - Status of safety blood results, particularly haemoglobin, neutrophils and lymphocytes
  - Benefit risk for the individual patients including curative vs palliative intent of treatment and response to olaparib/placebo
- If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib/placebo treatment should be interrupted and prompt investigation initiated to determine whether symptoms are due to COVID-19 or potentially drug-induced pneumonitis.
- Olaparib is cleared by metabolism, predominantly by the CYP3A4/5 isozymes. Therefore, the use of olaparib/placebo with the concomitant use of strong inhibitors of these isoenzymes including some antibiotics and antivirals (eg, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir and telaprevir) is not recommended.

References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

Appendix M Abbreviations

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
ADL	Activities of daily life
AE	Adverse event
AESI	Adverse events of special interest
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynecological Oncology Group)
AIHA	Autoimmune haemolytic anaemia
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
Anti-HBc	Hepatitis B core antibody
APTT	Activated Partial Thromboblastin Time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AxMPs	Auxiliary Medicinal Products
AZD2281	Olaparib
AZRand	AZ Global Randomisation System
B	Blood
bd	Twice daily
BICR	Blinded independent central review
BoR	Best overall response
BP	Blood pressure
BRCA	Breast cancer susceptibility gene
BRCAm	*BRCA* mutated
BRCAwt	*BRCA* wild-type
CA125	Cancer Antigen 125
CD	Cluster of differentiation
CDE	Centre of Drug Evaluation
CCI	CCI
CHF	Congestive heart failure
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials

Abbreviation or special term	Explanation
COVID-19	Novel coronavirus 2019
CrCL	Creatinine clearance
CR	Complete response
CRF	Case report form (electronic)
CRO	Contract research organisation
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CCI	CCI
CTIS	Clinical Trials Information System
CTLA	Cytotoxic T lymphocyte-associated
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DSB	Double strand break
ECG	Electrocardiogram
E-code	Enrolment code
ECOG	Eastern Cooperative Oncology Group: a performance status using scales and criteria to assess how a patient's disease is progressing
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitors
EMA	European Medicines Agency
ENGOT	European Network for Gynaecological Oncological Trial Groups
EORTC-QLQ-OV28	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 28
EORTC-QLQ-OV30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer 30
ePRO	Electronic Patient-reported outcomes
ePRO-CTCAE	Dlectronic Patient reported outcomes version of the Common Terminology Criteria for Adverse Events

Abbreviation or special term	**Explanation**
EQ5D-5L	EuroQoL five dimensions, five level health state utility index
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (US)
FFPE	Formalin fixed, paraffin embedded
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
gBRCA	Germline *BRCA*
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
G-CSF	Granulocyte colony stimulating factor
GIS	Genomic instability score
GMP	Good manufacturing practice
GOG	Gynecologic Oncology Group
Hb	Haemoglobin
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High density polyethylene
HER2	Human epidermal growth factor receptor 2
HGSOC	High grade serous ovarian cancer
HIV	Human immunodeficiency virus
HRCT	High Resolution Computed Tomography
HR	Homologous Recombination
HRD	Homologous Recombination Deficiency
HRR	Homologous Recombination Repair
HRRm	Homologous recombination repair related gene mutation
HRQoL	Health-related quality of life
IB	Investigator brochure
IC	Immune cells
ICF	Informed consent form
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.

Abbreviation or special term	Explanation
IDMC	Independent Data Monitoring Committee
IDS	Interval debulking surgery
IFN	Interferon
IgG1	Immunoglobulin G1
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International Normalised Ratio
im-AE	Immune-mediated adverse event
ITT	Intention to treat
IRT	Interactive response technology system
IV	Intravenous
IQR	Inter-quartile range
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MATE	Multidrug and toxin extrusion
MCV	Mean Cell volume
MDS	Myelodysplastic syndrome
MEDI4736	durvalumab
MMMT	Malignant mixed Mullerian tumour
MOA	Mechanism of action
MRI	Magnetic Resonance Imaging
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Non-evaluable
NED	No evaluable disease
NSCLC	Non small cell lung cancer
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
P	Plasma

Abbreviation or special term	Explanation
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase
PARPi	PARP inhibitor
pCR	Pathological complete response
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PFS2	Time to second progression
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PO	Per os (oral administration)
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PR	Partial response
PRCA	Pure red cell aplasia
PSR	Platinum-sensitive relapsed
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
Q12W	Every 12 weeks
Q24W	Every 24 weeks
QAPFS	Quality-adjusted progression-free survival
Q-TWiST	Quality-adjusted time without symptoms of disease or toxicity
RECIST	Response Evaluation Criteria in Solid tumours. This study will use RECIST version 1.1.
RoW	Rest of the world
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
S	Serum
SAE	Serious adverse event
SARS CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	statistical analysis plan
SCLC	Small cell lung cancer
SD	Stable disease
SoA	Schedule of Activities

Abbreviation or special term	**Explanation**
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase
SoC	Standard of care
SpO2	Saturation of peripheral oxygen
STING	Stimulator of interferon genes
T3	Triiodothyronine
T4	Thyoxine
TB	Tuberculosis
tBRCA	Tumour *BRCA*
TDT	Time to discontinuation or death
TFST	Time to first subsequent therapy
TIA	Transient ischemic attack
TIL	Tumour-infiltrating lymphocytes
TL	Target lesion
TP53	Tumour protein 53 (also known as p53)
TSH	Thyroid-stimulating hormone
TSST	Time to second subsequent therapy
ULN	Upper limit of normal
US	United states of America
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBDC	Web based data capture
WHO	World Health Organisation