# A Phase IIIb, Randomised, Double-blind, Placebo-controlled, Multicentre Study of Olaparib Maintenance Retreatment in Patients with Epithelial Ovarian Cancer Previously Treated With a PARPi and Responding to Repeat Platinum Chemotherapy (OReO)

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| **Clinical Study Protocol** | |
| Drug Substance | Olaparib, AZD2281, KU-0059436 |
| Study Code | D0816C00014 |
| ENGOT Number | ENGOT-ov38/OReO |
| Version | 4.0 |
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**Sponsor:** *AstraZeneca AB, 151 85 Södertälje, Sweden*



The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

| Amendment No. | Date of Amendment | Local Amendment No. | Date of Local Amendment |
|---|---|---|---|
| 1 | 11 December 2017 | | |
| 2 | 04 January 2019 | | |
| 3 | 15 October 2020 | | |

| Administrative Change No. | Date of Administrative Change | Local Administrative Change No. | Date of Local Administrative Change |
|---|---|---|---|
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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

# VERSION HISTORY

| Version 1.0, 09 January 2017 |
|---|
| Initial creation |
| Version 2.0, 11 December 2017<br><br>Changes to the protocol are summarised below. |
| Section 1.2 (Rationale for Study Design, Doses, and Control Groups): This section was updated to limit enrolment for patients with documented prior exposure to PARPi therefore patients who received blinded treatment in a trial with a PARPi as the experimental arm must be unblinded prior to enrolment.<br><br>Section 1.4 (Study Design): This section was updated to limit enrolment for patients with documented prior exposure to PARPi therefore patients who received blinded treatment in a trial with a PARPi as the experimental arm must be unblinded prior to enrolment.<br><br>Figure 1 (Flow Chart): This is updated to add more clear wording clear when olaparib treatment is discontinued and when continued in case of progression and no progression<br><br>Section 3.1 (Inclusion Criteria): This section was updated to<br><br>• better specify eligible histopathology by excluding carcinosarcoma, clear cell carcinoma and discussion for patients with mixed tumors.<br><br>• limit enrolment for patients with documented prior exposure to PARPi therefore patients who received blinded treatment in a trial with a PARPi as the experimental arm must be unblinded prior to enrolment.<br><br>• clarify partial or complete radiological response is due to most recent chemotherapy<br><br>• allow calculation of creatinine clearance (CrCl) estimate by using the Cockcroft-Gault equation of ≥51 mL/min or 24 hour urine test<br><br>Section 3.2 (Exclusion Criteria): This section was updated to<br><br>• allow eligibility of Neuropathy Grade 2 as Neuropathy Grade 1-2 is frequently present in subjects previously treated with repeated platinum and taxanes and olaparib monotherapy should not contribute to worsening of that condition |

• deletion of exclusion criteria "Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)" as this is not used in Ovarian Cancer and no treatment leading to total ablation of the bone marrow is ever given.

• Restrict eligibility for patients who have received a whole blood transfusion within 30 days prior to screening tests instead of 90 days prior to randomization as only 30 days is required to perform gBRCA testing therefore no interference in testing

Section 4.10 (Screen Failures) This section was updated to clarify re-screening is permitted and process to perform re-screening

Table 3 (Scheduled Assessments for on Study Treatment and Study Discontinuation): This section was updated to

• Add requirement that pregnancy testing for females of childbearing potential should be conducted at during each on site treatment visit

• Remove requirements to complete additional eCRF for when an AE for nausea or vomiting occurs

• Clarify that if a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

Section 8.5.4 (Interim Analysis): This section was updated to include a pre-specified interim analysis for futility, ensuring that exposure of patients to an ineffective treatment is excluded. IDMC unblinded interim (or ongoing) efficacy and safety review to pick out a major risk:benefit discrepancy. Results from the planned interim analyses will be shared with the IDMC who will make a recommendation on continuing or stopping a cohort.

Appendix D (Acceptable Birth Control Methods): This section was updated to add clarification when abstinence is in line with the preferred and usual lifestyle of the subject.

Appendix F (Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours): This section was updated to clarify that

• Chest x-ray, Ultrasound, Bone Scan and FDG-PET are not mandatory but can be used if clinically indicated and are acceptable methods for New lesion identification.

• CT examinations of the Chest, abdomen and pelvis, will be used to assess tumour burden at baseline and follow-up visits.

• Follow-up assessments will be performed every 12 weeks

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|---|
| • There will be no independent central review for this study |
| Version 3.0,<br><br>Changes to the protocol are summarised below.<br><br>Protocol Synopsis: Number of patients reduced to 228; Oxaliplatin added as acceptable platinum chemotherapy; inclusion criterion related to continued platinum sensitivity modified to allow patients who have no measurable disease following debulking surgery and a CA-125 which is not rising; changed assumptions about expected median PFS in placebo treated patients (4.5 months) based on prior data; calculations of sample size adjusted to support detection of a 0.5 Hazard Ratio in both cohorts; SOLO2 data added to Table 1; Text justifying sample size modified to explain the choice of 4.5 months, and the selection of a HR = 0.5 in both cohorts; Text on statistical assumptions of the study revised, with altered recruitment targets; Text added to indicate that the assumptions on sample size will be reviewed at the time of the interim analysis; Statistical assumptions for the interim analysis revised<br><br>Introduction: Section 1.1. Research Hypothesis: text altered to reflect change in inclusion criterion #5. Olaparib Mechanism of Action: text updated. Section 1.2 Rationale for Study Design, Doses and Control Doses: text revised, updated and new data added to improved rationale. Section 1.3: Benefit/Risk and Ethical Assessment: text moved to Section 1.4. Section 1.4 Study Design: Text changes consistent with the modification of Inclusion Criterion #5. Text relating to blinding and unblinding moved from Section 1.3<br><br>Inclusion Criteria: Section 3.1. Inclusion Criterion #5 modified to allow patients with no measurable disease following optimal debulking surgery, and CA-125 level that is normal or not rising to enter the study<br><br>Study Plan and Timing of Procedures: Section 4, Table 2. Removal of footnote requiring additional CRF for nausea and vomiting. Table 3. Footnote (a) enhanced to clarify that randomization can take place prior to Day 1 for operational reasons. Section 4.1 Clarification that screening should be done within 28 days of first dose (not randomisation). Section 4.2 Clarification that randomisation can be performed before before Day 1, that certain tests do not have to be repeated if performed within 7 days of Day 1 (not randomisation), and that ECOG status should be performed pre-dosing on Day 1. Section 4.5 Revised instructions (simplification) for completion of long term follow up.<br><br>Statistical Analyses by Astrazeneca Vendor: Section 8.2 Sample Size Estimate. Adjustment of assumptions for mPFS of placebo control, and recalculation of sample size. Section 8.5.1: Adjustment of the number of progression events for the primary analysis of PFS. Section 8.5.4: Adjustment in the statistical basis for and timing of the interim analysis |

Version 4.0, 15 October 2020

Changes to the protocol are summarised below.

Protocol Synopsis, Front page. Change of address for International Coordinating Investigator

Protocol Synopsis, Study Design. Addition of "and analysed" into the sentence "The BRCA1/2 (+ve) and BRCA1/2 (-ve) cohorts will be randomised and analysed separately".

Protocol Synopsis, Statistical Methods. Added "Data cut off and subsequent database lock for the Primary Analysis will occur after the later of the two cohorts reaches the defined number of progression or death events" for clarification.

Section 1.4, Study Design. Minor corrections to ensure consistency with study schedule

Section 3.8.2 Acceptable Birth Control Methods: change in requirement that women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective forms of contraception and their partners must use a male condom

Section 3.11, Discontinuation of the Study. Added "The study, or one cohort, may also be stopped at any time after the Primary Analysis if in the judgment of AstraZeneca, the ENGOT Principal Investigator and the Trial Steering Committee, there is insufficient clinical benefit from re-treatment."

Table 4, New Table: Scheduled Assessments: Patients Remaining on Study Treatment Post Primary Analysis

Section 4.5, Patients on Study Treatment Post Primary Analysis. New Section to detail assessments required in patients still on study treatment after Primary Analysis

Section 6.1.1: Update to AESI section to change MDS/AML from important potential risk to important identified risk

Section 8.1, Statistical Considerations. Added "Data cut off and subsequent database lock for the Primary Analysis will occur after the later of the two cohorts reaches the defined number of progression or death events"

Section 8.5.1, Analysis of the Primary Variable(s). Clarify requirements for Primary Analysis "The primary analysis for PFS for each cohort will be performed when both 85 progression or death events have occurred in the BRCA1/2 (+ve) cohort and 74 progression or death events in the BRCA1/2 (-ve) cohort (whichever occurs later)."

Section 8.5.2.1, Overall Survival. Amend defined timings for analyses of overall survival to "OS will be analysed at the time of the primary analysis for PFS, and again after 50% death events in either cohort, or 60 months after FSI, whichever is the earlier"

Section 9.3 Study Timetable and End of Study. Clarify timing of final DCO "The final DCO will take place after 50% death events in either cohort, or 60 months after FSI, whichever is the earlier". Added "The study, or one cohort, may also be stopped at any time after the Primary Analysis if in the judgment of AstraZeneca, the ENGOT Principal Investigator and the Trial Steering Committee, there is insufficient clinical benefit from re-treatment." to be consistent with Section 3.11

Appendix H Acceptable Birth Control Methods: change in requirement that women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective forms of contraception and their partners must use a male condom

ENGOT Number ENGOT-ov38/OReO

# PROTOCOL SYNOPSIS

## A Phase IIIb, Randomised, Double-blind, Placebo-controlled, Multicentre Study of Olaparib Maintenance Retreatment in Patients with Epithelial Ovarian Cancer Previously Treated With a PARPi and Responding to Repeat Platinum Chemotherapy (OReO)


**International Coordinating Investigator**

PPD

75008 Paris

France


### Study Site(s) and Number of Patients Planned

The study will be conducted in approximately 11 countries worldwide. Approximately 110 centres will be initiated to randomise approximately 228 patients.

Additional sites may be added dependent on recruitment rates.

| Study Period | | Phase of Development |
|---|---|---|
| Estimated date of first patient enrolled | Q2 2017 | IIIb |
| Estimated date of last patient completed | Q2 2022 | |

### Study Design

This is a Phase IIIb, randomised, double-blind, placebo-controlled, multicentre study to assess the efficacy and tolerability of Olaparib retreatment, versus matching placebo, in non-mucinous epithelial ovarian cancer (EOC) patients (including patients with primary peritoneal and/or fallopian tube cancer). To be eligible, patients must have received maintenance therapy with a polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation inhibitor

(PARPi) for a defined period (see Target Patient Population), and remain sensitive to platinum-based chemotherapy, based on their radiological or CA-125 response to their most recent course of platinum-based chemotherapy (carboplatin, cisplatin or oxaliplatin). Patients will be enrolled on the basis of their breast cancer susceptibility gene (*BRCA1, BRCA2*) status into one of two cohorts (*BRCA1*/2 (+ve) and *BRCA1*/2 (-ve)).

The *BRCA1/2* (+ve) and *BRCA1/2* (-ve) cohorts will be randomised and analysed separately. Within each cohort, patients will be randomised by prospective allocation in a 2:1 ratio (Olaparib:matching placebo) to the treatments as specified below:

- Olaparib tablets (oral [p.o.]), 300 mg twice daily (bd; except where this dose and formulation was previously not tolerated; Section 6.7)
- placebo tablets to match, p.o. bd

Randomisation will be stratified by:

- Use of prior bevacizumab (yes versus no)
- Number of prior regimens of platinum-containing chemotherapy (≤3 regimens versus ≥4 regimens)

Investigators will be required to provide tumour assessment information using the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 at baseline (a maximum of 28 days prior to randomisation). Following randomisation, patients in all study arms must have tumour assessments every 12 weeks (±7 days) until objective disease progression. More information is provided in Section 5.1.

Patients should continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 or as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

Once a patient has stopped treatment, a 30 days post last study drug visit will be performed during which adverse events (AEs), concomitant medications and the completed health-related quality of life (HRQoL) questionnaire will be collected. Thereafter, data on subsequent therapies according to routine clinical practice, adverse events of special interest (AESI) and survival will be collected until the data cut-off date for the final analysis.

## Objectives

The following objectives apply to both *BRCA1/2* (+ve) and *BRCA1/2* (-ve) cohorts.

| **Primary Objective** | **Outcome Measure** |
|---|---|
| To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of progression-free survival (PFS) | Time from randomisation to Investigator-assessed disease progression (according to RECIST version 1.1 guidelines) or death (by any cause in the absence of progression) |

| **Secondary Objective** | **Outcome Measure** |
|---|---|
| To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of overall survival (OS) | Time from randomisation to death from any cause |
| To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of time to progression by Gynecologic Cancer Intergroup (GCIG) criteria | Time from randomisation to the earliest of Investigator-assessed disease progression by RECIST or cancer antigen 125 (CA-125), or death (by any cause in the absence of progression) |
| To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of the use of subsequent therapies and study treatment discontinuation | • Time from randomisation to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment (TFST)<br>• Time from randomisation to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment (TSST)<br>• Time from randomisation to study treatment discontinuation or death if this occurs before discontinuation of study treatment (TDT) |
| To determine the HRQoL of Olaparib maintenance retreatment compared to matching placebo as measured by the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) Trial Outcome Index (TOI) | Change from baseline, time to deterioration and proportion improved |

| Safety Objective | Outcome Measure |
|---|---|
| To evaluate the safety and tolerability of Olaparib maintenance retreatment | AEs/serious adverse events (SAEs)/AESI<br>Collection of clinical chemistry/haematology parameters |

| Exploratory Objective | Outcome Measure |
|---|---|
| CCI [redacted] | [redacted] |
| [redacted] | |
| [redacted] | [redacted] |

**Target Patient Population**

The target population is patients with non-mucinous EOC (including patients with fallopian tube and/or primary peritoneal cancer) who have relapsed disease that remains sensitive to platinum-based chemotherapy (based on their radiological or CA-125 response to their most recent line of platinum-based chemotherapy), and who have previously received one course of PARPi therapy in a maintenance setting either alone or in combination with other agents (such as a vascular endothelial growth factor receptor inhibitor [VEGFRi]).

All patients must have a confirmed genetic status for *BRCA1* and *BRCA2*.

Patients will be allocated to one of two cohorts:

- The first cohort will enrol patients with confirmed *BRCA1*/2 (+ve) status (somatic, *sBRCA1*/2, or germline, *gBRCA1*/2)

- The second cohort will enrol patients who are known *gBRCA1*/2 (-ve) and may include some patients who have an undetected *sBRCA1*/2 mutation.

The minimum periods for which patients must have taken maintenance PARPi without progression to be eligible for this retreatment study are:

- For the *BRCA1*/2 (+ve) cohort, the duration of exposure must have been ≥18 months following a first line of chemotherapy or ≥12 months following a second line or subsequent line of chemotherapy

- For the *BRCA1*/2 (-ve) cohort, the duration of exposure must have been ≥12 months following a first line of chemotherapy or ≥6 months following a second line or subsequent line of chemotherapy.

A month is defined as being from the start date to the same date in the next month (e.g. 01 January to 01 July is 6 months). These periods are of continuous PARPi administration and are measured from the date of the first dose to the date of the last dose of PARPi. During this period no new anticancer treatment for disease progression can have been administered, but patients may have had short breaks (maximum 14 days on any occasion) for holidays, control of toxicity or non-cancer treatments, for example. Unblinding of patients who received blinded treatment with a PARPi as an experimental arm should be medically justified

Patients may have, but do not need to have, a specific confirmatory homologous recombination repair (HRR) or homologous recombination deficiency (HRD) test. Patients with *BRCA* variants of unknown significance will be regarded as *BRCA1*/2 (-ve) for the purposes of this study.

Patients should also have received subsequent platinum-based chemotherapy, excluding bevacizumab, following progression during or following prior PARPi therapy and have achieved, in the opinion of the Investigator, at least a partial radiological response, or not have a rising CA-125 following optimal debulking surgery with no measurable disease. In addition, patients must be randomised into the OReO study within 8 weeks of their last dose of platinum-based chemotherapy (last dose is the day of the last infusion).

**Duration of Treatment**

Unless patients experience unacceptable toxicity or withdraw from the study treatment or from the protocol, patients should continue to receive study treatment until there is objective radiological disease progression as assessed by RECIST 1.1 or as long as in the Investigator's opinion they are benefiting from treatment.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator.

**Study Treatment, Dosage, and Mode of Administration**

Olaparib is available as a film-coated tablet containing 150 mg or 100 mg of Olaparib. Patients will be administered study treatment orally at a dose of 300 mg bd. The planned dose of 300 mg bd will be made up of two 150 mg tablets bd with 100 mg tablets used to manage dose reductions (except where this dose and formulation was previously not tolerated; Section 7.2).

The comparator in the OReO study is placebo to match Olaparib 150 mg or 100 mg tablets.

**Statistical Methods**

All personnel involved with the analysis of the study will remain blinded to study treatment until database lock and protocol violators are identified. Data cut off and subsequent database lock for the Primary Analysis will occur after the later of the two cohorts reaches the defined number of progression or death events.

Efficacy data will be summarised for both cohorts using the full analysis set (FAS), including all randomised patients. The primary outcome, PFS, will be analysed using a stratified log-rank test and the effect of Olaparib retreatment will be estimated by the hazard ratio (HR) and associated 95% confidence interval and P-value. Kaplan-Meier plots will be presented by treatment arm. The analysis of other time-to-event endpoints will use the same methodology as for PFS (see Section 8).

HRQoL using the FACT-O tool will be analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline in TOI score for each scheduled post-baseline visit, based upon a subset of the FAS.

HRQoL mean scores will be analysed accounting for baseline scores and the stratification factors. Time to deterioration will be analysed using survival analysis methodology as per the PFS endpoint.

Sensitivity analysis and subgroup analysis of PFS and other time-to-event endpoints will be performed as appropriate and as described in the statistical analysis plan (SAP).

A comprehensive SAP will be prepared, and any subsequent amendments will be documented, with final amendments completed prior to un-blinding of the data. Analyses will be performed in collaboration between AstraZeneca or its representatives and representatives of GINECO-ENGOT (Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens et du sein [GINECO]; European Network for Gynaecological Oncological Trial [ENGOT]).

The analyses to be performed for the purpose of generating the clinical study report will be included in the study SAP that is prepared by the clinical research organisation (CRO), which

will be reviewed and agreed by AstraZeneca and GINECO-ENGOT. All analyses in the SAP will then be generated by the CRO.

**Sample Size**

The benefit of Olaparib retreatment over matching placebo will be evaluated in both cohorts through the primary endpoint of PFS.

Recently published data (Study 19, NOVA, SOLO2) of PARPi therapy following a second or subsequent line of platinum based chemotherapy indicated that a median PFS which does not exceed 5.5 months can be expected in the placebo-treated patients (Table 1).

**Table 1** **Median PFS of Study 19, SOLO2 (Olaparib) and NOVA (Niraparib) Patients According to *BRCA* Status and Treatment Arm, and Selection of Patients in OReO According to Previous Exposure to PARPi**

| | ***BRCAm*** **placebo arm late relapse** | ***BRCAm*** **Olaparib arm late relapse** | ***BRCAwt*** **placebo arm late relapse** | ***BRCAwt*** **Olaparib arm late relapse** |
|---|---|---|---|---|
| | **Median PFS (months)** | | | |
| Study 19 | 4.3 | 11.2 | 5.5 | 7.4 |
| NOVA | 5.5 | 21.0 | 3.9 | 9.3 |
| SOLO2 | 5.5 | 19.1 | n/a | n/a |
| Selection in OReO according to previous PARPi exposure for relapse patients | | > 12 | | > 6 |
| Selection in OReO according to previous PARPi exposure for first line patients | | > 18 | | > 12 |

*BRCAm* = *BRCA1*/2 mutated; *BRCAwt* = *BRCA1*/2 wild type; n/a = not applicable

This study tests the hypothesis that patients judged to have received benefit from an initial maintenance course of PARPi, based on a duration of prior exposure specified according to their *BRCA* status, and number of prior courses of platinum-based chemotherapy, and who retain sensitivity to platinum-based chemotherapy, will benefit from repeat exposure to olaparib. The data above indicates that in platinum sensitive patients, regardless of *BRCA* status, placebo maintenance following second-line chemotherapy results in a median PFS of

less than 5.5 months. Patients entering OreO may do so after a second or subsequent line of platinum based chemotherapy, and despite being selected for benefit from prior PARPi, are considered unlikely to demonstrate a longer median PFS on placebo than the similar patient populations tested in Study 19, SOLO2, and NOVA. Finally, the benefit from PARPi maintenance retreatment is assumed to be less than obtained on first treatment. So the expected median PFS for both the *BRCA1/2* (+ve) and *BRCA1/2* (-ve) cohorts has been estimated to be approximately 4.5 months for patients receiving placebo. Sample sizes have then been calculated based on an expectation of a clinically meaningful duration of benefit (HR 0.5 for both cohorts).

In the *BRCA1/2* (+ve) cohort it is assumed that the median PFS from randomisation for patients in the placebo arm will be approximately 4.5 months. In total, 85 progression or death events from 120 patients will have 85% power to demonstrate significant PFS benefit at the 2-sided 5% level if the assumed true treatment effect resulted in a HR of 0.5; this translates to a 4.5 month (100%) increase in median PFS beyond the 4.5 months expected for patients on placebo, if PFS is exponentially distributed and allowing a 10% drop-out rate. An observed HR of 0.63 or less will be required to achieve this level of significance. Assuming 34 months of non-linear recruitment, 85 events are expected to occur approximately 41 months after the first patient in (FSI) is enrolled into this cohort of the study.

In the *BRCA1/2* (-ve) cohort it is assumed that the median PFS from randomisation for patients in the placebo arm will be approximately 4.5 months. In total, 74 progression or death events from 108 patients will have 80% power to demonstrate significant PFS benefit at the 2-sided 5% level if the assumed true treatment effect resulted in a HR of 0.5; this translates to a 4.5 month (100%) increase in median PFS beyond the 4.5 months expected for patients on placebo, if PFS is exponentially distributed and allowing a 10% drop-out rate. An observed HR of 0.61 or less will be required to achieve this level of significance. Assuming 36 months of non-linear recruitment, 74 events are expected to occur approximately 42 months after the FSI is enrolled into this cohort of the study.

Considering both cohorts it is expected that approximately 228 patients in total will be enrolled into the study. The assumptions made in calculating the sample size will be evaluated at the time of the planned interim analysis.

**FAS (Intent-to-Treat Principle)**

The intent-to-treat (ITT) population will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the FAS. Therefore, all efficacy data will be summarised and analysed using the FAS on an ITT basis as the primary analysis set. Demographic and baseline characteristics will also be analysed using the FAS on an ITT basis.

**Safety Analysis Set**

All patients who received at least one dose of randomised study treatment, Olaparib or placebo, will be included in the safety analysis set. If a patient receives at least one dose of Olaparib study treatment they will be summarised in the Olaparib arm for safety summaries (e.g., Olaparib arm will include patients randomised to Olaparib who receive at least one dose of Olaparib or placebo patients who receive at least one dose of Olaparib study treatment in error at any time). If a patient randomised to Olaparib receives only placebo treatment then the patient will be summarised as a part of the placebo arm. All safety data will be summarised and analysed using the safety analysis set.

**Interim Analysis**

In the *BRCA1/2* (+ve) cohort an interim analysis for futility will be performed after 50% of the target PFS events (i.e. after 43 events). Based upon the assumed accrual and event rate it is estimated that this will occur after approximately 29 months. Using a conditional power non-binding futility analysis the cohort may stop for futility if the hazard ratio > 1.056. Under the null hypothesis the probability of stopping for futility is 0.433 and under the alternative hypothesis it is 0.01.

In the *BRCA1/2* (-ve) cohort an interim analysis for futility will be performed after 50% of the target PFS events (i.e. after 37 events). Based upon the assumed accrual and event rate it is estimated that this will occur after approximately 30 months. Using a conditional power non binding futility analysis the cohort may stop for futility if the hazard ratio > 1.02. Under the null hypothesis the probability of stopping for futility is 0.477 and under the alternative hypothesis it is 0.02.

Results from the planned interim analyses will be shared with the Independent data monitoring committee who will make a recommendation on continuing or stopping a cohort.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AML | Acute myeloid leukaemia |
| ANC | Absolute neutrophil count |
| APTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| bd | Twice a day |
| BP | Blood pressure |
| *BRCA1 and BRCA2* | Breast cancer susceptibility genes |
| *BRCAm* | *BRCA1/2* mutated |
| BUN | Blood urea nitrogen |
| CA-125 | Cancer antigen 125 |
| CI | Confidence interval |
| CR | Complete response |
| CrCl | Creatinine clearance |
| CRF | Case report form (electronic/paper) |
| CRO | Clinical research organisation |
| CSA | Clinical study agreement |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Event |
| CCI | [redacted] |
| CYP | Cytochrome P450 |
| DCIS | Ductal carcinoma in situ |
| DCO | Data cut-off |
| DILI | Drug-induced liver injury |
| DNA | Deoxyribonucleic acid |
| DSB | DNA double strand breaks |
| dUCBT | Double umbilical cord blood transplantation |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EE | Ethinyl estradiol |
| ENGOT | European Network for Gynaecological Oncological Trial |
| EOC | Epithelial ovarian cancer |
| ESMO | European Society for Medical Oncology |

| Abbreviation or special term | Explanation |
|---|---|
| Ethics committee | Synonymous with institutional review board (IRB) and independent ethics committee (IEC) |
| EWB | Emotional well-being |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FACT-G | Functional Assessment of Cancer Therapy – General |
| FACT-O | Functional Assessment of Cancer Therapy – Ovarian |
| FAS | Full analysis set |
| FFPE | Formalin fixed, paraffin embedded |
| FSI | First patient in |
| FWB | Functional well-being |
| *gBRCAm* | Germline *BRCAm* |
| GCIG | Gynecologic Cancer InterGroup |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte colony-stimulating factor |
| GINECO | Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens et du sein |
| GMP | Good Manufacturing Practice |
| Hb | Haemoglobin |
| HGSOC | High grade serous ovarian cancer |
| HIV | Human immunodeficiency virus |
| HL | Hy's Law |
| HR | Hazard ratio |
| HRCT | High resolution computed tomography |
| HRD | Homologous recombination deficiency |
| HRQoL | Health-related quality of life |
| HRR | Homologous recombination repair |
| IATA | International Airline Transportation Association |
| IB | Investigator brochure |
| ICH | International Conference on Harmonisation |
| IDMC | Independent data monitoring committee |
| IEC | Independent ethics committee |
| IMP | Investigational medicinal product |
| INR | International normalised ratio |
| International Coordinating Investigator | If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally |
| IRB | Institutional review board |
| ITT | Intent-to-treat |
| IUS | Intrauterine system |
| IVRS | Interactive voice response system |
| IWRS | Interactive web response system |
| K-M | Kaplan-Meier |
| MAR | (Data being) missing at random |

| Abbreviation or special term | Explanation |
|---|---|
| MATE | Multidrug and toxin extrusion (MATE1, MATE2K) |
| MCV | Mean corpuscular/cell volume |
| MDS | Myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MID | Minimally important difference |
| MMRM | Mixed model for repeated measures |
| MRI | Magnetic resonance imaging |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| OAT3 | Organic anion transporter 3 |
| OATP1B1 | Organic anion transporting polypeptide 1B1 |
| OCS | Ovarian cancer subscale |
| OCT | Organic cation transporter (OCT1, OCT2) |
| OS | Overall survival |
| PARP | Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation |
| PARPi | Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation inhibitor |
| PD | Progression of disease |
| PFS | Progression-free survival |
| P-gp | P-glycoprotein |
| PHL | Potential Hy's Law |
| p.o. | Oral |
| PR | Partial response |
| PRO | Patient reported outcome |
| PWB | Physical well-being |
| QoL | Quality of life |
| QTc | Corrected QT interval |
| RECIST | Response Evaluation Criteria In Solid Tumours |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Stable disease |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvate transaminase |
| SmPC | Summary of product characteristics |
| SSB | DNA single strand break |
| SWB | Social/family well-being |
| TBL | Total bilirubin |
| TDT | Time to study treatment discontinuation or death |
| TEAE | Treatment-emergent adverse event |
| TFST | Time to first subsequent treatment commencement or death |
| TL | Target lesion |
| TOI | Trial outcome index |

| Abbreviation or special term | Explanation |
|---|---|
| TSST | Time to second subsequent treatment commencement or death |
| ULN | Upper limit of normal |
| VEGFRi | Vascular endothelial growth factor receptor inhibitor |
| WBDC | Web-based data capture |

# 1 INTRODUCTION

## 1.1 Background and Rationale for Conducting This Study

### Research Hypothesis

Within the maintenance setting of relapsed breast cancer susceptibility gene mutated (*BRCA1/2* mutated or *BRCAm*), non-mucinous epithelial ovarian cancer (EOC), maintenance retreatment with Olaparib leads to significantly increased PFS compared with matching placebo, amongst patients who had previously benefitted from polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation inhibitor (PARPi) maintenance therapy.

Patients must have received a platinum-based chemotherapy regimen (carboplatin, cisplatin or oxaliplatin) and must have had, in the opinion of the Investigator, at least a partial radiological response, or not have a rising CA-125 following optimal debulking surgery with no measurable disease. The prior period of exposure to PARPi will be used as a measure of benefit from previous PARPi therapy.

### Olaparib Mechanism of Action

Investigators should be familiar with the current Olaparib (AZD2281) Investigator brochure (IB). Olaparib (AZD2281, KU-0059436) is a potent PARPi that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with other anti-cancer agents in several tumour types. Olaparib tablets are currently approved for the maintenance treatment of patients with platinum sensitive relapsed EOC both in the European Union and the United States of America.

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HRR). Tumours with homologous recombination deficiencies (HRDs), such as ovarian cancers in patients with *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types,

Olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

*BRCA1* and *BRCA2* defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models *in vivo* (Rottenberg et al. 2008, Hay et al. 2009) and in the clinic (Fong et al. 2009). The mechanism of action for Olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Murai et al. 2012, Helleday 2011). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HRR. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic *BRCA1/2* knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

AstraZeneca considers that the patient population involved in this study falls under the advanced cancer, limited life expectancy definition outlined in International Conference on Harmonisation (ICH) S9 guideline "Non-clinical Evaluation for Anticancer Pharmaceuticals" and meets the requirements outlined in the guideline.

## 1.2 Rationale for Study Design, Doses, and Control Groups

### Experience with Olaparib *BRCAm* Ovarian Cancer

The results of a pivotal Phase II trial (D0810C00019; Study 19), showed the benefit of Olaparib as maintenance monotherapy in patients with platinum sensitive relapsed High Grade Serous Ovarian Cancer (HGSOC) especially in *BRCAm*[1] tumours.

Study 19 was a randomised, double-blind, placebo-controlled study to evaluate `maintenance treatment with Olaparib (capsule formulation) in patients with platinum sensitive relapsed HGSOC (including patients with primary peritoneal and/or fallopian tube cancer) who had received ≥2 previous platinum regimens and were in partial or complete response following their last platinum-containing regimen.

The primary endpoint in Study 19 was Investigator-assessed PFS. In total, 265 patients were randomised to Olaparib 400 mg twice daily (bd; 136 patients) or placebo (129 patients). The primary analysis was carried out following 154 PFS events and demonstrated that maintenance treatment with Olaparib led to a significant PFS improvement versus placebo

[1] *BRCAm* status is defined as a mutation in *BRCA1* or *BRCA2* classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants (Richards et al. 2008). The OReO study will recruit patients with *BRCA1/2* mutations that are either germline (*gBRCAm*) or somatic (*sBRCAm*; i.e., occurring in the tumour only).

giving a hazard ratio (HR) of 0.35 with a 95% confidence interval (CI) of 0.25 to 0.49 (P<0.00001) (Ledermann et al. 2012).

A subgroup analysis (pre-specified in the statistical analysis plan [SAP]) showed that Olaparib led to a greater clinical benefit in patients with a known *gBRCAm*; *gBRCAm* status was determined retrospectively for all consenting patients (n=166) using blood samples taken before randomisation. Somatic (i.e., tumour only) *BRCA1/2* status was determined from archival tumour samples from 196 patients. The results showed an increased PFS benefit for *BRCAm* patients (HR, 0.18; 95% CI 0.10-0.31; median: 11.2 versus 4.3 months; P<0.00001) compared with non-*BRCAm* (HR,0.54; CI 0.34-0.85; median:7·4 months vs 5·5 months; P=0·0075)

In the latest analysis of overall survival (OS; 70% maturity), data for *BRCAm* patients resulted in an OS HR of 0.62 (95% CI 0.41-0.94; median: 34.9 months versus 30.2 months) (Ledermann et al. 2016).

Olaparib tolerability was similar in *BRCAm* patients and the overall population. The findings from Study 19 are supported by clinical data from over 350 additional patients with *BRCAm* ovarian cancer in 6 other Olaparib trials demonstrating consistent response rates. Results from the Phase III confirmatory trial (Study D0816C00002; the SOLO2 study) conducted with the tablet formulation (300 mg bd), in *BRCAm* patients showed a median PFS for the Olaparib treated patients of 19.1 months, compared with 5.5 months for the placebo group (HR of 0.3; 95% CI 0.22-0.41; P<0.0001).

The tablet dose was chosen based on data from Study D0810C00024 (Study 24). Study 24 explored the tablet formulation in terms of bioavailability, tolerability, and activity and selected the 300 mg bd dose for further development on the basis that this dose was considered to have similar efficacy in terms of tumour shrinkage in *BRCAm* ovarian cancer patients compared with the 400 mg bd capsule dose. In the Study 24 ovarian cancer population, comparison of the change in tumour size data for 300 mg Olaparib tablets bd with 400 mg Olaparib capsules bd showed the two treatments had similar effects on efficacy (Week 8 difference=1.8%, 95% CI: -22.8%, 26.4%; P=0.881).

Both capsule and tablet formulations have a similar tolerability profile. Toxicities considered to be associated with administration of Olaparib include haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, mean corpuscular volume [MCV] elevation), decreased appetite, nausea and vomiting, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache and dizziness. Further information is provided in the summary of product characteristics (SmPC).

Patients who have received platinum-based chemotherapy followed by PARPi as maintenance monotherapy to progression, and thereafter treated with a further line of platinum-based chemotherapy receive no further treatment until progression, according to current treatment paradigms.

EOC patients often show responses to multiple lines of platinum therapy (i.e., retreatment with platinum-based chemotherapy agents following initial progression). There is a potential that such patients could also respond to a retreatment with PARPi therapy, particularly those with *BRCA1/2* mutations, since genomic instability in *BRCA1* and *BRCA2* can be enhanced by chemotherapy agents affecting DNA repair, potentially making them more susceptible to PARP inhibition following a platinum therapy response. At present, it is not known whether retreatment with a PARPi therapy after a response to retreatment with platinum-based chemotherapy agents may work in a similar manner, but there is agreement amongst clinicians that exploring retreatment is an unmet need.

**Niraparib Experience in *gBRCA1/2* Ovarian Cancer**

ENGOT-OV16/NOVA was a Phase III, randomised, double-blind placebo-controlled trial of niraparib, a PARPi, as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with predominantly high-grade serous histologic features (Mirza et al. 2016). Patients were grouped according to the presence or absence of a germline *BRCA1/2* (*gBRCA1/2*) mutation (203 patients in the *gBRCA1/2* cohort and 350 patients in the non-*gBRCA1/2* cohort). They were randomised in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily.

Patients who received niraparib had a significantly longer median PFS duration than those who received the placebo: 21.0 versus 5.5 months in the *gBRCA1/2* cohort (HR, 0.27; 95% CI, 0.17 to 0.41) and 12.9 months versus 3.8 months in the non-*gBRCA1/2* cohort for patients who had tumours with HRD (HR, 0.38; 95% CI, 0.24 to 0.59) and 9.3 months versus 3.9 months in the overall non-*gBRCA1/2* cohort (HR, 0.45; 95% CI, 0.34 to 0.61). Therefore, compared to placebo, niraparib improved PFS (primary endpoint) regardless of *BRCA1/2* mutation or HRD tumour status (P was <0.001 in all three primary efficacy populations).

In the niraparib group, the most commonly reported grade 3 or 4 adverse events (AEs) were thrombocytopenia (in 33.8%), anaemia (in 25.3%) and neutropenia (in 19.6%), which were managed with dose modifications.

**Rationale for the OReO study**

Prior experience has demonstrated that PARPi therapy improves median PFS when used in patients who are at least partially platinum sensitive. Following progression on PARPi maintenance therapy many of these patients are found to retain sensitivity to platinum-based chemotherapy. It is not known whether these patients will benefit from an additional period of PARPi maintenance therapy. The OReO study will investigate the efficacy and safety of Olaparib maintenance retreatment in patients with relapsed non-mucinous EOC, who have had disease progression following maintenance therapy with a PARPi and who remain sensitive to platinum-based chemotherapy.

Multiple studies of patients given no maintenance therapy following first line platinum-based chemotherapy show that they can expect a median PFS of between 12 and 18 months, with the

longer periods being more common in patients with *BRCA* mutations (13.8 months in the recent SOLO1 study). This has provided the rationale for requiring patients who received PARPi initially after first line therapy to have been exposed for 18 months (*BRCA1/2+ve*) and 12 months (BRCA1/2-ve), in an attempt to select those patients benefiting from a PARPi. A similar approach has been adopted for those receiving their initial PARPi after later lines of chemotherapy, with the 12 months required for *BRCA1/2+ve* being consistent with the PFS seen in Study 19, and the 6 months for *BRCA1/2-ve*

## 1.3 Benefit/Risk and Ethical Assessment

Please see current edition of the SmPC for the most recent summary of the risks of Olaparib.

## 1.4 Study Design

This is a Phase IIIb, randomised, double-blind, placebo-controlled, multicentre study to assess the efficacy and tolerability of Olaparib retreatment, versus matching placebo, in non-mucinous EOC patients (including patients with primary peritoneal and/or fallopian tube cancer). To be eligible, patients must have received maintenance therapy with a PARPi, and must have had at least a partial radiological response to their most recent course of platinum-based chemotherapy, or may have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125. All patients must have a confirmed genetic status for *BRCA1/2*.

Patients will be randomised into one of two cohorts depending on their known *BRCA1/2* status (see Figure 1):

- The first cohort will enrol patients with confirmed *BRCA1*/2 (+ve) status (somatic, *sBRCA1*/2, or germline, *gBRCA1*/2)
- The second cohort will enrol patients who are known *gBRCA1*/2 (-ve) and may include some patients who have an undetected *sBRCA1*/2 mutation.

Within each cohort, patients will be randomised by prospective allocation in a 2:1 ratio (Olaparib:matching placebo) to the treatments as specified below:

- Olaparib tablets (oral [p.o.]), 300 mg bd (except where this dose and formulation was previously not tolerated; Section 6.7)
- placebo tablets to match, p.o. bd

Randomisation will be stratified by:

- Use of prior bevacizumab (yes versus no)

- Number of prior regimens of platinum-containing chemotherapy (≤3 regimens versus ≥4 regimens)

The minimum periods for which patients must have taken maintenance PARPi without progression to be eligible for this retreatment study are:

- For the *BRCA1*/2 (+ve) cohort, the duration of exposure must have been ≥18 months following a first line of chemotherapy or ≥12 months following a second line or subsequent line of chemotherapy

- For the *BRCA1*/2 (-ve) cohort, the duration of exposure must have been ≥12 months following a first line of chemotherapy or ≥6 months following a second line or subsequent line of chemotherapy

A month is defined as being from the start date to the same date in the next month (e.g. 01 January to 01 July is 6 months). These periods are of continuous PARPi administration and are measured from the date of the first dose to the date of the last dose of PARPi. During this period no new anticancer treatment for disease progression can have been administered, but patients may have had short breaks (maximum 14 days on any occasion) for holidays, control of toxicity or non-cancer treatments, for example.
Patients may have, but do not need to have, a specific confirmatory HRR or HRD test. Patients with *BRCA* variants of unknown significance will be regarded as *BRCA1*/2 (-ve) for the purposes of this study.

Patients should also have received subsequent platinum-based chemotherapy, excluding bevacizumab, following progression during or after prior PARPi therapy and remain platinum sensitive. For the purposes of this study, platinum sensitivity means that the patient had a Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 partial or complete response (as determined by the Investigator) to the most recent line of platinum-based chemotherapy, or may have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125.

In addition, patients must be randomised into the OReO study within 8 weeks of their last dose of platinum-based chemotherapy (last dose is the day of the last infusion).

Investigators will be required to provide tumour assessment information using RECIST 1.1 and health-related quality of life (HRQoL) questionnaires at baseline (a maximum of 28 days prior to randomisation). Following randomisation, patients in all study arms must have tumour assessments every 12 weeks (±7 days) until objective disease progression. More information is provided in Section 5.1.

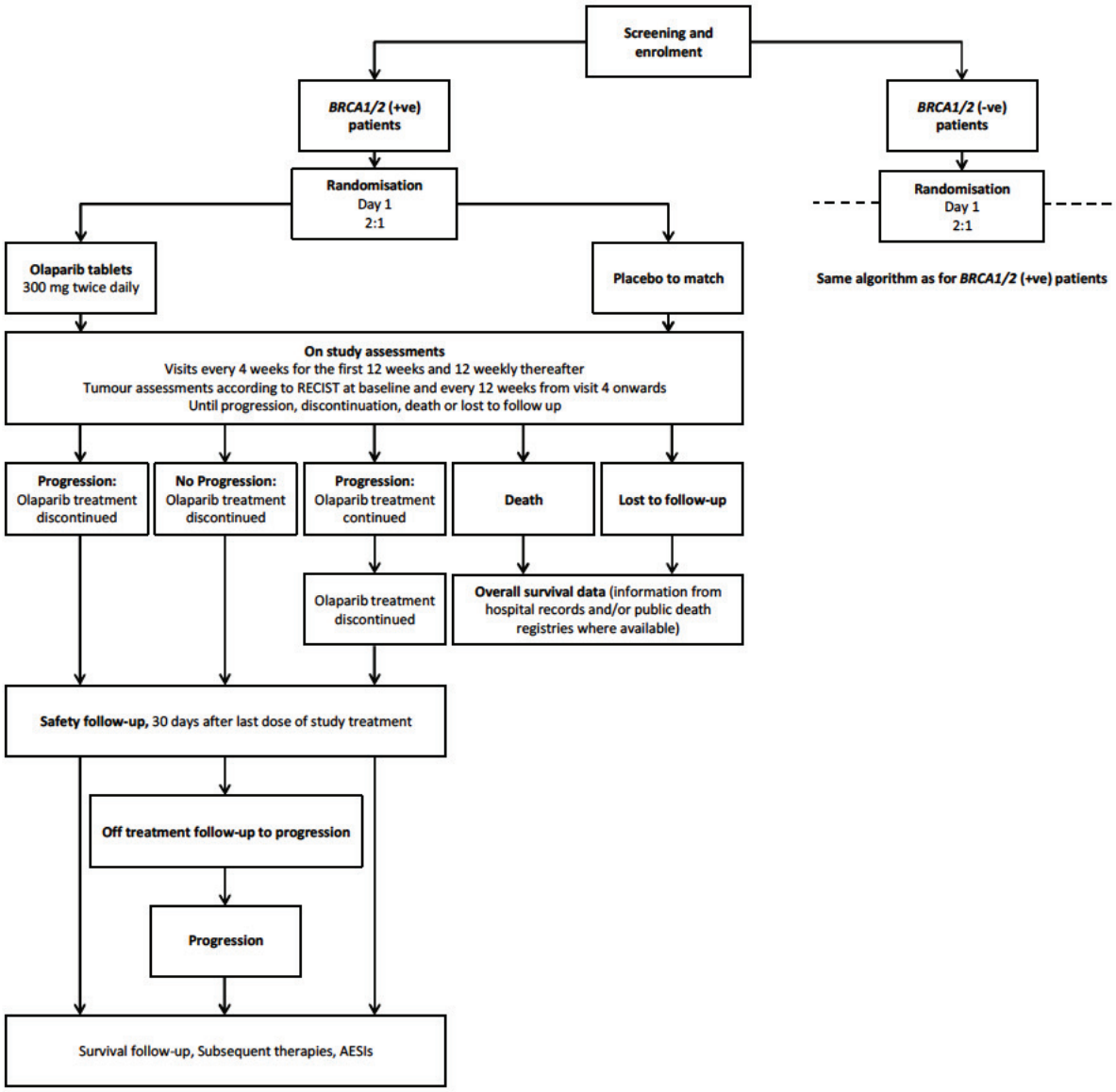
Patients should continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 or as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. Such patients should additionally:

- Not have symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease
- Not have a decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression
- Not have tumour progression at critical anatomical sites that cannot be readily managed and stabilised by protocol allowed medical interventions
- Be provided information deferring any standard treatment options that may exist in favour of continuing investigational product treatment at the time of initial progression.

Once a patient has stopped treatment, a 30 days post last study drug visit will be performed during which AEs, concomitant medications and the completed HRQoL questionnaire will be collected. Thereafter, data on subsequent therapies according to routine clinical practice, adverse events of special interest (AESI), FACT-O (up to 2 years post randomisation) and survival will be collected until the data cut-off date for the final analysis (see Section 4.6).

The methods for ensuring blinding are addressed in Section 3.6; methods for un-blinding are addressed in Section 3.7.

**Figure 1 OReO Study Flow Chart**



# 2 STUDY OBJECTIVES

The following objectives apply to both *BRCA1/2* (+ve) and *BRCA1/2* (-ve) cohorts.

## 2.1 Primary Objective

| Primary Objective | Outcome Measure |
|---|---|
| To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of progression-free survival (PFS) | Time from randomisation to Investigator-assessed disease progression (according to RECIST version 1.1 guidelines) or death (by any cause in the absence of progression) |

## 2.2 Secondary Objectives

| Secondary Objective | Outcome Measure |
|---|---|
| To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of overall survival (OS) | Time from randomisation to death from any cause |
| To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of time to progression by Gynecologic Cancer Intergroup (GCIG) criteria | Time from randomisation to the earliest of Investigator-assessed disease progression by RECIST or cancer antigen 125 (CA-125), or death (by any cause in the absence of progression) |
| To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of the use of subsequent therapies and study treatment discontinuation | • Time from randomisation to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment (TFST)<br>• Time from randomisation to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment (TSST)<br>• Time from randomisation to study treatment discontinuation or death if this occurs before discontinuation of study treatment (TDT) |

| | |
|---|---|
| To determine the HRQoL of Olaparib maintenance retreatment compared to matching placebo as measured by the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) Trial Outcome Index (TOI) | Change from baseline, time to deterioration and proportion improved |

## 2.3 Safety Objectives

| **Safety Objective** | **Outcome Measure** |
|---|---|
| To evaluate the safety and tolerability of Olaparib maintenance retreatment | AEs/serious adverse events (SAEs)/AESI<br>Collection of clinical chemistry/haematology parameters |

## 2.4 Exploratory Objectives

| **Exploratory Objective** | **Outcome Measure** |
|---|---|
| CCI [redacted] | [redacted] |
| CCI [redacted] | |
| CCI [redacted] | CCI [redacted] |

# 3 PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study (see Figure 2 and Figure 3). Under no circumstances can there be exceptions to this rule. Patients who fail screening for issues such as correctable laboratory abnormalities may be resubmitted for screening (see section 3.10.1)

## 3.1 Inclusion Criteria

For inclusion in the study patients should fulfil all of the following criteria:

1. Provision of informed consent prior to any study specific procedures

2. Patients must be ≥18 years of age

3. Female patients with histologically diagnosed relapsed non-mucinous EOC (including primary peritoneal and/or fallopian tube cancer). (Non-mucinous EOC includes patients with serous, endometrioid, and transitional cell tumours, and those with mixed histology where one of these subtypes is predominant (>50%). Inclusion of other subtypes should first be discussed with the Medical Monitor).

4. Documented *BRCA1/2* status

   – To be regarded as *BRCA1/2* (+ve), the patient must have a mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental / lead to loss of function)

5. Patients must have received one prior PARPi therapy

   – PARPi therapy includes any agent (including Olaparib) used in a maintenance setting

   – For the *BRCA1/2* (+ve) cohort, the duration of first PARPi exposure must have been ≥18 months following a first line of chemotherapy or ≥12 months following a second or subsequent line of chemotherapy

   – For the *BRCA1/2* (-ve) cohort, the duration of first PARPi exposure must have been ≥12 months following a first line of chemotherapy or ≥6 months following a second or subsequent line of chemotherapy

   For the last chemotherapy course immediately prior to randomisation on the study

   – Patients must have received a platinum-based chemotherapy regimen (carboplatin, cisplatin or oxaliplatin) and have received at least 4 cycles of treatment

- Patients must be, in the opinion of the investigator, in response (partial or complete radiological response), or may have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125, as defined below, following completion of this chemotherapy course
- Pre-treatment CA-125 measurements must meet criterion specified below:
  - If the first value is within upper limit of normal (ULN) the patient is eligible to be randomised and a second sample is not required
  - If the first value is greater than ULN a second assessment must be performed at least 7 days after the 1st. If the second assessment is ≥ 15% more than the first the patient is not eligible.
- Patients must **not** have received bevacizumab during this course of treatment. Bevacizumab use as part of an earlier line of chemotherapy is permitted
- Patients must not have received any investigational agent during this course of treatment
- Patients must be randomised within 8 weeks of their last dose of chemotherapy (last dose is the day of the last infusion)

6. Patients must have normal organ and bone marrow function measured within 28 days of randomisation, as defined below. In the event of minor deviations from these values which would lead to screen failure, repeat testing within the 28-day screening period (limited to the tests listed below) is allowed before the patient is declared a screen failure.

   - Haemoglobin ≥10.0 g/dL with no blood transfusion in the past 28 days
   - Absolute neutrophil count (ANC) ≥1.5 X $10^9$/L
   - Platelet count ≥100 X $10^9$/L with no platelet transfusion in the last 14 days
   - Total bilirubin (TBL) ≤1.5 X institutional ULN
   - Aspartate aminotransferase (AST), serum glutamic oxaloacetic transaminase (SGOT) / alanine aminotransferase (ALT), serum glutamic pyruvate transaminase (SGPT) ≤2.5 X institutional ULN, unless liver metastases are present in which case they must be ≤5 X ULN
   - Patients must have creatinine clearance (CrCl) estimated using the Cockcroft-Gault equation of ≥51 mL/min or based on a 24 hour urine test:

     $$\text{Estimated CrCl} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \quad (\times F)^a$$

     [a]where F=0.85 for females

7. ECOG performance status 0-1 (see Appendix E)

8. Patients must have a life expectancy ≥16 weeks

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

   Postmenopausal is defined as:

   – Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments
   – Luteinizing hormone and follicle stimulating hormone levels in the post-menopausal range for women under 50
   – Radiation-induced oophorectomy with last menses >1 year ago
   – Chemotherapy-induced menopause with >1 year interval since last menses
   – Surgical sterilisation (bilateral oophorectomy or hysterectomy).

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

11. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline with computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for repeated assessment

    OR

    No measurable disease following a complete response to most recent chemotherapy (+/- surgery)

12. A formalin fixed, paraffin embedded (FFPE) tumour sample from the cancer of sufficient quantity and quality (as specified in the Covance Central Laboratory Services Manual) **must** be available for future central testing of tumour genetic status. If a recent biopsied sample is provided, the biopsied tumour should not be assessed as target lesions as part of the RECIST assessments if there are other lesions available, and the biopsy should be taken after the baseline scan has been performed. Archival tissue samples may be from the primary tumour or metastatic tumour deposits. Archival bone metastases are not acceptable. Provision of blocks is preferred. Alternatively pre-cut 5µm thick, unstained sections from the FFPE block may be provided. Any exceptions to these conditions should be discussed with the Sponsor before randomisation of the patient.

13. For inclusion in the optional biomarker research, patients must fulfil the following criteria:

    – Provision of informed consent for biomarker research.

If a patient declines to participate in the optional biomarker research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study.

## 3.2 Exclusion Criteria

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

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

2. Previous randomisation in the present study

3. Participation in another clinical study with an investigational product during the chemotherapy course immediately prior to randomisation.

4. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with history of primary breast cancer may be eligible provided they completed their definitive anticancer treatment more than 3 years ago and they remain breast cancer disease free prior to start of study treatment

5. Resting electrocardiogram (ECG) with corrected QT interval (QTc) >470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome

6. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative radiotherapy) within 3 weeks prior to study treatment

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

8. Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents

9. Persistent toxicities (Common Terminology Criteria for Adverse Event [CTCAE] grade2 or higher) caused by previous cancer therapy, excluding alopecia and stable Grade 2 peripheral neuropathy

10. Patients with current or previous myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML

11. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days

12. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery

13. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high resolution computed tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent

14. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication

15. Breast feeding women

16. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV)

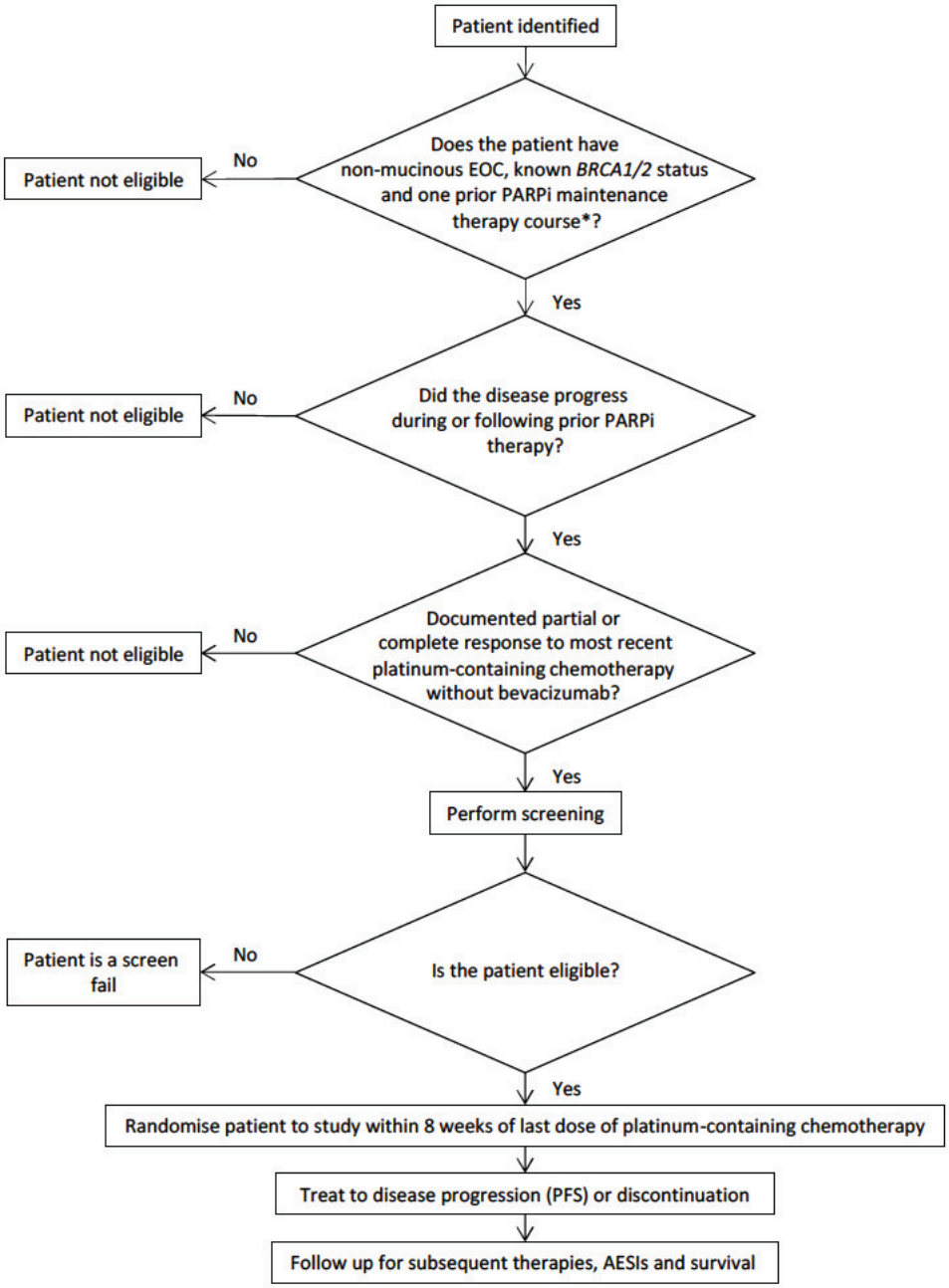
17. Patients with a known hypersensitivity to Olaparib or any of the excipients of the product

18. Patients with known active hepatitis (i.e., Hepatitis B or C)

19. Patient who have received a whole blood transfusion within 30 days prior to screening tests (packed red blood cells and platelet transfusions are acceptable).

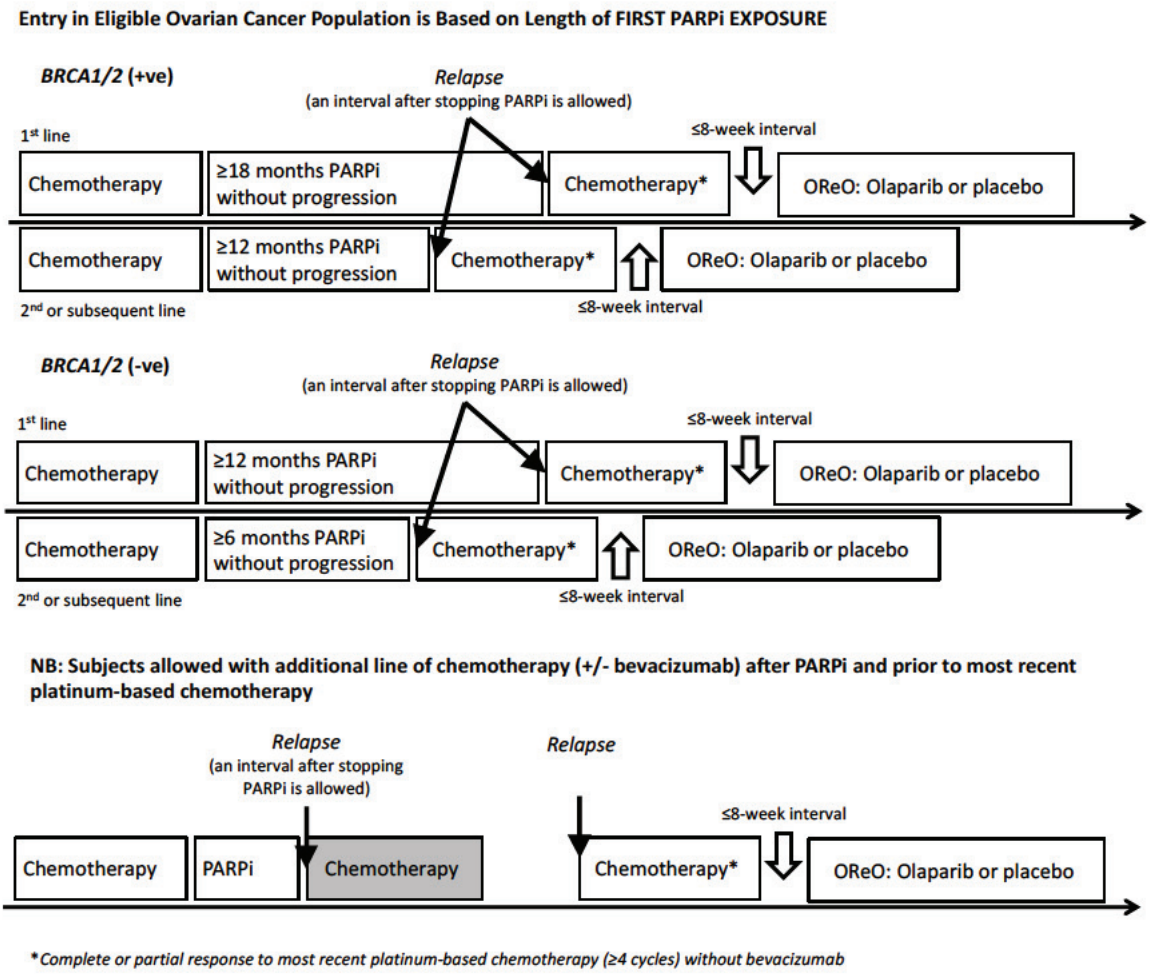
For procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

**Figure 2 OReO Study Screening and Eligibility Flow Chart**




* For the *BRCA1*/2 (+ve) cohort, the minimum duration of PARPi exposure without progression must have been 18 months following a first line of chemotherapy or 12 months following a second line or subsequent line of chemotherapy. For the *BRCA1*/2 (-ve) cohort, the minimum duration of PARPi exposure without progression must have been 12 months following a first line of chemotherapy or 6 months following a second line or subsequent line of chemotherapy.

**Figure 3 Overview of Treatments Before Study Randomisation**




**Complete or partial response to most recent platinum-based chemotherapy (≥4 cycles) without bevacizumab*

## 3.3 Patient Enrolment and Randomisation

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

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed

2. Assign potential patient a unique enrolment number, beginning with 'E#'

3. Determine patient eligibility. See Section 3

4. Request patient to complete the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire

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

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

## 3.4 Procedures for Handling Incorrectly Enrolled or Randomised Patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be 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 patient's circumstances should be discussed with the ENGOT trial Principal Investigator before the decision to withdraw is made. The AstraZeneca study physician must ensure all decisions are appropriately documented.

## 3.5 Methods for Assigning Treatment Groups

Eligible patients from both cohorts will be randomised separately in a 2:1 ratio (Olaparib:matching placebo). The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the Interactive Voice Response System / Interactive Web Response System (IVRS/IWRS) database. A blocked randomisation will be generated for all centres. The randomisation scheme will be stratified based on the following:

- Use of prior bevacizumab (yes versus no) and
- Number of prior regimens of platinum-containing chemotherapy (≤3 versus ≥4 regimens).

Specific information concerning the use of IVRS/IWRS will be provided in a separate manual. It is recommended that patients commence study treatment on the day of randomisation if possible, and if not, then ideally within 3 days.

## 3.6 Methods for Ensuring Blinding

Olaparib and matched placebo treatment will be blinded. The study medication will be labelled using a unique MedID number, which is linked to the randomisation scheme. The active and placebo tablets and their packaging will look identical to ensure blinding of the study medication.

## 3.7 Methods for Un-blinding

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

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca or its agent, without revealing 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 study treatment and that potentially require expedited reporting to regulatory authorities. Investigators and patients will not be un-blinded to study treatment for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented. After the final data cut-off (DCO), all patients will be un-blinded to study treatment.

## 3.8 Restrictions

### 3.8.1 Grapefruit Juice

It is not recommended to consume grapefruit juice while on study therapy.

### 3.8.2 Contraception

Female patients of child bearing potential, who are sexually active, must agree to the use of one highly effective forms of contraception and their partners must use a male condom throughout the period of taking study treatment and for 1 month (female patients) after last dose of study drug. For details refer to Appendix D (Acceptable Birth Control Methods).

## 3.9 Discontinuation of Study Treatment

Patients may be discontinued from study treatment in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Severe non-compliance with the study protocol as judged by the Investigator and/or AstraZeneca
- Bone marrow findings consistent with MDS/AML

- Objective progression according to the RECIST criteria as assessed by the Investigator (unless in the Investigator's opinion the patient is benefiting from the treatment and does not meet any other discontinuation criteria as outlined in Section 3.11).

### 3.9.1 Procedures for Discontinuation of a Patient from Study Treatment Product

At any time, patients are free to discontinue study treatment or withdraw from the study (i.e., study treatment and assessments – see Section 3.10), without prejudice to further treatment. The Principal Investigator/Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. They will also immediately inform AstraZeneca of the withdrawal. AEs will be followed up (see Section 6), completed questionnaires (e.g., for patient reported outcomes [PROs]) and all unused study treatment should be returned by the patient.

By discontinuing from study treatment, the patient is not withdrawing from the study. Patients should be followed for progression (if discontinuation in the absence of progression) and overall survival following treatment discontinuation as per the protocol schedule.

Any patient discontinuing study treatment should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the Principal Investigator/Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the electronic case report form (eCRF) the date of discontinuation, the reasons, manifestation, and treatment at the time of discontinuation. If patients discontinue study treatment, the site monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study medication 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 6.3.2). All new AEs and SAEs occurring during the 30 calendar days 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 6.4) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study medication to collect and/or complete AE information. For guidance on reporting AEs after the 30 day follow up period see Section 6.3.1.1.

Any patient who has not yet shown objective radiological disease progression at withdrawal from investigational product should continue to be followed as per RECIST as detailed in Section 5.1. All patients must be followed for AESIs, survival and subsequent therapies, up to the final analysis. If a patient is withdrawn from study, see Section 3.10.

## 3.10 Criteria for Withdrawal

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; i.e., the patient does not meet the required inclusion/exclusion criteria for the study. The patient's circumstances should be discussed with the ENGOT trial Principal Investigator and the sponsor AstraZeneca before the decision to withdraw is made.
- Patient lost to follow-up
- Death.

### 3.10.1 Screen Failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

RE-SCREEN: subjects that initially failed the screening process for minor, potentially correctable abnormalities, such as laboratory testing, are allowed to be resubmitted to the screening process.

Re-screened subjects will be re-consented and given a new subject number, as if they have not previously undergone the screening process. The site would follow the same procedures as they would with a new subject. The patient must still be randomised within 8 weeks from the last dose of chemotherapy.

### 3.10.2 Withdrawal of the Informed Consent

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

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

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

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

- Further participation in the study including any further follow up (e.g., survival calls)
- Withdrawal of consent to the use of their study generated data
- Withdrawal to the use of any samples (see Section 5.5.4).

The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an OS 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.

## 3.11 Discontinuation of the Study

The study may be stopped if, in the judgment of AstraZeneca, together with that of the ENGOT Principal Investigator and after the recommendation of the independent data monitoring committee (IDMC), the trial patients 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 patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

The study, or one cohort, may also be stopped at any time after the Primary Analysis if in the judgment of AstraZeneca, the ENGOT Principal Investigator and the Trial Steering Committee, there is insufficient clinical benefit from re-treatment.

In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the patients' interests.

# 4 STUDY PLAN AND TIMING OF PROCEDURES

The scheduled screening assessments are summarised in Table 2.

The scheduled assessments for on study treatment and study discontinuation are summarised in Table 3.

**Table 2 Screening (Visit 1) Study Schedule for OReO Patients (Locally Confirmed *BRCA1*/2 Mutation Status)**

| Day | Day -27 to Day 0 |
|---|---|
| Informed consent and inclusion / exclusion criteria review | X |
| Demographics including date of birth, gender, and where permitted race and/or ethnicity | X |
| Standard medical, medication and surgical history [a] | X |
| Prior cancer therapies including radiotherapy | X |
| History of blood transfusions [b] | X |
| Physical examination and ECOG | X |
| Vital signs (includes blood pressure [BP], pulse and temperature), body weight | X |
| ECG [c] | X |
| Haematology/clinical chemistry [d] | X |
| Urinalysis | X |
| Pregnancy test [e] | X |
| Blood sample for disease specific marker (CA-125) | X |
| *BRCA1*/2 status [f] | X |
| Tumour assessment (CT or MRI according to RECIST 1.1) [g] | X |
| AEs (from time of consent) | X |
| Concomitant medications | X |
| Archival or fresh tumour sample (mandatory) [h] | X |
| Response to current chemotherapy regimen | X |

[a] Medical history can be limited to relevant history of ovarian cancer (surgery, prior treatments), other conditions requiring ongoing treatment and any conditions potentially impacting trial participation.

[b] Include history of blood transfusion within previous 30 days prior to screening tests and the reasons e.g., bleeding or myelosuppression.

[c] ECG should be performed once the patient has been in the supine position for at least 5 minutes.

[d] International normalised ratio (INR) and activated partial thromboplastin time (APTT) should be performed at screening and if clinically indicated. Platelet count will be performed as part of haematology testing and fibrinogen only as clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.3.

[e] 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.

[f] Patients must have a documented *BRCA1*/2 status to be randomised in the study. A *BRCA1*/2 test should be performed as soon as a potentially eligible patient is identified who does not already have confirmed *BRCA1*/2 status as part of the screening assessments. Patients for whom their *gBRCA1*/2 status is already known should be consented to the study within 28 days prior to day 1 of study treatment.

[g] 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 individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment.

[h] All patients will need to submit either an archival sample or, if preferred, a recent tumour sample, for post-analysis testing of their genetic status. If a recent biopsied sample is provided, the biopsied tumour should not be assessed as target lesions as part of the RECIST assessments if there are other lesions available, and the biopsy should be taken after the baseline scan has been performed. Archival tissue samples may be from the primary tumour or metastatic tumour deposits. Archival bone metastases are not acceptable.

**Table 3 Scheduled Assessments for on Study Treatment and Study Discontinuation**

| **Visit number** | **2** | **3** | **4 onwards (subsequent on-treatment visits: every 4 weeks for 12 weeks, then every 12 weeks)** [a] | **Study treatment discontinued** | **Follow-up 30 days after last dose of study medication** | **Long-term follow-up (12-weekly beyond 30 days after last dose of study treatment)** |
|---|---|---|---|---|---|---|
| **Day** | **1** | **29** | **Day 1 of next visit period (Visit 4 equals day 57, Visit 5 equals day 85, etc.)** | | | |
| **Visit window** | | **±3d** | **±3d** | **±3d** | **±7d** | **±14d** |
| Randomisation | X[a] | | | | | |
| Physical exam (prior to dosing) [c] | X [b] | X | X | X | | |
| Vital signs (includes BP, pulse and temperature), body weight [c] | X [b] | X | X | X | X | |
| ECOG performance status | X | | X | X | | |
| ECG [c] | X [b] | | | | | |
| Haematology / clinical chemistry | X [d] | X | X | X | X | X [e] |
| Study treatment dispensed / returned [f] | X | X | X | X (Returned) | X (Returned) | |
| Urinalysis (if indicated) | X | | | | | |
| Pregnancy test [g] | X | | X | | X | |

**Table 3 Scheduled Assessments for on Study Treatment and Study Discontinuation**

| **Visit number** | **2** | **3** | **4 onwards (subsequent on-treatment visits: every 4 weeks for 12 weeks, then every 12 weeks)** [a] | **Study treatment discontinued** | **Follow-up 30 days after last dose of study medication** | **Long-term follow-up (12-weekly beyond 30 days after last dose of study treatment)** |
|---|---|---|---|---|---|---|
| **Day** | **1** | **29** | **Day 1 of next visit period (Visit 4 equals day 57, Visit 5 equals day 85, etc.)** | | | |
| **Visit window** | | **±3d** | **±3d** | **±3d** | **±7d** | **±14d** |
| Blood sample for disease specific marker (CA-125) [h] | | | X [Every 12 weeks (±7d)] | | | |
| Blood sample for biomarker analysis [p] | X | | | X (At progression) | | |
| Blood sample for confirmation of *gBRCA1*/2 [i] | X | | | | | |
| Tumour biopsy (optional) [j] | | | | X (At progression) | | |
| Tumour assessment (CT or MRI according to RECIST 1.1) [k] | | | X [Every 12 weeks (±7d)] | | | |
| AEs [l] | X | X | X | X | X | X |

**Table 3 Scheduled Assessments for on Study Treatment and Study Discontinuation**

| **Visit number** | **2** | **3** | **4 onwards (subsequent on-treatment visits: every 4 weeks for 12 weeks, then every 12 weeks)** [a] | **Study treatment discontinued** | **Follow-up 30 days after last dose of study medication** | **Long-term follow-up (12-weekly beyond 30 days after last dose of study treatment)** |
|---|---|---|---|---|---|---|
| **Day** | **1** | **29** | **Day 1 of next visit period (Visit 4 equals day 57, Visit 5 equals day 85, etc.)** | | | |
| **Visit window** | | **±3d** | **±3d** | **±3d** | **±7d** | **±14d** |
| Concomitant medications including blood transfusions [m] | X | X | X | X | X | |
| FACT-O [n] | X | X | X | X | X | X |
| Survival | | | | X | X | X |
| Subsequent cancer therapy following discontinuation of study treatment [o] | | | | | X | X |

[a] Randomisation can occur prior to Day 1 for operational reasons, provided the patient has completed screening and meets all inclusion/exclusion criteria. Subsequent visits take place relative to the date of first dose (Day 1). Visits occur on Day 1 of a 4-week (28-day) visit period for the first 12 weeks and then 12 weekly on Day 1 of a 12-week visit period .

[b] If assessed within 7 days before randomisation and meets the stated eligibility criteria (if applicable), it does not need to be repeated on Day 1 of study treatment unless Investigator believes that it is likely to have changed significantly.

[c] To be additionally performed if clinically indicated at any other time.

[d] Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the Investigator believes that it is likely to have changed significantly. Coagulation test should be performed at screening and if clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.3.

[e] Haematology tests, but no clinical chemistry tests. Coagulation tests will only be performed if clinically indicated.

[f] Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.

[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. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

[h] CA-125 to be measured at the same time points as CT/MRI scans. Repeat measurements should be taken ≥1 week after a value suggesting progression.

[i] All patients should have a blood sample taken and stored for subsequent confirmation of *gBRCA1*/2 status, although the test will not be performed unless required to further analyse the treatment response at the end of the study.

[j] Optional tumour sample at progression of disease.

[k] Follow-up assessments will be performed every 12 weeks (±7d) after randomisation until objective disease progression as defined by RECIST 1.1. If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by 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.

[l] All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution. Only AESIs will be collected during long-term follow-up.

[m] All concomitant medications will be collected at screening. At subsequent visits, only antibiotics, anti-emetics, transfusions, erythropoietin, granulocyte colony-stimulating factor (G-CSF) and concomitant medications associated with an AE will be collected.

[n] FACT-O to be completed at baseline (pre dose) and 4, 8, 12, 24, 36, and 48 week visits, then 12-weekly (±14 days) up to 2 years post patient randomisation.

[o] All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), start and stop dates, reason(s) for stopping and the Investigator's opinion of response to them plus the date of progression post discontinuation of study treatment need to be recorded.

[p] Optional in countries that do not permit this approach

NB. Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 6.7.1.

**Table 4 Scheduled Assessments for Patients Remaining on Study Treatment Post Primary Analysis**

| | Subsequent on-treatment visits every 12 weeks | Study treatment discontinued | Follow-up 30 days after last dose of study medication[c] |
|---|---|---|---|
| Adverse Events (includes SAE and AESI)[a] | X | X | X |
| Haematology/Clinical Chemistry[b] | X | | |
| Pregnancy | X | | |
| Concomitant Medication | X | X | X |
| FACT-O | X | X | X |
| Study Treatment Dispensed/Returned | X | X (Returned) | |
| Subsequent Cancer Treatment | | | X |
| Tumour Biopsy on Progression (optional) | | X | |
| Blood Sample for Biomarker Analysis | | X | |
| Survival | X | | X |

a All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution Only AESIs will be collected during long-term follow-up

b Other laboratory analyses, such as urinalysis, and physical examination, ECG and EGOG status may be performed as part of SOC but this data is not required post Primary Analysis

c Post 30-day follow up, patients will enter long term follow up per Table 3

## 4.1 Enrolment/Screening Period

Procedures will be performed according to the Study Plan.

At screening, consenting patients are assessed to ensure that they meet the eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

Prior to Randomisation:

- *BRCA1/2* test to be performed as soon as a potentially eligible patient is identified who does not already have confirmed *BRCA1/2* status

Within 4 Weeks (28 Days) Prior to First Dose:

- Demographics data and other characteristics will be recorded as will date of birth, gender and, where permitted, race and/or ethnicity
- A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient. A medical history can be limited to relevant history of ovarian cancer (surgery, prior treatments), other conditions requiring ongoing treatment and any conditions potentially impacting trial participation.
- Prior cancer therapies including radiotherapy will be recorded
- History of blood transfusions within the previous 30 days prior to screening tests and the reasons for transfusion, e.g., bleeding or myelosuppression
- Physical examination, ECOG performance status assessment, collection of vital signs, body weight
- ECG, which should be performed once the patient has been in the supine position for at least 5 minutes in each case
- Haematology and clinical chemistry tests. Coagulation tests will only be performed if clinically indicated
- Urinalysis
- Patients must be postmenopausal, or have evidence of non-childbearing status. Women of childbearing 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

- Blood sample for disease specific marker (CA-125)
- Baseline RECIST 1.1 assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis (no more than 28 days before randomisation, and as close as possible to start of study treatment.
- Recording of concomitant medications
- Recording of AEs (from time of consent)
- Provision of archival or fresh tumour sample (mandated for all patients) for post-analysis testing of genetic status
- Recording of response to current chemotherapy regimen.

## 4.2 Treatment Period

One cycle is 28 days. Unless otherwise specified, procedures should be conducted on the scheduled day (±3 days). This excludes Study Visit 2.

Study Visit 2 (Day 1 of Study Treatment):

- Randomisation (2:1, Olaparib:matching placebo) is allowed before study Day 1 for operational reasons if the patient has completed screening and met all inclusion and exclusion criteria
- Physical examination (does not need to be repeated if assessed within 7 days of Day 1 and eligibility requirements were met, unless Investigator believes patient status is likely to have changed significantly)
- Vital signs (includes BP, pulse and temperature), body weight (does not need to be repeated if assessed within 7 days of Day 1 and eligibility requirements were met, unless Investigator believes they are likely to have changed significantly)
- HRQoL baseline assessment with FACT-O questionnaires pre-dosing
- ECOG performance status pre-dosing
- Haematology/clinical chemistry (blood samples do not need to be repeated on Day 1 if assessed at least 3 weeks after last dose of chemotherapy but within 7 days before starting study treatment unless Investigator believes they are likely to have changed significantly. Coagulation tests only required if clinically indicated)

- Urinalysis (to be repeated only if clinically indicated)
- Patients must be postmenopausal or have evidence of non-childbearing status. Women of childbearing potential must have a confirmatory negative urine or serum pregnancy test before treatment on Day 1. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately)
- Recording of AEs
- Recording of concomitant medications, including blood transfusions
- Study treatment dispensed - Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice
- Blood samples for biomarker analysis (optional in countries that do not permit this approach)
- Blood sample taken and stored for subsequent confirmation of *gBRCA1/2* status (test will be performed at end of treatment only if required to further analyse the treatment response at the end of the study)
- ECG - if assessed within 7 days before Day 1 and meets the stated eligibility criteria (if applicable), it does not need to be repeated on Day 1 of study treatment unless Investigator believes that it is likely to have changed significantly.

Study Visit 3 (Day 29):

- Physical examination
- Vital signs (includes BP, pulse and temperature), body weight
- HRQoL assessment with FACT-O questionnaire
- Haematology/clinical chemistry
- Recording of AEs
- Recording of concomitant medications (only antibiotics, anti-emetics, transfusions, erythropoietin, G-CSF and concomitant medications associated with an AE will be collected)

- Study treatment dispensed - Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice
- Unused study treatment returned
- Pregnancy test if required.

Subsequent On-treatment Visits: Every 4 Weeks Then Every 12 Weeks

Every 4 weeks in the first 12 weeks, and thereafter every 12 weeks to coincide with the radiographic assessments (if not progressed and still on treatment). The visit day is Day 1 of the visit period, i.e., Visit 4=Treatment Day 57, Visit 5=Treatment Day 85, etc.

- Physical examination
- Vital signs (includes BP, pulse and temperature), body weight
- HRQoL assessment with FACT-O questionnaire
- ECOG performance status
- Haematology/clinical chemistry
- Blood sample for disease specific marker (CA-125) every 12 weeks (±7 days). Repeat measurements should be taken ≥1 week after a value suggesting progression.
- Tumour assessment (by RECIST 1.1) as assessed by the Investigator every 12 weeks (±7 days)
- Recording of AEs
- Recording of concomitant medications (only antibiotics, anti-emetics, transfusions, erythropoietin, G-CSF and concomitant medications associated with an AE will be collected)
- Study treatment dispensed - Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice
- Unused study treatment returned

- Pregnancy test if required.

## 4.3 Study Treatment Discontinuation

- Physical examination
- Vital signs (includes BP, pulse and temperature), body weight
- HRQoL assessment with FACT-O questionnaire
- ECOG performance status
- Haematology/clinical chemistry
- Recording of AEs
- Recording of concomitant medications (only antibiotics, anti-emetics, transfusions, erythropoietin, G-CSF and concomitant medications associated with an AE will be collected)
- Unused study treatment returned
- Tumour biopsy on progression (optional)
- Blood samples for biomarker analysis on progression (optional in countries that do not permit this approach)
- Survival status.

## 4.4 Follow-up Period

Unless otherwise specified, procedures should be conducted on the scheduled day (±7 days).

30 Days After Last Dose of Study Treatment:

- Vital signs (includes BP, pulse and temperature), body weight
- Recording of AEs
- HRQoL assessment with FACT-O questionnaire
- Haematology / clinical chemistry
- Recording of concomitant medications (only antibiotics, anti-emetics, transfusions, erythropoietin, G-CSF and concomitant medications associated with an AE will be collected)

- Recording of subsequent cancer therapy following discontinuation of study treatment; all anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), start and stop dates, reason(s) for stopping and the Investigator's opinion of response to them plus the date of progression post discontinuation of study treatment need to be recorded
- Unused study treatment returned
- Pregnancy test
- Blood samples for biomarker analysis on progression
- Survival status.

## 4.5 Long-Term Follow-up (12-Weekly Beyond 30 Days After Last Dose of Study Medication)

Unless otherwise specified, procedures should be conducted every 12 weeks (±14 days). If haematology testing is not indicated, long-term follow up, including FACT-O, can be conducted by phone.

- Recording of AESIs
- FACT-O (up to 2 years post randomisation)
- Recording of subsequent cancer therapy following discontinuation of study treatment; all anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), start and stop dates, reason(s) for stopping and the Investigator's opinion of response to them plus the date of progression post discontinuation of study treatment need to be recorded
- Survival status
- For patients with unresolved haematological toxicity only: haematology **or coagulation tests as judged clinically necessary**

## 4.6 Patients on Study Treatment Post Primary Analysis

Patients remaining on study treatment following the Data Cut Off for the Primary Analysis will follow a reduced data collection schedule (Table 4) on a 12 weekly basis until either progression or the decision to stop study treatment (see sections 4.3 and 4.4)

- Recording of Adverse Events (including AESI and SAE)

- Haematology and Clinical Chemistry
- Pregnancy Test
- HRQoL assessment with FACT-O questionnaire
- Recording of concomitant medications (only antibiotics, anti-emetics, transfusions, erythropoietin, G-CSF and concomitant medications associated with an AE will be collected)
- Survival
- Study treatment dispensed - Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice
- Unused study treatment returned

# 5 STUDY ASSESSMENTS

A web-based data capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the case report forms (CRFs) as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the clinical study agreement (CSA). The Investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study site.

The Principal Investigator/Investigator will record data on the observations, tests, and assessments specified in the protocol on the CRFs provided. The CRF will be accompanied with 'Instructions for the Investigator', which should be followed. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

## 5.1 Efficacy Assessments

### 5.1.1 CT and MRI Scans Assessments (RECIST 1.1)

Following the baseline assessment, subsequent tumour assessments according to RECIST 1.1 should be performed every 12 weeks (±7 days) relative to the date of randomisation, up to objective disease progression by RECIST 1.1.

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

The imaging modalities used for RECIST assessment will be CT or MRI scans of the chest, abdomen, and pelvis with other regions as clinically indicated for the assessment of disease. Any other sites at which new disease is suspected should also be appropriately imaged. The methods of assessment of tumour burden used at baseline must be used at each subsequent follow-up assessment.

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

All treatment decisions will be based on site assessment of scans.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit ±7 day window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their time points as originally scheduled. Patients will be evaluated until objective radiological disease progression by RECIST 1.1 as per the study schedule (see Table 2 and Table 3)regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

### 5.1.2 Tumour Evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment for determining PFS times. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response [CR], partial response [PR], stable disease [SD], or progression of disease [PD]) are presented in Appendix F.

The methods of assessment of tumour burden used at baseline - CT or MRI scans of chest, abdomen, pelvis, must be used 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.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 12 weeks ±7 days after randomisation, until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should also be appropriately imaged.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD, and PD. Target lesion (TL) progression will be calculated in

comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, and SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

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.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion 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. If 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 non-target lesions is usually not sufficient to quality for unequivocal progression status.

Following progression, patients should continue to be followed up for survival according to the institution's local practice as outlined in the study plan.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Table 2 and Table 3.

### 5.1.3 CA-125 Measurements

At the same time as the CT or MRI scans, CA-125 measurements will be taken, and used in conjunction with the (RECIST 1.1) radiological data using the GCIG criteria (see Appendix H) as a measure of tumour progression. The outcomes according to GCIG criteria will be assessed as a secondary objective.

It is important to follow the assessment schedule as closely as possible. If CA-125 assessment is performed outside of the scheduled visit ±7 day window interval, every attempt should be made to assess the next CA-125 at the scheduled time points. Repeat measurements should be taken ≥1 week after a value suggesting progression.

Patients will be evaluated until objective disease progression, based on progressive serial elevation of serum CA-125 according to the GCIG criteria, or until discontinuation for other reasons.

## 5.2 Safety Assessments

### 5.2.1 Physical Examination and ECOG

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

Physical examinations will be performed at screening, prior to dosing on Day 1, Day 29, and Day 1 of each successive visit period, and at study discontinuation.

### 5.2.2 Vital Signs and Weight

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 6.3.

Weight will be assessed according to the Study Schedule (see Table 2 and Table 3) and as clinically indicated at any other time. (Height will be assessed only when relevant for additional study treatments.)

#### 5.2.2.1 Pulse and Blood Pressure

Pulse and BP (systolic and diastolic) will be assessed at screening (Visit 1, within 28 days prior to start of study treatment), Visit 2 (Day 1 of the treatment period), Visit 3 (Day 29), Day 1 of each successive visit period, at treatment discontinuation, and at the follow-up visit (30 days after last dose of study medication).

#### 5.2.2.2 Body Temperature

Body temperature will be assessed at screening (Visit 1, within 28 days prior to start of study treatment), Visit 2 (Day 1 of the treatment period), Visit 3 (Day 29), Day 1 of each successive visit period, at treatment discontinuation, and at the follow-up visit (30 days after last dose of study medication).

### 5.2.3 Laboratory Safety Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation (only if clinically indicated), and urinalysis will be taken at the times indicated in the study plan (see Section 4).

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

The 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 the

laboratory method used and routine practice at the site. Every effort should be made to ensure that the same local laboratory is used for all tests.

The following laboratory variables will be measured:

**Table 5 Laboratory Safety Variables**

| Haematology/Haemostasis (Whole Blood) | Clinical Chemistry (Serum or Plasma) |
|---|---|
| B-Haemoglobin (Hb) | S/P-Creatinine |
| B-Leukocyte count | S/P-Bilirubin, total |
| B-Absolute neutrophil count | S/P-Alkaline phosphatase (ALP) |
| B-Absolute lymphocyte count | S/P-Aspartate transaminase (AST) |
| B-Platelet count | S/P- ALT |
| B-MCV | S/P-Albumin |
| | S/P- Calcium |
| | S/P-Potassium |
| **Urinalysis (Dipstick)** | S/P-Sodium |
| U-Hb/Erythrocytes/Blood | S/P-Urea or Blood Urea Nitrogen (BUN) |
| U-Protein/Albumin | S/P-Total Protein |
| U-Glucose | |

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

**NB.** In case a patient shows an AST **or** ALT ≥3 X ULN **or** TBL ≥2 X ULN please refer to Appendix C (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law) for further instructions.

#### 5.2.3.1 Coagulation

APTT will be performed at screening and if clinically indicated

INR will be performed at screening and if clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Platelet count will be performed as part of haematology testing and fibrinogen only as clinically indicated.

Each coagulation test result will be recorded in eCRF.

#### 5.2.3.2 Bone Marrow or Blood Cytogenetic Samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 6.7.1.

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.

### 5.2.4 ECG

#### 5.2.4.1 Resting 12-lead ECG

ECGs are required within 7 days prior to starting study treatment and when clinically indicated.

12-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.

### 5.2.5 Other Safety Assessments

#### 5.2.5.1 Serum or Urine Pregnancy Test

Pregnancy tests on blood or urine samples will be performed for pre-menopausal women of child-bearing potential, one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

At 30 day follow-up a repeat pregnancy test should be performed.

## 5.3 Other Assessments

### 5.3.1 Patient Reported Outcomes (HRQoL: FACT-O)

The FACT-O (version 4) is a valid and reliable assessment of the quality of life (QoL) of women with ovarian cancer (Basen-Engquist et al. 2001). The FACT-O will be self-reported through paper-based patient questionnaires according to the study plan. No proxy reporting will be permitted as the equivalence of patient-completed versus proxy FACT-O reports has not been established. The questionnaire covers a 7-day recall period. All patients will be asked to complete the FACT-O. The FACT-O questionnaire will be administered prior to

dosing at baseline, at Day 29, then every 4 weeks (±7 days) for the first 12 weeks, and then every 12 weeks until 2 years from the date of randomisation. In addition, QoL questionnaires will be collected at the discontinuation of study treatment visit, at 30 days post last dose. The timing of assessments coincide with other clinical assessments (when the patient will be attending clinic) in order to minimise patient burden while maximizing both compliance and the association of the PRO with the clinical outcomes. Patients who had RECIST 1.1 disease progression will complete the questionnaires during the 12-weekly survival follow-ups for up to a period of 2 years from patient randomisation. The reason for any missing assessment will be collected in the CRF.

Subscales will be derived from the FACT-O according to the Functional Assessment of Chronic Illness Therapy (FACIT) Administration and Scoring Guidelines (See Section 8.4.5 for full details). The endpoint for HRQoL analysis will be the FACT-O Trial Outcome Index (TOI).

Other subscales will be considered as exploratory endpoints.

## 5.4 Biomarker Analysis

### 5.4.1 Collection of Samples

Blood samples for biomarker analysis will be taken during the study.

#### 5.4.1.1 CA-125

Blood samples for the disease specific marker, CA-125, will be collected at screening (Visit 1) and every 12 weeks (±7 days), at the same time as the CT or MRI scans, until objective disease progression, based on progressive serial elevation of serum CA-125 according to the GCIG criteria, or until discontinuation for other reasons.

#### 5.4.1.2 Archival or Fresh Tumour Sample

All patients are required to submit an archival tumour sample or, if preferred, a recent tumour sample, for post-analysis testing of their genetic status. Confirmation is required in clinical notes regarding availability of sample during the screening period; however, samples are only required to be submitted once the patient has been randomised.

Samples should be submitted as paraffin blocks, alternatively, sections mounted on glass slides prepared from the block can be provided.

Material provided will be used for additional exploratory work, which may be conducted to elucidate the mechanism of response, understand the mode of action of study treatment, or improve the understanding of disease progression.

Please refer to the laboratory manual for further details regarding tissue collection, shipping and storage.

#### 5.4.1.3 Blood Sample for Confirmation of *gBRCA*

All patients are required to provide a 9 ml blood sample at Visit 2 for subsequent confirmation of *gBRCA* status. BRCA testing will not be performed unless required to further analyse the treatment response at the end of the study.

Samples may be used for additional CCI work, which may be conducted to elucidate the mechanism of response, understand the mode of action of study treatment, or improve the understanding of disease progression.

Please refer to the laboratory manual for further details regarding blood sample collection, shipping and storage.

#### 5.4.1.4 Blood Samples for Biomarker Analysis

The following blood sample will be taken at Visit 2 and at disease progression:

1 X 20 mL whole blood to provide plasma

Samples may be used for additional CCI work, which may be conducted to elucidate the mechanism of response, understand the mode of action of study treatment, or improve the understanding of disease progression.

Please refer to the laboratory manual for further details regarding blood sample collection, shipping, and storage.

#### 5.4.1.5 Optional Tumour Samples

Wherever possible, and also subject to optional informed consent, an on-study tumour biopsy sample obtained either from the progressed lesion or from a new lesion may be collected at disease progression, CCI . Biopsies may be particularly valuable where there is a marked phenotypic change in a particular lesion.

Tumour tissue collected during the study should be immediately fixed and processed to a FFPE block. Alternatively, sections mounted on glass slides prepared from the block can be provided.

In both cases, material will be used for additional CCI work, which may be conducted to elucidate the mechanism of response, understand the mode of action of study treatment, or improve the understanding of disease progression.

Please refer to the laboratory manual for further details regarding tissue collection, shipping, and storage.

## 5.5 Biomarker Analysis

The patient's consent to the use of optional donated biological samples is mandatory (optional in countries that do not permit this approach).

Biological samples (e.g., archived tumour samples) will be collected and may be analysed for CCI biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes, and toxicity.

### 5.5.1 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 clinical study report (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.

### 5.5.2 Labelling and Shipment of Biological Samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual.

### 5.5.3 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).

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 in the AstraZeneca Biobank during the entire life cycle.

### 5.5.4 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 optional part of the study, then the patient may continue in the study.

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 laboratory(ies) 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 central laboratory(ies) 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.

# 6 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.

## 6.1 Definition of AEs

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

### 6.1.1 Olaparib AEs of Special Interest

AESIs are events of scientific and medical interest specific to the further understanding of Olaparib's safety profile and require close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI may be serious or non-serious. AESIs for Olaparib are the important identified risks of MDS/AMLand the important potential risks of new primary malignancy (other than MDS/AML) and pneumonitis.

ANY event of MDS/AML, new primary malignancy, or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE (e.g., non-melanoma skin cancer) or SAE, and regardless of Investigator's assessment of causality or knowledge of the treatment arm.

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

## 6.2 Definitions of SAE

A SAE is an AE occurring during any study phase (i.e., 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/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

## 6.3 Recording of AEs

### 6.3.1 Time Period for Collection of AEs

AEs will be collected from time of signature of informed consent, throughout the treatment period and including the 30-day follow-up period after the last dose of treatment. Only AESIs will be collected during long-term follow-up.

SAEs will be recorded from the time of informed consent.

After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

#### 6.3.1.1 AEs After the 30 day Follow-up Period

For Pharmacovigilance purposes and characterisation, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE [e.g., non-melanoma skin cancer] or SAE, and regardless of Investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival 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 the investigational product, the Investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post DCO 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 (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

### 6.3.2 Follow-up of Unresolved AEs

Any SAE or non-serious AE that is ongoing at the time of the 30-day follow up, 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.

### 6.3.3 Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the study treatment (yes or no)

- Action taken with regard to study treatment
- Treatment administered with the following as a result of the AE: antibiotics oral, antibiotics I.V., red blood cell transfusion, platelet transfusion, granulocyte-macrophage colony-stimulating factor or G-CSF, erythropoietin, anticoagulant p.o., parenteral anticoagulant
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- 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 in relation to Other medication
- Description of AE.

**Severity of AE**

For each episode of an AE, all changes to the CTCAE grade attained as well as the highest attained CTCAE 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 Section 6.2. 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 Section 6.2. 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 Section 6.2.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate, and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation program website (http://ctep.cancer.gov).

### 6.3.4 Causality Collection

The Investigator will assess causal relationship between study treatment 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 treatment product?'

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

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

### 6.3.5 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: '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.

### 6.3.6 AEs Based on Examinations and Tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and ECG abnormalities should therefore only be reported as AEs if one of the following is met:

- Any criterion for an SAE is fulfilled
- Causes study treatment discontinuation
- Causes study treatment interruption

- Causes study treatment dose reduction
- The Investigator believes that the abnormality should be reported as an AE.

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 (e.g., anaemia versus low haemoglobin 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.

### 6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 X ULN together with TBL ≥2 X ULN may need to be reported as SAEs. Please refer to Appendix C: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law.

### 6.3.8 Disease Progression

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

### 6.3.9 New Cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE (see Section 6.1.1). 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.

### 6.3.10 Lack of Efficacy

When there is deterioration in the cancer, 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 AstraZeneca 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.

### 6.3.11 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day 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 6.4 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 maybe 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.

## 6.4 Reporting of Serious AEs

All SAEs have to be reported, whether or not considered causally related to the study treatment, 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 i.e., 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 i.e., 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 WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

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

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

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

## 6.5 Overdose

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

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

## 6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

### 6.6.1 Maternal Exposure

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

The outcomes of any conception occurring from the date of the first dose of study medication until 1 month after the last dose of study medication must be followed up and documented.

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., 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 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

### 6.6.2 Paternal Exposure

Not applicable.

## 6.7 Management of Study Treatment Related Toxicities (Dose Reductions)

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. 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.

Patients known to be intolerant of the standard dose of the tablet formulation, based on previous use, may start on a dose of 250 mg Olaparib/placebo bd. They may then step down

to 200 mg bd if required. Patients who are known to be intolerant of 200 mg bd of the tablet formulation should not enter the study.

Once dose is reduced, escalation is not permitted.

## 6.7.1 Management of Haematological Toxicity

### 6.7.1.1 Management of Anaemia

**Table6 Management of Anaemia**

| Haemoglobin | Action to be taken |
|---|---|
| Hb <10 but ≥8 g/dL (CTCAE Grade 2) | Give appropriate supportive treatment and investigate causality.<br>Investigator judgement to continue study treatment with supportive treatment (e.g., transfusion) or interrupt dose for a maximum of 4 weeks.<br>If repeat Hb <10 but ≥8 g/dL, dose interrupt (for max of 4 weeks) until Hb ≥10 g/dL and upon recovery dose reduction to 250 mg bd as a first step and to 200 mg bd as a second step may be considered. |
| Hb <8 g/dL (CTCAE Grade 3) | Give appropriate supportive treatment (e.g., transfusion) and investigate causality.<br>Interrupt study treatment for a maximum of 4 weeks until improved to Hb ≥10 g/dL.<br>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. |

Common treatable causes of anaemia (e.g., 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 Section 6.7.1.3 for the management of this.

### 6.7.1.2 Management of Neutropenia, Leukopenia and Thrombocytopenia

**Table7 Management of Neutropenia, Leukopenia and Thrombocytopenia**

| Toxicity | Study treatment dose adjustment |
|---|---|
| CTCAE Grade 1-2 | Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation |
| CTCAE Grade 3-4 | Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce study treatment to 250 mg bd as a first step and 200 mg bd as a second step |

AE of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow up and interruption of study drug if CTCAE grade 3 or worse neutropenia occurs.

Primary prophylaxis with G-CSF is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

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

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse), refer to Section 6.7.1.3.

#### 6.7.1.3 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 CTCAE 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 CTCAE grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

### 6.7.2 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 AE occurs which the Investigator considers to be related to administration of study treatment.

#### 6.7.2.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (e.g., 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.

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.

#### 6.7.2.2 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with Olaparib treatment. In study D0810C00019 nausea was reported in 71% of the Olaparib treated patients and in 36% of the placebo treated patients, and vomiting was reported in 34% of the Olaparib treated patients and in 14% of the placebo treated patients. 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, study treatment tablets can be taken with a light meal/snack (e.g., 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 e.g., dopamine receptor antagonist, antihistamines or dexamethasone.

#### 6.7.2.3 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.

Study 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 study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to Olaparib may include asthenia, fatigue, and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

**Table8 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 |

## 6.8 Study Governance and Oversight

### 6.8.1 Steering Committee

This will consist of the Global Principal Investigator, a representative from each participating group of GINECO-ENGOT (Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens et du sein [GINECO]; European Network for Gynaecological Oncological Trial [ENGOT]), AstraZeneca and GINECO-ENGOT Statisticians, AstraZeneca Medical Representative, an operational representative (observer) and/or research representative (agenda driven).

### 6.8.2 Data Monitoring Committee

An IDMC will be involved in this study. The committee will be consulted as described in the data monitoring committee charter.

### 6.8.3 Scientific Advisory Committee

A scientific advisory committee will not be involved in this study.

# 7 STUDY TREATMENT AND OTHER TREATMENTS

## 7.1 Identity of Study Treatment(s)

| Study treatments[a] | Dosage form and strength |
|---|---|
| Olaparib/Placebo | *150 mg* tablet |
| Olaparib/Placebo | *100 mg* tablet |

[a] Descriptive information for Olaparib can be found in the Olaparib IB. Manufacturer will also be included in the Quality section of the Investigational Medicinal Product Dossier.

## 7.2 Dose and Treatment Regimens

For all centres, study treatment tablets will be packed in high-density polyethylene bottles with child-resistant closures. Each container will contain sufficient medication for at least 28 days plus overage. Study treatment will be dispensed to patients on Day 1 and every 28 days for the first 12 weeks, and then 12 weekly thereafter until the patient completes the study, withdraws from the study or closure of the study.

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

Patients will be administered study treatment orally bd at 300 mg bd continually, or lower if 300 mg is not tolerated on initial PARPi treatment. Two x 150 mg Olaparib (or placebo) study treatment 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. Study treatment tablets can be taken with or without food.

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 (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Unless patients experience unacceptable toxicity or withdraw from the study treatment or from the protocol, patients should continue to receive study treatment until there is objective radiological disease progression as assessed by RECIST 1.1 or as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator. Patients and Investigators will not be routinely un-blinded

to study treatment prior to the final analysis. No cross-over to Olaparib is permitted for patients who have progressed on the placebo treatment arm.

**Dose Reductions**

For guidance on dose reductions for management of AEs refer to Section 6.7.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Section 7.7.

**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/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated CrCl by Cockcroft-Gault equation of between 31 and 50 mL/min) for any reason during the course of the study: the dose of study treatment should be reduced to 200 mg bd.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the Investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that study treatment be discontinued.

## 7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing.

The patient emergency contact details will not be on the label, but can be found in the informed consent and the "Patient Dispensing Card". For emergency purposes the patient must be in possession of the emergency contact details at all times.

## 7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The study treatment label on the bottle specifies the appropriate storage.

## 7.5 Compliance

The administration of all medication (including study treatments) must be recorded in the appropriate sections of the CRFs.

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

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

Patients must return all containers and any remaining tablets at the end of the study.

## 7.6 Accountability

The study drug provided for this study is for use only as directed in the study protocol. It is the Investigator/institution's responsibility to establish a system for handling study treatments, including IPs, so as to ensure that:

- Deliveries of such products from AstraZeneca or its representative are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to patients in accordance with the protocol.

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

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the Investigator. This record is in addition to any drug

accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist, and copies retained in the Investigator site file. Dispensing and accountability records will continue to be collected for as long as patients continue to receive study treatment, although they will not be entered on the database after the database has closed. Study site personnel, if applicable, or the AZ monitor 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.

## 7.7 Concomitant and Other Treatments

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the CRF. All concomitant medications will be collected at screening. At subsequent visits, only antibiotics, anti-emetics, transfusions, erythropoietin, G-CSF and concomitant medications associated with an AE will be collected.

**Medications That May NOT Be Administered**

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (hormone replacement therapy is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

Live virus and live bacterial vaccines should not be administered whilst 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 Olaparib are unknown.

**Restricted Concomitant Medications**

*Strong or Moderate CYP3A inhibitors*

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with study treatment.

If there is no suitable alternative concomitant medication then the dose of study treatment should be reduced for the period of concomitant administration. The dose reduction of study treatment should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of study treatment 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 study treatment 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 study treatment dose can be re-escalated.

*Strong or moderate CYP3A inducers*

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide, and St John's Wort) and moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil) of CYP3A should not be taken with study treatment.

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of Olaparib.

If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of study treatment.

*P-glycoprotein (P-gp) inhibitors*

It is possible that co-administration of P-gp inhibitors (e.g., amiodarone, azithromycin) may increase exposure to Olaparib. Caution should therefore be observed.

*Effect of Olaparib on other drugs*

Based on limited *in vitro* data, Olaparib may increase the exposure to substrates of CYP3A4, P-gp, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT1, OCT2), organic anion transporter 3 (OAT3), and multidrug and toxin extrusion proteins (MATE1, MATE2K.).

Based on limited *in vitro* data, Olaparib may reduce the exposure to substrates of CYP3A4, 2B6, 2C9, 2C19 and P-gp.

The efficacy of hormonal contraceptives may be reduced if co-administered with Olaparib.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine

- CYP2B6 – bupropion, efavirenz

- CYP2C9 – warfarin
- CYP2C19 – lansoprazole, omeprazole, S-mephenytoin
- P-gp – simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 – bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 – serum creatinine
- OAT3 – furosemide, methotrexate.

**Anticoagulant Therapy**

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time, INR and APTT be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

**Anti-emetics/Anti-diarrhoeal Drugs**

From screening onwards, should a patient develop nausea, vomiting, and/or diarrhoea, then these symptoms should be reported as AEs (see Section 6.3) and appropriate treatment of the event given.

**Palliative Radiotherapy**

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**

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 and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

**Subsequent Therapies for Cancer**

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the CCI analysis of overall survival.

### 7.7.1 Other Concomitant Treatment

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

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

## 7.8 Post Study Access to Study Treatment

Not applicable.

# 8 STATISTICAL ANALYSES BY ASTRAZENECA VENDOR

## 8.1 Statistical Considerations

All personnel involved with the analysis of the study will remain blinded to study treatment until database lock and protocol violators are identified. Data cut off and subsequent database lock for the Primary Analysis will occur after the later of the two cohorts reaches the defined number of progression or death events. Analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared and any subsequent amendments will be documented, with final amendments completed prior to un-blinding of the data. Further details of the analyses will be provided in the SAP.

## 8.2 Sample Size Estimate

The benefit of Olaparib maintenance retreatment over matching placebo will be evaluated through the primary endpoint of PFS and supporting secondary endpoints. Recently published data (Study 19, NOVA, SOLO2) of PARPi therapy following a second or subsequent line of platinum based chemotherapy indicated a median PFS of less than 5.5 months can be expected in the placebo treated patients (see Table 1), irrespective of whether they are *BRCA1/2* (+ve) or *BRCA1/2* (-ve).

In the *BRCA1/2* (+ve) cohort it is assumed that the median PFS from randomisation for patients in the placebo arm will be approximately 4.5 months. In total, 85 progression or death events from 120 patients will have 85% power to demonstrate significant PFS benefit at the 2-

sided 5% level if the assumed true treatment effect resulted in a HR of 0.5; this translates to a 4.5 month (100%) increase in median PFS beyond the 4.5 months expected for patients on placebo, if PFS is exponentially distributed and allowing for a 10% drop-out rate. An observed HR of 0.63 or less will be required to achieve this level of significance. Assuming 34 months of non-linear recruitment, 85 events are expected to occur approximately 41 months after the first patient in (FSI) is enrolled into this cohort of the study.

In the *BRCA1/2* (-ve) cohort it is assumed that the median PFS from randomisation for patients in the placebo arm will be approximately 4.5 months. In total, 74 progression or death events from 108 patients will have 80% power to demonstrate significant PFS benefit at the 2-sided 5% level if the assumed true treatment effect resulted in a HR of 0.5; this translates to a 4.5 month (100%) increase in median PFS beyond the 4.5 months expected for patients on placebo, if PFS is exponentially distributed and allowing for a 10% drop-out rate. An observed HR of 0.61 or less will be required to achieve this level of significance.. Assuming 36 months of non-linear recruitment, 74 events are expected to occur approximately 42 months after the FSI is enrolled into this cohort of the study.

Considering both cohorts it is expected that approximately 228 patients in total will be enrolled into the study.

## 8.3 Definitions of Analysis Sets

### 8.3.1 Full Analysis Set (Intent-to-Treat Principle)

The intent-to-treat (ITT) population will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the full analysis set (FAS). Therefore, all efficacy and HRQoL data will be summarised and analysed using the FAS on an ITT basis as the primary analysis set. Demographic and baseline characteristics will also be analysed using the FAS on an ITT basis.

### 8.3.2 Safety Analysis Set

All patients who received at least one dose of randomised study treatment, Olaparib or placebo, will be included in the safety analysis set. If a patient receives at least one dose of Olaparib study treatment they will be summarised in the Olaparib arm for safety summaries (e.g., Olaparib arm will include patients randomised to Olaparib who receive at least one dose of Olaparib or placebo patients who receive at least one dose of Olaparib study treatment in error at any time). If a patient randomised to Olaparib receives only placebo treatment then the patient will be summarised as a part of the placebo arm.

### 8.3.3 Pharmacokinetic Analysis Set

Not applicable.

### 8.3.4 PRO Analysis Set

The PRO analysis set will consist of the FAS patients with at least a baseline and one other post-baseline assessment (excluding end of treatment and post-progression follow up assessments).

## 8.4 Outcome Measures for Analyses

| Outcome variable | Populations |
|---|---|
| **Efficacy Data** | |
| Primary: PFS | FAS (ITT) |
| Secondary: OS, TFST, TSST, TDT, Time to earliest progression by RECIST or CA-125, or death | FAS (ITT) |
| Secondary: HRQoL | PRO |
| Demography and baseline characteristics | FAS (ITT) |
| **Safety data** | |
| Exposure | Safety |
| AEs and AESIs | Safety |
| Laboratory measurements | Safety |
| Vital signs | Safety |

### 8.4.1 Progression-free Survival

The primary endpoint of PFS is defined as the time from randomisation until the date of Investigator assessed objective radiological disease progression according to RECIST 1.1 or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to disease 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 evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. Given the scheduled visit assessment scheme two missing visits will equate to more than 26 weeks since the previous RECIST assessment, allowing for early and late visits. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline (25 weeks allowing for visit window).

The PFS time will always be derived based on scan/assessment dates not visit dates.

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

(a) Date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that triggered the progression.

(b) When censoring a patient for PFS the patient will be censored at the **latest** of the RECIST assessment/scan dates contributing to a particular overall visit assessment.

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Objective progression is defined as at least a 20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) and an absolute increase of >5 mm, or an overall non-target lesion assessment of progression or a new lesion.

### 8.4.2 Overall Survival

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

Note: Survival calls will be made in the week following the DCO date for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO.

### 8.4.3 Time to Subsequent Therapies

As a supportive summary to PFS, time to start of first subsequent therapy or death will be assessed. Time to first subsequent therapy or death is defined as the time from the date of randomisation to the earlier of first subsequent therapy start date, or death date. Any patient not known to have had a further subsequent therapy or death will be censored at the last known time to have not received subsequent therapy. If a patient terminated the study for reason other than death before first subsequent therapy, these patients will be censored at the earliest of their last known to be alive and termination dates.

Additionally, time to start of second subsequent therapy or death will be assessed. Time to second subsequent therapy or death is defined as the time from the date of randomisation to the earlier of the date of second subsequent therapy start date, or death date. Any patient not known to have had a further second subsequent therapy or death will be censored at the last known time to have not received second subsequent therapy. If a patient terminated the study for reason other than death before second subsequent therapy, these patients will be censored at the earliest of their last known to be alive and termination dates.

### 8.4.4 Time to Study Treatment Discontinuation

Time to study treatment discontinuation is defined as the time from randomisation to study treatment discontinuation or death if this occurs before discontinuation of study treatment. Any patient not known to have died at the time of analysis and not known to have

discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive.

### 8.4.5 Time to Earliest Progression (RECIST or CA-125) or Death

Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125, according to the following GCIG criteria (note GCIG criteria is not validated for this trial population):

- For patients with elevated CA-125 on or before the date of randomisation (i.e. greater than the upper limit of normal (ULN)),

(a) If CA-125 does not fall to within the normal range post randomisation then there must be evidence of CA-125 greater than, or equal to, 2 times the nadir value in the 28-day period before day 1 on two occasions at least 1 week apart

(b) Where CA-125 does fall to within the normal range post randomisation (and the patient has not already progressed by way of a) above), then there must be evidence of CA-125 greater than, or equal to, 2 times the ULN on two occasions at least 1 week apart

- Patients with CA-125 in the normal range on or before the date of randomisation and no results greater than ULN on or before the date of randomisation must show evidence of CA- 125 greater than, or equal to, 2 times the ULN on two occasions post randomisation at least 1 week apart.

- CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted.

Time to progression by RECIST or CA-125 or death is defined as the time from randomisation to the earlier date of RECIST progression or CA-125 progression or death by any cause. Patients without a CA-125 progression or a RECIST progression who are still alive at the time of analysis will be censored at the time of their last evaluable RECIST assessment and/or their last available CA-125 measurement, whichever is the earliest at the time of analysis. Patients that do not have any evaluable RECIST assessments or any CA-125 results post randomisation will be censored at the date of randomisation.

### 8.4.6 Calculation or Derivation of HRQoL Endpoints

The FACT-O consists of 39 questions: the 27 Functional Assessment of Cancer Therapy – General (FACT-G) items and 12 Additional Concerns items consisting of specific ovarian cancer symptoms). The questionnaire will be scored into subscales according to the FACIT scoring guidelines as follows:-

- Physical Well-Being (PWB): Score range 0-28

- Social/Family Well-Being (SWB): Score range 0-28
- Emotional Well-Being (EWB): Score range 0-24
- Functional Well-Being (FWB): Score range 0-28
- Ovarian Cancer Subscale (OCS): Score range 0-44
- FACT-O TOI, Score range 0-100. Derived using PWB+FWB+OCS
- FACT-O total score, Score range 0-152, Derived using PWB+FWB+SWB+EWB+OCS
- FACT-G total score: Score range 0-108. Derived using PWB+FWB+EWB+SWB.

The higher the score, the better the HRQoL for all subscales. Missing items will be dealt with as described in the FACIT Administration and Scoring Guidelines. If at least 50% of items in a subscale have been answered the subscale score will be prorated. Subscale scores will be missing if less than 50% of items within that subscale have been answered. Total scores will only be calculated if all component subscales have valid scores. The reason for any missing assessment will be collected in the CRF.

The subscale of primary interest will be the TOI score. Other subscales will be considered as exploratory.

Change from baseline scores will be calculated at each visit.

Four outcome measures will be calculated:

- Change from baseline score
- The actual change from baseline score will be derived for each visit where there is available data. For example; at visit X, the calculation will be (subscale score at visit X – Baseline subscale score). Actual change from baseline for the individual subscale scores will be calculated in a similar way. Subscale-specific minimally important differences (MID) will be used for interpretation where available (Yost and Eton 2005).
- Proportion of patients with a PRO response (improved PRO Score)

The proportion of patients with an improved score (≥MID points change from baseline), worsened (≤ MID points change from baseline) or no change (changes of less than MID points in either direction) will be calculated at each visit. The denominator will consist of the FAS population with a baseline PRO.

- Best overall response

Best overall improvement (improvement in the absence of subsequent cancer therapy) will be defined as a change from baseline of ≥MID sustained for at least 28 days, the denominator consisting of a subset of the FAS population who have a baseline score. It will be derived as the best symptom improvement response the patient achieved, based on evaluable QoL data collected from randomisation up to the earliest of starting any subsequent cancer therapy or death. Therefore, the following criteria will be used to assign a best overall score response for each patient based on the individual visit responses (Table ).

**Table 9 HRQoL: Best Overall Score**

| Best overall score response | Criteria |
|---|---|
| Improved | Two visit responses of "improved" a minimum of 28 days apart without an intervening visit response of "worsened" |
| No change | Does not qualify for overall score response of "improved". Two visit responses of either "no change" or "improved and "no change" a minimum of 28 days apart without an intervening visit response of "worsened" |
| Worsened | Does not qualify for overall score response of "improved" A visit response of "worsened" without a response of "improved" or "no change" within 28 days. |
| Other | Does not qualify for one of the above. |

An improvement rate (in the absence of subsequent cancer therapy) will be calculated as the % of all analysed patients with a best overall score response of improved. In the calculation of the proportion of patients that have a response of Improved, No Change or Worsened, the denominator used in the calculation will use the number evaluable for the subscale score at baseline.

- PRO deterioration-free survival

Time from randomisation to definitive deterioration of PRO subscale score (≤MID points change from baseline with no further improvement of ≥MID points or subsequent missing data) or PFS/death if these events occur prior to definitive deterioration in PRO subscale.

### 8.4.7 Calculation or Derivation of Safety Variables

Safety and tolerability will be assessed in terms of AEs, SAEs, AEs leading to discontinuation of study drug from randomisation to 30 days after last study treatment, AESIs, laboratory data including chemistry and haematology, and vital signs. The latest NCI-CTCAE version will be used to grade toxicities.

AESI will be identified by an AstraZeneca medically qualified expert on consultation with relevant members of the study team. These AEs will be determined prior to database lock and documented appropriately.

### 8.4.8 Calculation or Derivation of Exploratory Variables

CCI [redacted]

## 8.5 Methods for Statistical Analyses

Demographic and baseline characteristics will be summarised by treatment group using descriptive statistics. Descriptive statistics used to summarise continuous data will include the mean, median, standard deviation, minimum, maximum and number of observations. Categorical data will include frequency counts and percentages for each category. All data will be presented separately for each cohort.

### 8.5.1 Analysis of the Primary Variable(s)

PFS for the two treatment groups will be compared using a 2-sided stratified log-rank test at the 5% significance level, based on the two stratification factors at the time of randomisation: use of prior bevacizumab (yes versus no) and number of prior regimens of platinum-containing chemotherapy (≤3 versus ≥4 regimens), and using the Breslow approach for handling ties. PFS will be analysed using Kaplan-Meier (K-M) methodology and the median and its 95% CI will be provided for each treatment group, together with PFS rates at clinically relevant time points. K-M curves will also be provided, with tick marks to identify censored observations.

The HR and its 95% CI will be estimated (HR less than 1.0 favours Olaparib) from a Cox Proportional Hazards model (with ties = Efron and the stratification factors as covariates) and the CI will be calculated using a profile likelihood approach. The primary analysis for PFS for each cohort will be performed when both 85 progression or death events have occurred in the BRCA1/2 (+ve) cohort and 74 progression or death events in the *BRCA1/2* (-ve) cohort (whichever occurs later). The primary analysis will be based on Investigator assessment of disease progression according to RECIST 1.1.

### 8.5.2 Analysis of the Secondary Variable(s)

#### 8.5.2.1 Overall Survival

OS for the two treatment groups will be compared using a 2-sided stratified log-rank test at the 5% significance level, based on the two stratification factors at the time of randomisation: use of prior bevacizumab (yes versus no) and number of prior regimens of platinum-containing chemotherapy (≤3 versus ≥4 regimens), and using the Breslow approach for handling ties. OS will be analysed using K-M methodology and the median and its 95% CI will be provided for each treatment group, together with survival rates at clinically relevant

time points. K-M curves will also be provided, with tick marks to identify censored observations.

The HR and its 95% CI will be estimated (HR less than 1.0 favours Olaparib) from a Cox Proportional Hazards model (with ties = Efron and the stratification factors as covariates) and the CI will be calculated using a profile likelihood approach. OS will be analysed at the time of the primary analysis for PFS and after 50% death events in either cohort, or 60 months after FSI, whichever is the earlier.

#### 8.5.2.2 Time to Subsequent Therapies or Death

Time to first subsequent treatment or death and time to second subsequent treatment or death for the two treatment groups will be compared using a 2-sided stratified log-rank test at the 5% significance level, based on the two stratification factors at the time of randomisation: use of prior bevacizumab (yes versus no) and number of prior regimens of platinum-containing chemotherapy (≤3 versus ≥4 regimens).

The HR and its 95% CI will be estimated (HR less than 1.0 favours Olaparib) using the same methods as for PFS and OS. A K-M analysis will also be performed and K-M curves presented.

These endpoints will be analysed at the time of the primary analysis of PFS and again at the end of study follow-up.

#### 8.5.2.3 Time to Study Treatment Discontinuation or Death

Time to study treatment discontinuation or death will be compared between the two treatment groups using a 2-sided stratified log-rank test as defined for the previous endpoints. The HR and its 95% CI will be estimated (HR less than 1.0 favours Olaparib) using the same methods as described for PFS and OS.

A K-M analysis will also be performed and K-M curves presented.

This endpoint will be analysed at the time of the primary analysis of PFS and again at the end of study follow-up.

#### 8.5.2.4 Time to Earliest Progression by RECIST or CA-125 or Death

Time to progression by RECIST 1.1, CA-125 or death will be performed at the same time as the primary analysis of PFS and will use the same methodology and model.

The number (%) of patients reporting a CA-125 progression, an objective RECIST 1.1 progression and both a CA-125 and/or objective RECIST progression will be tabulated.

#### 8.5.2.5 HRQoL Index Score

FACT-O completion rates will be calculated out of the number of randomised patients and also the number of patients expected to have a PRO assessment (alive and on-treatment).

Reasons for missing data will be summarised. Missing data will be explored in order to assess the assumption of data being missing at random (MAR). Raw scores and change from baseline scores will be summarised descriptively for all visits and all subscales. Cumulative distribution curves will be presented (details of analysis in the SAP).

Longitudinal PRO data will be compared between randomised treatment groups using a mixed model for repeated measures (MMRM). The response variable will be the PRO score.

Baseline scores and randomisation stratification factors will be accounted for in the model. Adjusted change from baseline scores and 95% CIs will be reported at each visit. The estimate of overall change from baseline difference between the groups, 95% CI, and P-value will be reported. The clinical relevance of the estimated differences will be assessed using the MID relevant to each subscale (Yost and Eton 2005). Sensitivity analyses will be used should the assumption of MAR be violated, although the MMRM is generally robust to deviations from the assumption (Bell and Fairclough 2014).

The proportion of patients with a PRO response will be reported and compared across treatment groups at key visits using the Cochran-Mantel-Haenszel test to account for the randomisation stratification factors.

Best overall response will be summarised as number and proportion of patients with each response level by treatment group. The proportion with a best overall response of improved will be compared using the Cochran-Mantel-Haenszel test to account for the randomisation stratification factors.

PRO deterioration-free survival will be analysed using Cox regression accounting for the randomisation stratification factors to compare treatment groups. Median time until PRO deterioration-free survival will be reported for each group and for the difference between groups with 95% CIs. K-M curves will be used to show unadjusted time to deterioration.

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#### 8.5.2.6 Safety and Tolerability

Summary tables of AEs will include only treatment-emergent adverse events (TEAEs), defined as events developing or worsening in severity (from baseline severity) on or after the first day of Olaparib or placebo administration up to and including 30 days after the last dose of Olaparib or placebo (defined as the treatment period). Any AE occurring before the first dose of Olaparib or placebo and AEs occurring 30 days after last dose will be listed only and not included in the summaries. Any AEs that occur after a patient has received further therapy for cancer (following discontinuation of Olaparib or placebo) will be flagged in the data listings. The number of patients experiencing each AE will be summarised by treatment group by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and worst CTCAE grade. The number and percentage of patients

with AEs in different categories (e.g., causally related, CTCAE grade ≥3 etc.) will be summarised by treatment group, and events in each category will be further summarised by MedDRA system organ class and preferred term. SAEs and deaths will be summarised and listed.

Each AE event rate (per 1000 patient years) will also be summarised by preferred term within each system organ class. For each preferred term, the event rate will be presented and will be defined as the number of patients with that AE divided by the sum of the duration from the start of treatment to 30 days after the last treatment dose (for patients without the event) and the time to the AE (for patients with the event) in each group multiplied by 1000.

Haematology and clinical chemistry will be summarised by treatment group for change from baseline using descriptive statistics (mean, median, standard deviation, minimum, maximum and number of observations) and by worst grade during the treatment period using descriptive statistics (frequency and percent). Shift tables for change in grade from baseline by treatment group may be presented. For all laboratory variables which are included in the current version of CTCAE, the grade will be calculated.

Vital signs will be summarised by treatment group using descriptive statistics (mean, median, standard deviation, minimum, maximum and number of patients).

### 8.5.3 Subgroup Analysis

In the final analysis of PFS and other time-to-event endpoints, subgroup analyses may be conducted to assess consistency of treatment effect across potential or expected prognostic factors. An analysis will not be performed if there are too few events available for a meaningful analysis of a particular subgroup (i.e., if there are less than 20 events in a subgroup). Pre-specified subgroups will be described in the SAP.

### 8.5.4 Interim Analysis

In the *BRCA1/2* (+ve) cohort an interim analysis for futility will be performed after 50% of the target PFS events (i.e. after 43 events). Based upon the assumed accrual and event rate it is estimated that this will occur after approximately 29 months. Using a conditional power non binding futility analysis the cohort may stop for futility if the hazard ratio > 1.056. Under the null hypothesis the probability of stopping for futility is 0.433 and under the alternative hypothesis it is 0.01.

In the *BRCA1/2* (-ve) cohort an interim analysis for futility will be performed after 50% of the target PFS events (i.e. after 37 events). Based upon the assumed accrual and event rate it is estimated that this will occur after approximately 30 months. Using a conditional power non binding futility analysis the cohort may stop for futility if the hazard ratio > 1.02. Under the null hypothesis the probability of stopping for futility is 0.477 and under the alternative hypothesis it is 0.02.
Results from the planned interim analyses will be shared with the IDMC who will make a recommendation on continuing or stopping a cohort.

### 8.5.5 Sensitivity Analysis

Sensitivity analyses on PFS will be performed to assess potential censoring bias and possible time assessment bias. Other sensitivity analyses may be performed as appropriate and will be described in the SAP.

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## 9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA VENDOR

### 9.1 Training of Study Site Personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures including PROs system(s) utilised as applicable.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

### 9.2 Monitoring of the Study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

### 9.2.1 Source Data

Refer to the CSA for location of source data.

### 9.2.2 Study Agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

### 9.2.3 Archiving of Study Documents

The Investigator follows the principles outlined in the CSA.

## 9.3 Study Timetable and End of Study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The final DCO will take place after 50% death events in either cohort, or 60 months after FSI, whichever is the earlier. At this time point, the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with study treatment. For patients who do continue to receive treatment beyond the time of this DCO, Investigators will continue to report all AESIs and SAEs to AstraZeneca Patient Safety until 30 days after study treatment is discontinued, in accordance with Section 6.4 (Reporting of Serious AEs). 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 study treatment, the Investigator should notify AstraZeneca, Patient Safety. Additionally as stated in Section 6.3 (Recording of AEs), any SAE or non-serious AE that is ongoing at the time of this DCO, 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.

The study is expected to start in Q2 2017 and to end by Q2 2022.

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 Olaparib.

The study, or one cohort, may also be stopped at any time after the Primary Analysis if in the judgment of AstraZeneca, the ENGOT Principal Investigator and the Trial Steering Committee, there is insufficient clinical benefit from re-treatment.

## 9.4 Data Management by AstraZeneca Designated Clinical Research Organisation

Data management will be performed by a clinical research organisation (CRO) according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the WHO Drug Dictionary. Classification coding will be performed by the CRO.

The data collected through third party sources will be obtained and reconciled against study data.

AEs and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the CRO.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

**SAE Reconciliation**

AE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

**Data Associated with Human Biological Samples**

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

**Management of External Data**

The data collected through third party sources will be obtained and reconciled against study data.

# 10 ETHICAL AND REGULATORY REQUIREMENTS

## 10.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 10.2 Patient Data Protection

The Master Informed Consent Form will explain that:

- Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation
- Patient data will be maintaining confidentiality in accordance with national data legislation
- For data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an institutional review board (IRB)/independent ethics committee (IEC) may require direct access to parts of the hospital or practice source records relevant to the study, including patients' medical histories
- All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).

If applicable, AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

If applicable, 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. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

## 10.3 Ethics and Regulatory Review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees, and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the Ethics Committees with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study treatment. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

## 10.4 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.

## 10.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the International coordinating Investigator, National Coordinating Investigator, and the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

## 10.6 Audits and Inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

# 11 LIST OF REFERENCES

**Basen-Engquist et al. 2001**
Basen-Engquist, K., D. Bodurka-Bevers, M. A. Fitzgerald, K. Webster, D. Cella, S. Hu & D. M. Gershenson (2001) Reliability and validity of the functional assessment of cancer therapy-ovarian. *J Clin Oncol,* 19**,** 1809-17.

**Bell and Fairclough 2014**
Bell, M. L. & D. L. Fairclough (2014) Practical and statistical issues in missing data for longitudinal patient-reported outcomes. *Stat Methods Med Res,* 23**,** 440-59.

**Cella et al. 1993**
Cella, D. F., D. S. Tulsky, G. Gray, B. Sarafian, E. Linn, A. Bonomi, M. Silberman, S. B. Yellen, P. Winicour, J. Brannon & et al. (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol,* 11**,** 570-9.

**Fong et al. 2009**
Fong, P. C., D. S. Boss, T. A. Yap, A. Tutt, P. Wu, M. Mergui-Roelvink, P. Mortimer, H. Swaisland, A. Lau, M. J. O'Connor, A. Ashworth, J. Carmichael, S. B. Kaye, J. H. Schellens & J. S. de Bono (2009) Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med,* 361**,** 123-34.

**Hay et al. 2009**
Hay, T., J. R. Matthews, L. Pietzka, A. Lau, A. Cranston, A. O. Nygren, A. Douglas-Jones, G. C. Smith, N. M. Martin, M. O'Connor & A. R. Clarke (2009) Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. *Cancer Res,* 69**,** 3850-5.

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

**Ledermann et al. 2012**
Ledermann, J., P. Harter, C. Gourley, M. Friedlander, I. Vergote, G. Rustin, C. Scott, W. Meier, R. Shapira-Frommer, T. Safra, D. Matei, E. Macpherson, C. Watkins, J. Carmichael & U. Matulonis (2012) Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med,* 366**,** 1382-92.

**Ledermann et al. 2016**
Ledermann, J. A., P. Harter, C. Gourley, M. Friedlander, I. Vergote, G. Rustin, C. Scott, W. Meier, R. Shapira-Frommer, T. Safra, D. Matei, A. Fielding, S. Spencer, P. Rowe, E. Lowe, D. Hodgson, M. A. Sovak & U. Matulonis (2016) Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving Olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol*.

**Mirza et al. 2016**
Mirza, M. R., B. J. Monk, J. Herrstedt, A. M. Oza, S. Mahner, A. Redondo, M. Fabbro, J. A. Ledermann, D. Lorusso, I. Vergote, N. E. Ben-Baruch, C. Marth, R. Madry, R. D. Christensen, J. S. Berek, A. Dorum, A. V. Tinker, A. du Bois, A. Gonzalez-Martin, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B. J. Rimel, J. Buscema, J. P. Balser, S. Agarwal, U. A. Matulonis & E.-O. N. Investigators (2016) Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med*.

**Murai et al. 2012**
Murai, J., S. Y. Huang, B. B. Das, A. Renaud, Y. Zhang, J. H. Doroshow, J. Ji, S. Takeda & Y. Pommier (2012) Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer Res,* 72**,** 5588-99.

**Richards et al. 2008**
Richards, C. S., S. Bale, D. B. Bellissimo, S. Das, W. W. Grody, M. R. Hegde, E. Lyon, B. E. Ward & A. L. Q. A. C. Molecular Subcommittee of the (2008) ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007. *Genet Med,* 10**,** 294-300.

**Rottenberg et al. 2008**
Rottenberg, S., J. E. Jaspers, A. Kersbergen, E. van der Burg, A. O. Nygren, S. A. Zander, P. W. Derksen, M. de Bruin, J. Zevenhoven, A. Lau, R. Boulter, A. Cranston, M. J. O'Connor, N. M. Martin, P. Borst & J. Jonkers (2008) High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc Natl Acad Sci U S A,* 105**,** 17079-84.

**Yost and Eton 2005**
Yost, K. J. & D. T. Eton (2005) Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Prof,* 28**,** 172-91.

# Appendix A Additional Safety Information

## Further Guidance on the Definition of a SAE

### 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 (e.g., hepatitis that resolved without hepatic failure).

### Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (e.g., 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 Intervention

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 intervention 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 (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse





## A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

# Appendix B International Airline Transportation Association 6.2 Guidance Document

**Labelling and Shipment of Biohazard Samples**

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. 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, e.g., 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 e.g., Hepatitis A, B, C, D, and E viruses, HIV types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- They 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.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment

standards are encouraged wherever possible when road or rail transport is used.

# Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

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

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

## Definitions

Potential Hy's Law

AST or ALT ≥3 X ULN **together with** TBL ≥2 X ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

AST or ALT ≥3 X ULN **together with** TBL ≥2 X ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## 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 X ULN
- AST ≥3 X ULN
- TBL ≥2 X ULN

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

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

When the identification criteria are met from local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF.

**Follow-up**

**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.

**Potential Hy's Law Criteria Met**

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team.

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

**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.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

– The 'Medically Important' serious criterion should be used if no other serious criteria apply

– 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 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

**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 Potential Hy's Law Criteria Met of this Appendix

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

**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 e.g., chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Potential Hy's Law Criteria Met of this Appendix

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 Section **Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment**.

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

## References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

# Appendix D Acceptable Birth Control Methods

Olaparib is regarded as a compound with medium/high foetal risk

- Women of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective forms of contraception and their partners must use a male condom (as listed below), throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

**Acceptable Non-hormonal Birth Control Methods Include:**

- Total/True abstinence: When the subject 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 1 month after the last dose of study drug. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom.
- Intrauterine device PLUS male condom. Provided coils are copper-banded.

**Acceptable Hormonal Methods:**

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin/ethinyl estradiol (EE) transdermal system PLUS male condom
- Intrauterine system (IUS) device (e.g., levonorgestrel releasing IUS - Mirena®) PLUS male condom





- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom.

# Appendix E ECOG Performance Criteria

GRADE

| | |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair |
| 5 | Dead |

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

# Appendix F Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

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# 1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D0816C00014 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

# 2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated and not chosen for biopsy during the screening period.

**Measurable:**

A lesion, not previously irradiated and not chosen for biopsy during the screening period, 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. If only one measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

**Non-measurable:**

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- 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**
- Skin lesions assessed by clinical examination
- Brain metastasis

- Lesions biopsied within the screening period (exception: If only one measurable lesion exists, it is acceptable to be used [as a target lesion] as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed).

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**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 Non-Target Lesions (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.

**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 target lesions (TL) at baseline.

**Non-Target lesions:**

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

## 3. METHODS OF ASSESSMENT

**The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.**

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

**App. Table 1 Summary of Methods of Assessment**

| Target Lesions | Non-Target Lesions | New Lesions |
|---|---|---|
| CT (preferred) | CT (preferred) | CT (preferred) |
| MRI | MRI | MRI |
| | Clinical examination | Clinical examination |
| | X-ray, Chest x-ray* | X-ray, Chest x-ray* |
| | | Ultrasound* |
| | | Bone Scan* |
| | | FDG-PET* |

*Not mandatory per D0816C00014 protocol; can be used if clinically indicated and are acceptable methods for New lesion identification.

## 3.1. 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 D0816C00014 study it is recommended that CT examinations of the Chest, abdomen and pelvis, will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method although CT is acceptable.

## 3.2. Clinical examination

In the D0816C00014 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

## 3.3. X-ray

### 3.3.1. Chest X-ray

In the D0816C00014 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.

### 3.3.2. Plain X-ray

In the D0816C00014 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

## 3.4. Ultrasound

In the D0816C00014 study, ultrasound examination will not be used for assessment of TL and NTL 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 an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

## 3.5. Endoscopy and laparoscopy

In the D0816C00014 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

## 3.6. Tumour markers

In the D0816C00014 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

## 3.7. Cytology and histology

In the D0816C00014 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.

## 3.8. Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D0816C00014 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.

## 3.9. FDG-PET scan

In the D0816C00014 study 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 FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

# 4. TUMOUR RESPONSE EVALUATION

## 4.1. 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 no more than 28 days before the start of study treatment (refer to Study Plan and section 5.1 from the study protocol). Follow-up assessments will be performed every 12 weeks (± 1 week) after randomisation until objective disease progression as defined by RECIST 1.1 even if a patient discontinues treatment prior to progression or receives other anti-cancer treatment. 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.

## 4.2. Target lesions (TL)

### 4.2.1. 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 millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

**Special cases:**

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, 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 two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- 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 e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

### 4.2.2. Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

**App. Table 2 Evaluation of target lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions 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 target lesions, 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 5mm. |
| Not Evaluable (NE) | Only relevant if any of the target lesions 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 target lesion response |

## 4.3. Non-Target lesions (NTL)

### 4.3.1. 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.

**App. Table 3 Evaluation of Non-Target Lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis). |
| Non CR/Non PD | Persistence of one or more NTL |
| Progression (PD) | Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy. |
| Not Evaluable (NE) | Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit.<br>Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met. |

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

## 4.4. 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: i.e. 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.

## 4.5. 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.

## 4.6. Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

**App. Table 4 Overall Visit Response**

| Target lesions | Non-Target lesions | New Lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | NA | No | CR |
| CR | Non CR/Non PD | No | PR |
| CR | NE | No | PR |
| PR | Non PD or NE | No | PR |
| SD | Non PD or NE | No | SD |
| NE | Non PD or NE | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no NTLs at baseline).

# 5. CENTRAL REVIEW

No independent central review will be performed for this study.

# 6. REFERENCES

**Eisenhauer et al 2009**
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247.

# Appendix G FACT-O QoL Questionnaire

FACT-O (Version 4), English (Universal), Copyright 1987, 1997

http://www.facit.org/LiteratureRetrieve.aspx?ID=42283

NB: TOI is a targeted summary index of physical/functional outcomes and has been shown to be responsive to changes in the clinical trial setting (http://www.facit.org/FACITOrg/FAQ). The TOI is considered to target the most relevant symptoms together with function and physical well-being and can be directly related to signs and symptoms and AEs (Cella et al. 1993).

# Appendix H GCIG Criteria

Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, du Bois A, Kristensen G, Jakobsen A, Sagae S, Greven K, Parmar M, Friedlander M, Cervantes A, Vermorken J; Gynecological Cancer Intergroup. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21(2):419-23.

Available for free at
http://journals.lww.com/ijgc/Fulltext/2011/02000/Definitions_for_Response_and_Progression_in.34.aspx

# Appendix I Signatures

ENGOT Number ENGOT-ov38/OReO

AstraZeneca Signature(s)

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A Phase IIIb, Randomised, Double-blind, Placebo-controlled, Multicentre Study of Olaparib Maintenance Retreatment in Patients with Epithelial Ovarian Cancer Previously Treated With a PARPi and Responding to Repeat Platinum Chemotherapy (OReO)

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca review.

I agree to the terms of this study protocol.

AstraZeneca Representative

PPD

Date
(Day Month Year)

Cambridge, CB2 8PA, UK

ENGOT Number ENGOT-ov38/OReO

AstraZeneca Signature(s)

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A Phase IIIb, Randomised, Double-blind, Placebo-controlled, Multicentre Study of Olaparib Maintenance Retreatment in Patients with Epithelial Ovarian Cancer Previously Treated With a PARPi and Responding to Repeat Platinum Chemotherapy (OReO)

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PPD

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(Day Month Year)

Cambridge, CB2 8PA, UK

ENGOT Number ENGOT-ov38/OReO

SIGNATURE OF INTERNATIONAL COORDINATING INVESTIGATOR

---

A Phase IIIb, Randomised, Double-blind, Placebo-controlled, Multicentre Study of Olaparib Maintenance Retreatment in Patients with Epithelial Ovarian Cancer Previously Treated With a PARPi and Responding to Repeat Platinum Chemotherapy (OReO)

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International Coordinating Investigator

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# SIGNATURE PAGE

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