| **Clinical Study Protocol** | |
|---|---|
| Drug Substance | Olaparib, AZD2281, KU 0059436 |
| Study Code | D0816C00020 |
| Version | 3.0 |
| Date | 26 October 2018 |

# OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

**Sponsor:** *AstraZeneca AB, 151 85 Södertälje, Sweden*

**EudraCT number: 2017-002767-17**

# VERSION HISTORY

| **Version 1.0, 27 July 2017** |
|---|
| Initial creation |
| **Version 2.0, 30 August 2017** |
| **Sections:** 4. Study plan and timing of procedures, Table 1 – Study Schedule – Screening (Visit 1), Table 2 - Study Plan Detailing the Procedures, 4.2.4 - Visits 5 and Subsequent on-treatment tumour assessment visits, 5.6 - Genetics<br>**Description of change with reason:**<br>**1.** Removed FACT-O and EQ-5D-5L questionnaires from Screening and added to Baseline and Day 29 to align with Sections 5.3.1 and 5.3.2.<br>**2.** Corrected footnote "e" of Table 1 from inclusion criterion 5 to 6 to reflect proper reference to inclusion criterion. A new footnote "g" was added to Table 1 to clarify the nature of the sample: "All patients are required to submit an archival tumour sample for retrospective testing of their genetic status. Samples should be submitted as paraffin blocks, alternatively, sections mounted on glass slides prepared from the block can be provided. Please refer to the laboratory manual for further details regarding tissue collection, shipping and storage."<br>**3.** Removed ECOG performance status from Safety visits from Table 2 and Section 4.2.4 to align with Section 5.2.2. Wording of heading of Table 2 in respect to Visit 4 and Visit 5 and subsequent safety visits has been clarified to indicate that safety visits (repeats of Visit 5) alternate with assessment visits (repeats of Visit 4) for the first year.<br>**4.** The sample collection for retrospective g*BRCA* testing had been omitted in both Table 2 and body of the protocol. This test has been added to Table 2 and Section 5.6.<br>**5.** A new footnote "g" was added to Table 2 to clarify when retrospective g*BRCA* testing needs to be performed. A new footnote reads: "Unless patient was tested at Myriad as part of screening. All patients are required to provide a 9 ml blood sample for confirmation of g*BRCA* status. Please refer to the laboratory manual for further details regarding blood sample collection,shipping and storage.". With the insertion of a new footnote, the referencing of the rest of the footnotes was changed accordingly in Table 2.<br>**6.** Portion of footnote "d" of Table 2 ("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") was deleted as it duplicated footnote "b". |

**Section:** 5.7 Biomarker Analysis
**Description of change with reason:** This section was updated to reflect blood amount to be taken for this test and and at which visits in order to align with Table 2.

**Version 3.0, 26 October 2018**

**Sections:** Synopsis, Objectives; target patient populations, Table of Contents and List of Abbreviations; Section 1.2 Rationale for Study Design, Doses and Control Groups; Section 1.4 Study design, Figure 1 Protocol Schedule, Section 2.2 - Secondary Objectives; Section 2.4 - Exploratory Objectives; 3.1 - Inclusion Criteria; 3.2 - Exclusion Criteria; 3.8 - Restrictions; Section 3.9.1 - Discontinuation of Investigational Product; Section 3.10 – Criteria for Withdrawal; Section 4 Table 1,Table 2; Section 4.1.1 Testing for g*BRCA* mutations for patients with unknown g*BRCA* status; Section 4.2.3 Visit 4 (Day 57) and subsequent on-treatment tumour assessment visits; Section 4.3.2 Long-term follow up beyond 30 days after last dose of study medication; Section 5 Study Assessments; Section 5.2.1.2 Bone marrow or blood cytogenetic samples; Section 5.3.3 Other Assessments; Section 5.6 Genetics; Section 5.7 Biomarker Analysis; Section 6 Safety Reporting and Medical Management; Section 6.3; Recording of Adverse Events; Section 6.8 Management of Investigational Product Related toxicities Table 4; Section 7.7 Concomitant and Other Treatments; Section 8.4 Outcome measures for Analyses; Section 8.5.1 Analysis of the primary variable; Section 8.5.2 Analysis of the secondary/exploratory variables; Section 8.5.3 Interim Analysis; Section 9.3 Study Timetable and End of Study; Appendix F; Appendix I.

**Description of changes with reason:**

1. Synopsis: Change of address for International Coordinating Investigator.“High grade endometrioid cancer” changed throughout to “high grade endometrioid ovarian cancer” for clarity (and throughout the protocol). New study countries added, Japan deleted, number of patients planned and study period clarified for new OS analysis; Objectives – OS has become a secondary objective and OS by TP53 disruption status an exploratory objective per CHMP request. Target Patient Population – oxaliplatin added as additional acceptable platinum-based chemotherapeutic. Text added in statistical section on timing of primary analysis and analysis for new OS secondary objective. Clarification of which Myriad tests are to be used and other minor text changes.

2. Table of Contents: Section 9.2.2. Direct access to source data in Japan removed as section has been deleted. List of abbreviations, MHLW Ministry of Health, Labour and Wefare, Japan deleted. Correction in inconsistencies between List of Abbreviations and protocol text. Add wt = wild-type.

3. Section 1.2 Rationale for Study Design, Doses and Control Groups: updated text summarizing previous study findings. Add m to g*BRCA*m in title of section on rational for patient selection.

4. Section 1.4 Study Design: text updated for clarity.

5. Figure 1: Protocol Schedule: Revised to clarify that patients must be negative for g*BRCA*.

6. Section 2.2 Secondary objectives: Moved measurement of OS from Exploratory Objectives (Section 2.4) to Secondary Objectives section per CHMP request. Clarification of Myriad tests to be used. Ensure consistenct of wording with sysnopsis.

7. Section 2.4 Exploratory objectives: OS objective moved to Section 2.2; added analysis of OS by TP53 disruption status per CHMP request. Other minor text changes for clarity and to ensure consistency with synopsis.

8. Section 3.1 Inclusion Criteria: Text on special requirements for Japanese subjects removed (IC 2);text on g*BRCA* testing revised for clarity; oxaliplatin added as an acceptable platinum agent (IC 5); 24-hour urine added as alternative measure of Creatinine Clearance (IC 7) in line with new AZ standard guidance.

9. Section 3.2 Exclusion Criteria: Hormonal therapy added as an excluded therapy (EC4); revised AZ standard wording for EC 7 in line with new guidance.

10. Section 3.8 Restrictions: Subsection 3.8.1 Grapefruit juice - wording has been strengthened from saying ‘not recommended’ to ‘prohibited’ as per revised AZ standard guidance and grapefruit added.

11. Section 3.9.1 Procedures for discontinuation of a patient from investigational product: Removal of repeated sentence, “A patient that decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible they will be seen and assessed by an Investigator(s). AEs will be followed up(see Section 6)”. The sentence “At any time, patients are free to discontinue IP or withdraw from the study (i.e. IP and assessments; see Section 3.10)” has been moved to the top of the section. Detail has been added to the penultimate sentence for clarification, with “up to the final analysis” being replaced

by "until 135 OS events (~54% maturity) have been recorded, estimated to be approximately 36 months after the first subject is enrolled."

12. Section 3.10 Criteria for Withdrawal: Amended definition of "lost to follow up" in line with AZ Standard protocol.

13. Section 4 Table 1: Altered to show that confirmation of non-g*BRCA* status is required before screening. Clarification of when the tumour sample is to be obtained, both in the table and in the text of footnote g, replacing "All patients are required to submit an archival tumour sample for retrospective testing of their genetic status" with "All patients are required to submit either an archival tumour sample, or a fresh biopsy if an archival sample is not available, for retrospective testing of their genetic status. If archival tissue, the presence of adequate tissue needs to be confirmed prior to screening, but it will not be shipped to the central lab before Day1. If fresh, the biopsy should be taken after the baseline scan has been performed.". Clarification of note e.

14. Section 4 Table 2: Add "blood" and delete "plasma" in describing samples to be taken for ctDNA and the retrospective g*BRCA* test. Add "all samples should be taken prior to first dose" to footnote d for clarity.

15. Section 4.1.1 Testing for g*BRCA* mutations for patients with unknown g*BRCA* status: replaced "early" with "before screening", "g*BRCA* mutation screening" with g*BRCA* mutation testing" and "lab" with "laboratory", for clarity.

16. Section 4.2.3 Visit 4 (Day 57) and subsequent on-treatment tumour assessment visits: Added "until progression" at the end of the first pargraph, for clarity.

17. Section 4.3.2 Long-term follow up beyond 30 days after last dose of study medication: First sentence amended for clarity with addition of text shown in italics "Long-term follow up will be conducted until First Subsequent Treatment *(or prior death)*, and for Overall Survival…"

18. Section 5: Deleted reference to Japan.

19. Section 5.2.1.2 Bone marrow or blood cytogenetic samples: The first sentence "Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 6.8.1" has been amended

to read. “In patients with prolonged haematological toxicities, bone marrow or blood cytogenetic samples may be indicated as defined in Section 6.8.1.3” for clarity.

20. Section 5.6 Genetics: Added “testing” and “(unless determined centrally at screening)” to the first sentence for clarity and consistency with Table 2. Deleted “compared with the broader population and historical controls”. Added additional sentence “The tumour samples will be analysed for deleterious or suspected deleterious mutations of TP53, and the effect of the presence of such mutations on PFS and OS explored” to reflect the new exploratory objective. Added text describing in detail which outcome measures will be explored (consistent with SAP).

21. Section 5.7 Biomarker Analysis: Blood sample size increased from 18mL to approximately 20mL to reflect change in standard collection tube size.

22. Section 6 Safety Reporting and Medical Management, subsection 6.1.1: Minor revisions in line with revised AZ standard guidance, and to clarify that the questionnaire information is not part of the study database.

23. Section 6.3 Recording of Adverse Events, subsections 6.3.1.1 and 6.3.10: Minor revisions in line with revised AZ standard guidance. Subsection 6.3.12 deletion of “post study” in the first sentence to avoid misunderstanding, as 30 day follow-up is part of study.

24. Section 6.8 Management of Investigational Product Related toxicities: Table 4 Management of Anaemia: Inserted revised section on ‘action to be taken’taken in line with new AZ standard guidance.

25. Section 7.7 Concomitant and Other Treatments: Text on potential drug-drug interactions revised and updated in line with new AZ standard guidance.

26. Section 8.2 Sample Size Estimate: Addition of “A supplementary analysis of OS will be performed when 135 OS events (~54% maturity) have been recorded, estimated to be approximately 36 months after the first subject is enrolled” to the end of first paragraph, to align with other protocol sections.

27. Section 8.3 Definition of Analysis Sets:Deletion of sentence relating to Japan.

28. Section 8.4.Outcome Measures for Analyses: 8.4.1. Amended definition of Time to Study Discontinuation or Death (TDT). Calculation or derivation of patient reported outcome variables (Health related quality of life): a new final sentence "In this study the 10-point minimum clinically important difference will be applied only to deterioration" has been added, consistent with analysis plan.

29. Section 8.5.1 Analysis of the primary variable (comparison to historical controls): Text shown in italics added to clarify status of this analysis "In a *post-hoc* exploratory analysis, outcomes from this trial may be compared to historical data from published studies in a comparable patient population treated with placebo. *Such an analysis does not form part of the formal study objectives".* Added "non-*BRCA* mutated" to bullet 3 of subgroup analyses to be consistent with study objectives. Added "Histological subtype (HGSOC vs High grade endometrioid ovarian cancer)" as a further important clinical characteristic for PFS summaries.

30. Section 8.5.2: First sentence amended by addition of "..median and.." to reflect more accurately the intended analysis.

31. Section 8.5.3 Interim Analysis: Text "..for internal planning purposes, and to provide ongoing data to external bodies" added to clarify the purpose of the interim analysis.

32. Section 9.2.2 Direct access to source data in Japan: deleted.

33. Section 9.3 Study Timetable and End of Study: Text modifications to align with new study end date and explain that data will be added to the database after the primary analysis

34. Appendix F: Pre study germline *BRCA* Testing: Clarification of instructions on g*BRCA* testing and alignment with Section 3.1

35. Appendix I: Summary of RECIST 1.1: updated to align better with study design and purpose.

# CLINICAL STUDY PROTOCOL SYNOPSIS

## OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

**International Coordinating Investigator**

PPD

PPD

INITIA ONCOLOGY

Hospital Quironsalud

Prof Severo Ochoa, 14

Planta baja

46010 Valencia, Spain

**Study sites and number of patients planned**

The study will enrol approximately 250 patients with platinum sensitive high-grade serous ovarian cancer (HGSOC) (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid ovarian cancer who are in complete or partial response following platinum based chemotherapy and who are germline *BRCA*1 and/or *BRCA*2 negative. The study will be conducted in approximately 19 countries worldwide, including Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, Israel, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

Additional countries may be added depending on recruitment rates.

| **Study period (includes follow-up for OS)** | | **Phase of development** |
|---|---|---|
| Estimated date of first patient enrolled | Q1 2018 | IIIb |
| Estimated date of last patient enrolled | Q1 2019 | |
| Estimated date of last patient completed[1] | Q1 2021 | |
| Estimated date of clinical study report[2] | Q1 2021 | |

[1]including follow-up for survival (estimated at 36 months after first patient enrolled)

[2]based on primary analysis (estimated at 30 months after first patient enrolled)

## Study design

This is a Phase IIIb, single-arm, open-label, multicentre study to assess the efficacy and safety of single-agent olaparib as a maintenance treatment in patients with relapsed HGSOC (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid ovarian cancer who do not have known deleterious or suspected deleterious germline *BRCA* mutations (non-g*BRCA*m) and who had responded following platinum based chemotherapy. Tumour assessments will be conducted every 8 weeks for the first 12 months, and thereafter every 12 weeks up to disease progression.

## Objectives

| Primary Objective: | Outcome Measure: |
|---|---|
| To determine the efficacy by progression-free survival (PFS) (investigator-recorded assessments according to modified Response Evaluation Criteria In Solid Tumors [RECIST v1.1]) of olaparib maintenance monotherapy in non-g*BRCA*m platinum sensitive relapsed (PSR) ovarian cancer | • PFS: Time from date of first dose until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) |

| Secondary Objectives: | Outcome Measures: |
|---|---|
| To determine the efficacy of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer by assessment of time to first subsequent therapy or death (TFST) | • TFST: Time from date of first dose to date of first subsequent treatment commencement or death due to any cause if this occurs before commencement of first subsequent treatment |
| To determine the efficacy of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer by assessment of time to treatment discontinuation or death (TDT) | • TDT: Time from date of first dose to date of study drug discontinuation or death due to any cause if this occurs before study drug discontinuation |
| To determine the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance in non-g*BRCA*m PSR ovarian cancer according to tumour homologous recombination deficiency (HRD) status using the Myriad myChoice plus HRD test | • PFS in the following subgroups: -<br>1. Somatic *BRCA* mutated and HRD scar positive;<br>2. HRD scar positive, non-*BRCA* mutated;<br>3. HRD scar negative, non-*BRCA* mutated |
| To determine the efficacy of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer by assessment of chemotherapy-free interval (CT-FI) | • CT-FI: Time from the date of the last dose of platinum chemotherapy prior to olaparib maintenance therapy until the date of initiation of the next anticancer therapy |
| To determine the overall survival (OS) of non-g*BRCA*m PSR ovarian cancer patients treated with olaparib maintenance monotherapy | • OS: Time from the date of first dose of olaparib to date of death from any cause |

| | |
|---|---|
| To investigate the Health-related Quality of Life (HRQoL) of non-g*BRCA*m PSR ovarian cancer patients treated with olaparib maintenance monotherapy as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) | • Proportion of patients with any improvement from baseline in TOI score at any point during the treatment period<br>• Proportion of patients with a 10 point deterioration from baseline in TOI score at any point during the treatment period |

| **Safety Objective:** | **Outcome Measures:** |
|---|---|
| To assess the safety and tolerability of olaparib maintenance monotherapy in patients with non-g*BRCA*m PSR ovarian cancer | • Adverse events/serious adverse events<br>Collection of clinical chemistry/haematology parameters |

| **Exploratory Objective** | **Outcome Measure** |
|---|---|
| To explore the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer patients stratified into a range of molecular sub-groups including mutations in Homologous recombination repair (HRR) genes, microsatellite instability (MSI) status, and tumour mutation load score. | • PFS by molecular measures of HRR and genomic instability |
| To explore the impact of TP53 disruption status on both OS and PFS | • OS and PFS by TP53 disruption status |
| To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L) | • EQ-5D index score and the EQ-VAS score including the change from baseline for both scores |
| To explore the feasibility of reliably identifying mutations in homologous recombination genes from circulating tumour DNA (ctDNA) and to enable future diagnostic development. | • Correlation between HRD status from tumour and ctDNA in matched patient samples |

**Screening and follow-up**

Patients must have an existing known and documented g*BRCA* test result. Patients with known deleterious or suspected deleterious g*BRCA* mutations will be excluded. All patients should additionally have a tumour sample available for the Myriad myChoice® HRD plus test, plus other molecular tests that measure homologous recombination repair competency and genomic instability. The g*BRCA* status of enrolled patients will be confirmed retrospectively using the Myriad BRCAnalysis CDx test.

Following screening assessments, all patients should have radiological (CT or MRI) tumour assessments at baseline (within 28 days of starting treatment), then every 8 weeks (±7 days) for the first 12 months, and then every 12 weeks (± 7 days) until documented evidence of objective radiological disease progression in accordance with modified RECIST 1.1, irrespective of treatment decisions (i.e. RECIST follow up until progression even if a patient discontinues study treatment prior to progression and/or receives subsequent therapy prior to progression). At baseline, eligible patients can have measurable disease (target lesions) or non-measurable disease (non-target lesions or no evidence of disease).

Once a patient has progressed, the patient will be treated as per local clinical practice and will be followed to first subsequent treatment, and then approximately every 12 weeks for survival.

**Target patient population**

- Patients with platinum sensitive relapsed (PSR) high grade serous ovarian cancer (this includes any patients with primary peritoneal and / or fallopian tube cancer) or high grade endometrioid ovarian cancer without a g*BRCA* mutation. Patients will be in complete or partial response following completion (a minimum of 4 treatment cycles) of platinum-based chemotherapy

- Patients must have completed at least 2 previous lines of platinum-based therapy (e.g. containing carboplatin, cisplatin or oxaliplatin) before entry to the study and must be considered to have been platinum sensitive after the penultimate platinum-based chemotherapy - defined as disease progression greater than 6 months after completion (last dose) of the penultimate platinum chemotherapy

- Patients must not have received bevacizumab during the chemotherapy course immediately prior to screening. Cytoreductive surgery is allowed before this course of chemotherapy.

**Duration of treatment**

Patients should continue to receive study treatment until objective disease progression as assessed by the investigator, or unacceptable toxicity or for as long as they do not meet any other discontinuation criteria. Patients should continue with therapy to RECIST progression despite rises in CA-125. Patients may continue to receive treatment beyond progression as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 3.9. Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator.

**Investigational product, dosage and mode of administration**

Olaparib will be supplied to the investigator as film-coated tablets containing 150 mg or 100 mg of olaparib.

Patients will be administered olaparib orally twice daily (bd) at 300 mg. The planned dose of 300 mg twice daily will be made up of two 150 mg tablets twice daily, with 100 mg tablets used to manage dose reductions which may be required in patients experiencing toxicities related to olaparib treatment, or because of concomitant medication. Guidance on dose reductions are outlined in Sections 6.8 and 7.7

Olaparib tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with a glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without a meal.

**Statistical methods**

The primary endpoint is investigator assessed PFS using modified RECIST criteria version 1.1. A sample size of approximately 250 patients is proposed for this study in order to provide an adequate level of precision around the primary endpoint in the whole population. The primary analysis is planned to be undertaken after approximately 30 months with an interim analysis after approximately 18 months. Assessments for survival will continue to be performed every 12 weeks following the primary analysis for PFS, until 135 OS events (~54% maturity) have been recorded, estimated to be approximately 36 months after the first subject is enrolled.
In two randomized placebo controlled studies (Study 19, Nova) where non-g*BRCA*m patients were treated with a Poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi), the median PFS for patients treated with a PARPi ranged from 8 to 9 months compared to 4 – 5.5 months for those treated with placebo. Clinical trial simulations were performed assuming 250 patients enrolled over a 12 month period with 50% of patients enrolled after 8 months, a median PFS of 8.5 months and a piecewise exponential model for PFS. Across 500 simulations it is estimated that the mean number of PFS events is approximately 135 at 18 months (54% maturity) and 180 at 30 months (72% maturity), with corresponding mean 95% confidence interval (CI) widths of 3.87 and 3.27 months respectively.
All efficacy analyses will be based on the full analysis set (all enrolled patients assigned to olaparib) with safety data summarised from the safety-analyses set (all enrolled patients who have received at least one dose of olaparib). Kaplan-Meier (KM) plots of PFS will be presented for all non-g*BRCA*m patients and for subgroups determined by the tumour HRD status. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (progression or death) will be provided along with median PFS and 95% CIs. Other time-to-events endpoints will be summarised in a similar manner. Data from patients treated with olaparib in the current study may be compared with historical data from published studies in a comparable patient population treated with placebo having adjusted for the prevalence of known prognostic factors.

# TABLE OF CONTENTS PAGE

TITLE PAGE ..... 1
VERSION HISTORY ..... 2
CLINICAL STUDY PROTOCOL SYNOPSIS ..... 8
TABLE OF CONTENTS ..... 14
1. INTRODUCTION ..... 23
1.1 Background and Rationale for Conducting This Study ..... 23
1.2 Rationale for Study Design, Doses and Control Groups ..... 23
1.3 Benefit/Risk and Ethical Assessment ..... 26
1.4 Study Design ..... 26
1.5 Study Governance and Oversight ..... 27
2. STUDY OBJECTIVES ..... 29
2.1 Primary Objective ..... 29
2.2 Secondary Objectives ..... 29
2.3 Safety Objectives ..... 30
2.4 Exploratory Objectives ..... 30
3. PATIENT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL ..... 31
3.1 Inclusion Criteria ..... 31
3.2 Exclusion Criteria ..... 34
3.3 Patient Screening and Registration ..... 36
3.4 Procedures for Handling Incorrectly Enrolled Patients ..... 37
3.5 Methods for Assigning Treatment Groups ..... 37
3.6 Methods for Ensuring Blinding ..... 37
3.7 Methods for Unblinding ..... 37
3.8 Restrictions ..... 37
3.8.1 Grapefruit juice ..... 37
3.8.2 Contraception ..... 37
3.9 Discontinuation of Investigational Product ..... 37
3.9.1 Procedures for discontinuation of a patient from investigational product ..... 38

3.10 Criteria for Withdrawal ..... 39
3.10.1 Screen failures ..... 39
3.10.2 Withdrawal of the informed consent ..... 39
3.11 Discontinuation of the Study ..... 40
4. STUDY PLAN AND TIMING OF PROCEDURES ..... 40
4.1 Screening/Enrolment Period ..... 45
4.1.1 Testing for g*BRCA* mutations for patients with unknown g*BRCA* status ..... 45
4.2 Treatment Period ..... 45
4.2.1 Visit 2 (Baseline Visit, Day 1) ..... 45
4.2.2 Visit 3 (Day 29) ..... 45
4.2.3 Visit 4 (Day 57) and subsequent on-treatment tumour assessment visits ..... 45
4.2.4 Visits 5 and Subsequent safety test visits ..... 45
4.2.5 Study treatment discontinued ..... 46
4.3 Follow-up Period ..... 46
4.3.1 Follow up 30 days after last dose of study medication ..... 46
4.3.2 Long-term follow up beyond 30 days after last dose of study medication ..... 46
5. STUDY ASSESSMENTS ..... 46
5.1 Efficacy Assessments ..... 46
5.1.1 Tumour evaluation ..... 46
5.2 Safety Assessments ..... 47
5.2.1 Laboratory safety assessments ..... 47
5.2.1.1 Coagulation ..... 47
5.2.1.2 Bone marrow or blood cytogenetic samples ..... 48
5.2.2 Physical examination and ECOG ..... 48
5.2.2.1 Vital signs and weight ..... 48
5.2.2.2 Pulse and blood pressure ..... 48
5.2.2.3 Body temperature ..... 48
5.2.3 Other safety assessments ..... 49
5.2.3.1 Serum or urine pregnancy test ..... 49
5.3 Other Assessments ..... 49
5.3.1 Patient Reported Outcomes (PRO: FACT-O) ..... 49
5.3.2 EQ-5D-5L ..... 49
5.4 Pharmacokinetics ..... 49
5.5 Pharmacodynamics ..... 49
5.6 Genetics ..... 50
5.7 Biomarker Analysis ..... 50
6. SAFETY REPORTING AND MEDICAL MANAGEMENT ..... 50
6.1 Definition of Adverse Events ..... 50
6.1.1 Olaparib adverse events of special interest ..... 51

6.2 Definitions of Serious Adverse Event ..... 51
6.3 Recording of Adverse Events ..... 51
6.3.1 Time period for collection of adverse events ..... 51
6.3.1.1 Adverse events after the 30-day follow-up period ..... 52
6.3.2 Follow up of unresolved adverse events ..... 52
6.3.3 Variables ..... 52
6.3.4 Causality collection ..... 54
6.3.5 Adverse events based on signs and symptoms ..... 54
6.3.6 Adverse events based on examinations and tests ..... 54
6.3.7 Hy's Law ..... 55
6.3.8 Disease progression ..... 55
6.3.9 Disease under study ..... 55
6.3.10 New cancers ..... 55
6.3.11 Lack of efficacy ..... 55
6.3.12 Deaths ..... 55
6.4 Reporting of Serious Adverse Events ..... 56
6.5 Overdose ..... 56
6.6 Pregnancy ..... 57
6.6.1 Maternal exposure ..... 57
6.7 Medication Error ..... 57
6.8 Management of Investigational Product Related Toxicities ..... 58
6.8.1 Management of haematological toxicity ..... 59
6.8.1.1 Management of anaemia ..... 59
6.8.1.2 Management of neutropenia, leukopenia and thrombocytopenia ..... 60
6.8.1.3 Management of prolonged haematological toxicities while on study treatment ..... 60
6.8.2 Management of non-haematological toxicity ..... 61
6.8.2.1 Management of new or worsening pulmonary symptoms ..... 61
6.8.2.2 Management of nausea and vomiting ..... 61
6.8.2.3 Interruptions for intercurrent non-toxicity related events ..... 61
7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS ..... 62
7.1 Identity of Investigational Product ..... 62
7.2 Dose and Treatment Regimens ..... 62
7.3 Labelling ..... 63
7.4 Storage ..... 64
7.5 Compliance ..... 64
7.6 Accountability ..... 64
7.7 Concomitant and Other Treatments ..... 65
7.7.1 Other concomitant treatment ..... 67

7.8 Post Study Access to Study Treatment – Not Applicable ..... 67
8. STATISTICAL ANALYSES BY ASTRAZENECA ..... 67
8.1 Statistical Considerations ..... 67
8.2 Sample Size Estimate ..... 67
8.3 Definitions of Analysis Sets ..... 67
8.4 Outcome Measures for Analyses ..... 68
8.4.1 Calculation or derivation of efficacy variables ..... 68
8.4.2 Calculation or derivation of safety variables ..... 69
8.4.3 Calculation or derivation of patient reported outcome variables ..... 70
8.5 Methods for Statistical Analyses ..... 71
8.5.1 Analysis of the primary variable ..... 71
8.5.2 Analysis of the secondary/exploratory variables ..... 72
9. STUDY AND DATA MANAGEMENT ..... 73
9.1 Training of Study Site Staff ..... 73
9.2 Monitoring of the Study ..... 73
9.2.1 Source data ..... 73
9.2.2 Study agreements ..... 73
9.2.3 Archiving of study documents ..... 74
9.2.4 Deviation from the clinical study protocol ..... 74
9.3 Study Timetable and End of Study ..... 75
9.4 Data Management by Designated Clinical Research Organisation ..... 76
10. ETHICAL AND REGULATORY REQUIREMENTS ..... 76
10.1 Ethical Conduct of the Study ..... 76
10.2 Patient Data Protection ..... 76
10.3 Ethics and Regulatory Review ..... 77
10.4 Informed Consent ..... 78
10.5 Changes to the Clinical Study Protocol and Informed Consent Form ..... 78
10.6 Audits and Inspections ..... 79
11. LIST OF REFERENCES ..... 80

## LIST OF TABLES

Table 1 Study Schedule – Screening (Visit 1) ..... 40
Table 2 Study Plan Detailing the Procedures ..... 42

Table 3 Laboratory Safety Variables ..... 47
Table 4 Management of Anaemia ..... 59
Table 5 Management of Neutropenia, Leukopenia and Thrombocytopenia ..... 60
Table 6 Dose Reductions for Study Treatment ..... 62

## LIST OF FIGURES

Figure 1 Protocol Schedule ..... 28

## LIST OF APPENDICES

Appendix A Additional Safety Information ..... 81
Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document ..... 83
Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law ..... 84
Appendix D Acceptable Birth Control Methods ..... 89
Appendix E ECOG Performance Status ..... 91
Appendix F Pre study germline *BRCA* Testing ..... 92
CCI [redacted]
Appendix I Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours) ..... 99
Appendix J Signatures ..... 108

# 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 |
|---|---|
| ADP | Adenosine diphosphate |
| AE | Adverse event |
| AESI | Adverse events 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 |
| *BRCA*1, *BRCA*2 | Breast cancer susceptibility genes |
| BUN | Blood urea nitrogen |
| CA | Cancer antigen |
| CI | Confidence interval |
| CrCl | Creatinine clearance |
| CR | Complete response |
| CRF | Case report form (electronic/paper) |
| CRO | Clinical research organisation |
| CSP | Clinical study protocol |
| CT | Computed tomography |
| CT-FI | Chemotherapy free interval |
| CTC(AE) | Common terminology criteria (for adverse event) |
| CYP | Cytochrome P450 |
| DCIS | Ductal carcinoma in situ |
| DCO | Data cut off |
| DILI | Drug-induced liver injury |
| DNA | Deoxyribonucleic acid |
| DSB | Double strand break |
| dUCBT | Double umbilical cord blood transplantation |
| E-code | Enrolment code |
| eCRF | Electronic Case Report Form |

| Abbreviation or special term | Explanation |
|---|---|
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group; a performance status using scales and criteria to assess how a subject's disease is progressing |
| EQ-5D-5L | EuroQoL five dimensions, five level |
| ESMO | European Society for Medical Oncology |
| EWB | Emotional well-being |
| FACT-O | Functional Assessment of Cancer Therapy – Ovarian |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FOSI | FACT/NCCN Ovarian Symptom Index |
| FSH | Follicle-stimulating hormone |
| FWB | Functional well-being |
| g*BRCA*m | Germline *BRCA1*/2 mutation |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte colony-stimulating factor |
| GMP | Good Manufacturing Practice |
| Hb | Haemoglobin |
| HGSOC | High-grade serous ovarian cancer |
| HIV | Human immunodeficiency virus |
| HL | Hy's Law |
| HR | Homologous recombination |
| 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 |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| 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. |
| INR | International normalised ratio |
| IMP | Investigational medicinal product |

| Abbreviation or special term | Explanation |
|---|---|
| IP | Investigational product |
| IRB | Institutional Review Board synonymous to ethics committee |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| KM | Kaplan-Meier |
| LH | Luteinizing hormone |
| MATE | Multidrug and toxin extrusion (MATE1, MATE2K) |
| MCV | Mean cell volume |
| MDS | Myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| MSI | Micro satellite instability |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| OAE | Other significant adverse event |
| OAT | Organic anion transporter (OAT1, OAT2, OAT3) |
| OATP1B1 | Organic anion transporting polypeptide 1B1 |
| OCT | Organic cation transporter (OCT1, OCT2) |
| OS | Overall survival |
| PARP | Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase |
| PARPi | Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase inhibitor |
| PD | Progressive disease |
| PFS | Progression-free survival |
| P-gp | P-glycoprotein |
| PHL | Potential Hy's Law |
| PR | Partial response |
| PRO | Patient reported outcomes |
| PSR | Platinum sensitive relapsed |
| PWB | Physical well-being |
| QoL | Quality of life |
| QT(c) | (Corrected) QT interval |
| RCT | Randomized controlled trial |
| RECIST | Response Evaluation Criteria in Solid Tumours |

| Abbreviation or special term | Explanation |
|---|---|
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| s*BRCA*m | Somatic *BRCA* mutation |
| SD | Stable disease |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvate transaminase |
| SSB | Single strand breaks |
| SWB | Social well-being |
| TBL | Total bilirubin |
| TFST | Time from first dose to first subsequent treatment or death |
| TSST | Time to second subsequent therapy |
| TDT | Time to study treatment discontinuation or death |
| TOI | Trial outcome index |
| UCBT | Umbilical cord blood transplantation |
| ULN | Upper limit of normal |
| VAS | Visual analogue scale |
| VUS | Variants of uncertain clinical significance or Variant of unknown significance |
| WBDC | Web based data capture |
| WHO | World Health Organization |
| wt | Wild-type |

# 1. INTRODUCTION

## 1.1 Background and Rationale for Conducting This Study

### Research Hypothesis

Maintenance monotherapy with the potent polyadenosine 5'diphosphoribose [Poly (ADP-ribose)] polymerisation (PARP) inhibitor (PARPi) olaparib will significantly prolong progression-free survival (PFS) in platinum sensitive relapsed non-germline breast cancer susceptibility gene (*BRCA)* mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy

### Olaparib Mechanism of Action

Investigators should be familiar with the current olaparib (AZD2281, KU-0059436) Investigator brochure (IB).
Olaparib is a potent PARPi (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anticancer agents.
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 PARP enzymes 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 (HR) repair. Tumours with HR 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 (Rottenberg et al 2008). The mechanism of action for olaparib results from the trapping of inactive PARP onto the SSBs preventing their repair (Helleday 2011; Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic *BRCA* knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.
AstraZeneca considers that the relapsed ovarian cancer 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

In patients with platinum sensitive relapsed (PSR) disease, platinum based chemotherapy is recommended for 6 cycles with no clear benefit of extending the chemotherapy cycles beyond 6 and risk of accumulating unacceptable toxicity (NCCN Clinical Practice Guidelines in Oncology 2016). There is therefore a window of opportunity to introduce a maintenance

treatment with a drug suitable for long term use that can prolong the benefit achieved with the chemotherapy and continue to provide active anti-tumour control after chemotherapy has been completed to significantly and meaningfully delay the next recurrence for patients, extending PFS and delaying the time until further chemotherapy treatment is required.

Platinum sensitivity and response to platinum-containing therapy are clinical selection factors that can be used to identify patients that are likely to benefit from olaparib treatment. Olaparib is a highly specific PARPi that is generally well tolerated, and as maintenance therapy can fulfil a high unmet medical need and provide patients with PSR ovarian cancer an opportunity for prolonged disease control, meaningfully extended PFS and a longer chemotherapy-free interval.

Clinical evidence to support olaparib as a maintenance treatment was first shown in a Phase II randomized, double-blind, placebo-controlled, multicentre study (D0810C00019 [Study 19]) in patients with PSR ovarian cancer. A second study, a Phase III randomized, double-blind, placebo-controlled, multicentre study, D0816C00002 (SOLO2), investigated olaparib 300 mg bd (2 x 150 mg bd) tablet formulation as a maintenance treatment in g*BRCA*m PSR ovarian cancer patients. In both SOLO2 and Study 19, patients with platinum-sensitive relapsed disease who were in response (complete or partial) to their final platinum regimen and who had received at least two previous lines of platinum-based therapy were randomized to receive either olaparib or placebo. The primary endpoint in both SOLO2 and Study 19 was PFS.

The SOLO2 data confirm that maintenance treatment with olaparib 300 mg bd (tablet formulation) offers a substantial efficacy improvement by prolonging PFS by 13.6 months compared to placebo and delaying the requirement for further anticancer treatment in patients with g*BRCAm* PSR ovarian cancer who are in response to platinum-based chemotherapy. Safety data from SOLO2 confirm that olaparib tablets are suitable for long-term use in a maintenance setting. The clinical benefit observed in SOLO2, along with the acceptable safety and tolerability profile and the convenience of an oral administration are critical factors in the consideration of an optimal maintenance regimen. Data from Study 19 provide evidence for the clinical activity of olaparib in the broader PSR ovarian cancer patients irrespective of their g*BRCA* status in the maintenance treatment setting, together with an acceptable safety and tolerability profile.

The totality of the data from SOLO2 and Study 19 demonstrates that olaparib maintenance therapy has a positive benefit-risk profile in the treatment of PSR ovarian cancer.

Clinical experience with olaparib is fully described in the current version of the olaparib IB.

**Rationale for non-g*BRCA*m patient selection**

While multiple randomized controlled trials (RCTs) have demonstrated that platinum-sensitive *BRCA*m patients have profound response to maintenance treatment with PARP inhibitors, PARP inhibitors target cells with homologous recombination deficiency (HRD), of which *BRCA* mutation is only one type. Consistent with the mechanism of action of PARP inhibition, response has also been seen in multiple RCTs in patients who are platinum-sensitive but whose tumours do not harbor *BRCA* mutations (Study 19 and NOVA). Presumably these responders have defects in other components of HRR pathways, though currently available diagnostic technology is not adequate to reliably identify the full spectrum of HRR deficiencies. Instead, these data support the hypothesis that platinum sensitivity itself is a clinical selection factor for HRD.

**Experience with Olaparib in Gynaecological Cancer**

The results from two clinical studies (Study 19 and NOVA) have demonstrated the potential benefit of two different PARPi (olaparib and niraparib) as maintenance therapy in platinum-sensitive ovarian cancer patients who do not have *BRCA* mutations.

**Study D0810C00019 (NCT no. NCT00753545; EudraCT no. 2008-003439-18)**

This was a Phase II study (D0810C00019/Study 19) in PSR ovarian cancer patients.
The study compared the efficacy of olaparib maintenance treatment of a capsule formulation [400 mg (8 x 50 mg capsules) twice daily] taken to progression with no maintenance treatment in 265 (136 olaparib and 129 placebo) PSR patients who were in response (complete or partial) following completion of platinum containing chemotherapy. The primary endpoint was PFS based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included overall survival (OS), disease control rate (DCR), Health Related Quality of Life (HRQoL), and disease related symptoms. Exploratory analyses of Time to first subsequent therapy or death (TFST) and Time to second subsequent therapy or death (TSST) were also performed.
The study met its primary objective of demonstrating a statistically significant and clinically relevant improvement in PFS for olaparib compared with placebo: Hazard Ratio (HR) 0.35; 95% confidence interval (CI) 0.25-0.49; p<0.00001; median 8.4 months olaparib vs 4.8 months placebo. Final OS (data cut off [DCO] 09 May 2016; 79% maturity) with a median duration of follow-up for OS of 6.5 years, showed favourable prolongation of OS for olaparib treated patients compared to placebo-treated patients. The reduced risk of death in the olaparib treated patients is reflected by a clinically meaningful although not statistically significant HR of 0.73 (95% CI 0.55 to 0.95, nominal p=0.02138) with a 2.0 month longer median OS for olaparib treated patients compared to placebo treated patients (29.8 months vs 27.8 months, respectively). Similar OS HRs favouring olaparib were observed irrespective of patients' g*BRCA* mutation status.

Preplanned subgroup analysis identified patients with *BRCA*m ovarian cancer (n=136, 51.3%) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. In *BRCA*m patients the median PFS improvement was 6.9 months over placebo (HR 0.18; 95% CI 0. 10-0.31; p<0.00001; median 11.2 months olaparib vs 4.3 months placebo). However, clinical benefit was also observed in the *BRCA* wild type (wt) patient population (7·4 months [95% CI 5·5-10·3] median PFS in the olaparib group vs 5·5 months [95% CI 3·7-5·6] in the placebo group; HR 0·54 [95% CI 0·34-0·85]; p=0·0075).
Long term benefit has been observed in PSR ovarian cancer patients, with olaparib maintenance therapy providing unprecedented periods of remission in some patients:

- In the overall population, substantially more patients received olaparib vs placebo for ≥2 years (24% vs 4%, respectively) and ≥6 years (11% vs 1%, respectively). With the caveat of small numbers of patients, at least a third of the patients deriving long term (≥6 years) benefit from olaparib did not carry a g*BRCA* mutation.
- In the overall population at the 09 May 2016 DCO analysis, 14 patients (including 5 patients without a g*BRCA* mutation) were still receiving olaparib therapy compared to

only one placebo treated patient. The duration of olaparib therapy in these patients ranged between 6.3 and 7.1 years.

**No statistically significant or clinically relevant differences in HRQoL were olaparib and placebo, as measured by the FACT/NCCN Ovarian Symptom total Functional Assessment of Cancer Therapy–Ovarian FACT-O scores**

**Study PR-30-5011-C/ NOVA (NCT no. NCT01847274; EudraCT no. 2013-000685-11)**

Study PR-30-5011-C was a randomized, double-blind, phase 3 trial to evaluate the efficacy of niraparib versus placebo as maintenance treatment for patients with platinum-sensitive, recurrent ovarian cancer (niraparib 300 mg or placebo once daily). Of 553 enrolled patients, 203 were in the g*BRCA* cohort (niraparib [n=138] , placebo[n=65]) and 350 patients were in the non-g*BRCA* cohort (niraparib [n=234] , placebo [n=116]). All the patients had shown sensitivity to platinum-based treatment and had received at least two such regimens. For the penultimate platinum-based chemotherapy before study enrolment, a patient must have had platinum-sensitive disease after this treatment which was defined as having a complete or partial response and disease progression more than 6 months after completion of the last round of platinum therapy. Patients in the niraparib group had a significantly longer median duration of PFS (primary endpoint) than did those in the placebo group, including 21.0 vs. 5.5 months in the g*BRCA* cohort as compared with 12.9 months vs. 3.8 months in the non-g*BRCA* cohort for patients who had tumours with homologous recombination deficiency and 9.3 months vs. 3.9 months in the overall non-g*BRCA* cohort. Among patients with platinum-sensitive, recurrent ovarian cancer, the median duration of PFS was significantly longer among those receiving niraparib than among those receiving placebo, regardless of the presence or absence of g*BRCA* mutations or HRD status, with moderate bone marrow toxicity. Grade 3 or 4 treatment-emergent events in the niraparib group (74.1%) were managed with dose modifications. (Mirza et al 2016).

## 1.3 Benefit/Risk and Ethical Assessment

Olaparib has been well tolerated across various cancer entities. The proposed study will be limited to patients with advanced ovarian cancer who are relapsed, non-g*BRCA* mutated, for whom clinical activity can be expected based on the results of the studies discussed in section 1.2. Therefore, a positive benefit/risk profile is expected and no ethical issues are identified from exposing patient to olaparib within the planned clinical study.
Please see the current edition of the IB for the most recent summary of the risks of olaparib.

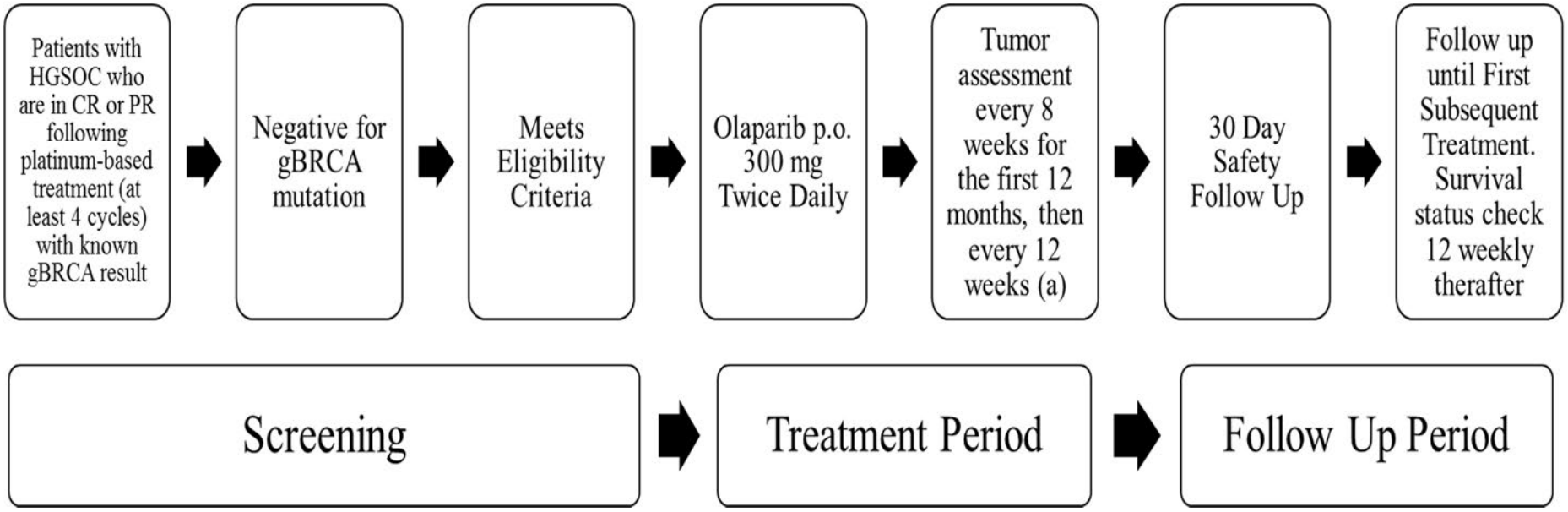
## 1.4 Study Design

A Phase IIIb, single-arm, open-label multicentre study. to assess the efficacy and safety of single-agent olaparib as a maintenance treatment in patients with relapsed HGSOC (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid ovarian cancer who do not have known deleterious or suspected deleterious germline *BRCA* mutations (non-g*BRCA*m) and who had responded following platinum based chemotherapy.
Olaparib will be administered to all patients in this single-arm study (see Figure 1).
Tumour assessments will be conducted every 8 weeks for the first 12 months, and thereafter every 12 weeks up to disease progression.

## 1.5 Study Governance and Oversight

Not applicable

**Figure 1 Protocol Schedule**




(a) Patients will continue to receive treatment until objective radiological disease progression (according to RECIST 1.1), or for as long as they are receiving clinical benefit in the opinion of the investigator, unless any of the criteria for discontinuation are met first
If patients discontinue olaparib treatment in the absence of progression, they should continue to be followed for progression every 8 weeks for 12 months after first dose ,and every 12 weeks therafter.

HGSOC, High Grade Serous Ovarian Cancer; PR, Partial Response; CR Complete Response

# 2. STUDY OBJECTIVES

## 2.1 Primary Objective

| Primary Objective: | Outcome Measure: |
|---|---|
| To determine the efficacy by progression-free survival (PFS) (investigator-recorded assessments according to modified Response Evaluation Criteria In Solid Tumors [RECIST v1.1]) of olaparib maintenance monotherapy in non-g*BRCA*m platinum sensitive relapsed (PSR) ovarian cancer | • PFS: Time from date of first dose until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) |

## 2.2 Secondary Objectives

| Secondary Objectives: | Outcome Measures: |
|---|---|
| To determine the efficacy of olaparib maintenance monotherapy in non g*BRCA*m PSR ovarian cancer by assessment of time to first subsequent therapy or death (TFST) | • TFST: Time from date of first dose to date of first subsequent treatment commencement or death due to any cause if this occurs before commencement of first subsequent treatment |
| To determine the efficacy of olaparib maintenance monotherapy in non g*BRCA*m PSR ovarian cancer by assessment of time to treatment discontinuation or death (TDT) | • TDT: Time from date of first dose to date of study drug discontinuation or death due to any cause if this occurs before study drug discontinuation |
| To determine the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance in non-g*BRCA*m PSR ovarian cancer according to tumour homologous recombination deficiency (HRD) status using the Myriad myChoice HRD plus test | • PFS in the following subgroups: -<br>1. Somatic *BRCA* mutated and HRD scar positive;<br>2. HRD scar positive, non-*BRCA* mutated;<br>3. HRD scar negative, non-*BRCA* mutated |
| To determine the efficacy of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer by assessment of chemotherapy-free interval (CT-FI) | • CT-FI: Time from the date of the last dose of platinum chemotherapy prior to olaparib maintenance therapy until the date of initiation of the next anticancer therapy |

| | |
|---|---|
| To determine the overall survival (OS) of non-g*BRCA*m PSR ovarian cancer patients treated with olaparib maintenance monotherapy | • OS: Time from the date of first dose of olaparib to the date of death from any cause. |
| To investigate the Health-related Quality of Life (HRQoL) of non-g*BRCA*m PSR ovarian cancer patients treated with olaparib maintenance monotherapy as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) | • Proportion of patients with any improvement from baseline in TOI score at any point during the treatment period<br>• Proportion of patients with a 10 point deterioration from baseline in TOI score at any point during the treatment period |

## 2.3 Safety Objectives

| **Safety Objective:** | **Outcome Measures:** |
|---|---|
| To assess the safety and tolerability of olaparib maintenance monotherapy in patients with non-g*BRCA*m PSR ovarian cancer | • Adverse events/serious adverse events<br>Collection of clinical chemistry/haematology parameters |

## 2.4 Exploratory Objectives

| **Exploratory Objective** | **Outcome Measure** |
|---|---|
| To explore the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance monotherapy in non-g*BRCA*m PSR ovarian cancer patients stratified into a range of molecular sub-groups including mutations in Homologous recombination repair (HRR) genes, microsatellite instability (MSI) status, and tumour mutation load score. | • PFS by molecular measures of HRR and genomic instability: |
| To explore the impact of TP53 disruption status on both OS and PFS | • OS and PFS by TP53 disruption status |
| To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L) | • EQ-5D index score and the EQ-VAS score including the change from baseline for both scores |

| Exploratory Objective | Outcome Measure |
|---|---|
| To explore the feasibility of reliably identifying mutations in homologous recombination genes from circulating tumour DNA (ctDNA) and to enable future diagnostic development. | • Correlation between HRD status from tumour and ctDNA in matched patient samples |

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

## 3.1 Inclusion Criteria

Patients without deleterious or suspected deleterious g*BRCA* mutations will be included. The g*BRCA* status of enrolled patients will be confirmed retrospectively using a central laboratory g*BRCA* test (Myriad BRCAnalysis CDx).
Testing of g*BRCA* status should normally have been performed as part of national or institutional practice guidelines for the management of ovarian cancer, such as in the assessment of treatment options after chemotherapy. Under exceptional circumstances, *gBRCA* testing of potentially eligible patients whose *gBRCA* status is not yet known can be considered (by agreement with the Sponsor). In these cases the *gBRCA* test must be completed prior to other screening procedures. To ensure this, patients may be consented from the end of cycle 3 of their current chemotherapy if, in the opinion of the investigator, they are responding to treatment, and if it appears that the patient is likely to meet other eligibility requirements. The 28-day screening period will be considered to have started only after the availability of the g*BRCA* status report at the site, at the start of the screening procedures listed in Table 1, column 2. Please refer to Appendix F for further details about the procedure and to the Laboratory Manual for further details of the test. Study sites should also offer access to a genetic counsellor (given that this is a genetic test which may have familial implications in the case of a positive result).

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 HGSOC (including primary peritoneal and / or fallopian tube cancer) or high grade endometrioid ovarian cancer

4. Documented g*BRCA1/2* mutation status

   Evidence that the patients do not have a g*BRCA* mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental / lead to loss

of function). g*BRCA1* and/or g*BRCA2* variants that are classified as "Variants of uncertain clinical significance" or "Variant of unknown significance (VUS)" are eligible, as well as "Variant, favor polymorphism" or "benign polymorphism".

Evidence of the absence of a somatic *BRCA* mutation is not required. Patients with a tumour *BRCA* test result only must undergo a g*BRCA* test to determine whether the *BRCA* aberration is germline or somatic in origin. If this analysis identifies the aberration as germline the patient is not eligible

5. Patients must have completed at least 2 previous courses of platinum containing therapy:

(a) For the penultimate chemotherapy course prior to enrolment on the study:

- Treatment must have contained a platinum agent (e.g. carboplatin, cisplatin or oxaliplatin per standard clinical practice; there are no other specific requirements)
- Patient was platinum sensitive after this treatment; defined as disease progression greater than 6 months after completion of their last dose of platinum chemotherapy
- Maintenance treatment is allowed at the end of the penultimate platinum regimen, including bevacizumab

(b) For the last chemotherapy course immediately prior to enrolment on the study

- 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
- Patient must have received a platinum based chemotherapy regimen (e.g. carboplatin, cisplatin or oxaliplatin) and have received at least 4 cycles of treatment
- Patients must not have received bevacizumab during this course of treatment
- Patients must not have received any investigational agent during this course of treatment
- Patients must initiate treatment within 8 weeks of their last dose of chemotherapy (last dose is the day of the last infusion)

6. 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 enrolled 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

7. Patients must have normal organ and bone marrow function measured within 28 days of starting study treatment, 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

   – Total bilirubin (TBL) ≤1.5 X 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, estimated using the Cockcroft-Gault equation (below), or based on a 24 hour urine test, of ≥51 mL/min:

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

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

9. Patients must have a life expectancy ≥16 weeks

10. 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 any of the following:

    – Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments

- For women under 50 years old, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range
- Radiation-induced oophorectomy with interval of 1 year or more since last menses
- Chemotherapy-induced menopause with >1 year interval since last menses
- Surgical sterilisation (bilateral oophorectomy or hysterectomy).

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

12. 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 evidence of disease following a complete response to chemotherapy (with or without cytoreductive surgery)

13. An appropriately prepared tumour sample from the cancer, of sufficient quantity and quality (as specified in the 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 usually preferred. Any exceptions to these conditions should be discussed with the Sponsor before enrollment of the patient.

## 3.2 Exclusion Criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled. Those asterisked* should be excluded before a request can be considered to perform a g*BRCA* test prior to full screening. Investigator judgement of patient's potential eligibility to the study should be assessed as per Table 1 and by reviewing the below exclusion criteria.

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 enrolment in the present study*

3. Participation in another clinical study with an investigational product (IP) during the most recent chemotherapy course*

4. Patients receiving any systemic hormonal therapy, chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to start of study treatment

5. Any previous treatment with PARP inhibitor, including olaparib*

6. Patients with a germline *BRCA* mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental / lead to loss of function).

7. Other malignancy unless curatively treated with no evidence of disease for ≥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.

8. Concomitant use of known strong 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 olaparib is 2 weeks*.

9. Concomitant use of known strong (e.g., phenobarbital, 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 olaparib is 5 weeks for phenobarbital and 3 weeks for other agents*

10. Persistent toxicities (≥ Grade 2 Common Terminology Criteria for Adverse Event (CTCAE) adverse event) caused by previous cancer therapy, excluding alopecia

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

12. Patients with symptomatic uncontrolled brain metastases. 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 (SD) for 28 days*

13. Major surgery within 3 weeks of starting study treatment and patients must have recovered from any effects of any major surgery

14. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection.

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

16. Currently pregnant (confirmed with a positive pregnancy test) or breastfeeding women*

17. Immuno-compromised patients e.g., Human Immunodeficiency Virus (HIV) requiring treatment or active Hepatitis B or C*

18. Patients with a known hypersensitivity to olaparib or any of the excipients of the product*

19. Patients with known active hepatitis (i.e., hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids*

20. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)*

21. Patients having g*BRCA* testing should not have had whole blood transfusions in the last 30 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable)

22. Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely or unable to comply with study procedures, restrictions and requirements.

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

## 3.3 Patient Screening and Registration

Investigators should keep a record, the Patient Screening Log, of patients who entered screening.The Investigators will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed that are not part of routine medical care

2. Obtain a unique patient reference number through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). This number is the patient's unique identifier and will be maintained throughout the study

3. Determine Patient eligibility (see Section 3.1 and 3.2)

If a patient does not meet eligibility criteria or withdraws from participation in the study, then their number cannot be reused. Re-screening for patients who fail screening and were NOT exposed to olaparib may be allowed, but a new number must be used. Patients who fail screening for minor abnormalities of haematology or biochemistry may be retested within the screening period and, if the value has returned to the range allowed by the protocol, they may be included.

## 3.4 Procedures for Handling Incorrectly Enrolled Patients

Patients are considered enrolled once (i) it is confirmed that they meet all eligibility criteria (including g*BRCA* status) and (ii) the request has been made by the Investigator for the provision of study treatment for that patient.

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 initiated on treatment, and must be withdrawn from the study.

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

## 3.5 Methods for Assigning Treatment Groups

Not applicable

## 3.6 Methods for Ensuring Blinding

Not applicable

## 3.7 Methods for Unblinding

Not applicable

## 3.8 Restrictions

### 3.8.1 Grapefruit juice

Consumption of grapefruit or grapefruit juice while on olaparib therapy is prohibited.

### 3.8.2 Contraception

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination (as described in Appendix D). This should be started from the signing of the informed consent and continue 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 (as described in Appendix D). For details of acceptable methods of contraception refer to Appendix D.

## 3.9 Discontinuation of Investigational Product

Patients may be discontinued from IP in the following situations:

- Patient decision; the patient is at any time free to discontinue treatment, without prejudice to further treatment
- Disease progression as assessed by the investigator
- Unacceptable toxicity (patients can temporarily discontinue IP due to toxicity; IP can be re-started provided the disease has not progressed since discontinuation)

- Adverse Event
- Severe non-compliance with the Clinical Study Protocol
- Bone marrow findings consistent with MDS/AML
- Positive pregnancy test

Patients may continue to receive olaparib beyond Investigator-assessed progression as long as, in the Investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria.

### 3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (i.e., IP and assessments; see Section 3.10), without prejudice to further treatment. If possible, they will be seen and assessed by an Investigator(s). A patient who discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. 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. Adverse events (AEs) will be followed up (See Section 6); all unused study drug should be returned by the patient.

By discontinuing from study treatment, the patient is not withdrawing from the study. Patients should continue to be followed for progression (if discontinuation in the absence of progression), TFST and OS following treatment discontinuation as per the protocol schedule.
Any patient discontinuing IP 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. 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. Patients will be required to attend the treatment discontinuation visit.
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 patient 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 the AstraZeneca representative 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.
All patients must be followed for survival, until 135 OS events (~54% maturity) have been recorded, estimated to be approximately 36 months after the first subject is enrolled.
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 who do not meet the required inclusion/exclusion criteria for the study and do not receive any dose of IP.
- Patients lost to follow up. A patient unreachable at the end of the study should be considered to be lost to follow up with unknown vital status at end of study and censored at latest follow up contact.
- 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 enrolled. These patients should have the reason for study withdrawal recorded as 'Screen failure' (the potential patient who does not meet one or more criteria required for participation in the trial; this reason for study withdrawal is only valid for patients who were not enrolled).

### 3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP 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 his/her enrolment 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)
- the use of their study generated data
- the use of any samples

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, 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 CRF. All reasons for discontinuation of treatment must be documented.
In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

# 4. STUDY PLAN AND TIMING OF PROCEDURES

The schedule of assessments for the screening visit is shown in Table 1. On-study assessments are shown in Table 2.

**Table 1 Study Schedule – Screening (Visit 1)**

| **Day** | **Before screening period** | **-28 to -1** |
|---|---|---|
| Informed consent | X | |
| IVRS/IWRS unique patient number obtained | X | |
| Demographics | | X |
| Medical and surgical history | | X |
| Prior cancer therapies including radiotherapy, best response to prior chemotherapy regimen | | X |
| History of blood transfusions [a] | | X |
| Inclusion/exclusion criteria | | X |
| ECOG performance status | | X |
| Physical examination | | X |
| Vital signs (includes blood pressure, pulse and temperature), body weight | | X |
| Haematology / clinical chemistry [b,f] | | X |
| Urinalysis | | X |
| Pregnancy test for women of childbearing potential [c] | | X |
| Confirmed as having non-Germline *BRCA* Mutated ovarian cancer [d] | X | |

| Day | Before screening period | -28 to -1 |
|---|---|---|
| Tumour assessment [e] | | X |
| AEs (from time of consent) | | X |
| Concomitant medications | | X |
| Archival or fresh tumour biopsy sample for post treatment analysis confirmation of HRD status [g] | X | X |

[a] Include history of blood transfusion within previous 120 days from start of study treatment and the reasons, e.g., bleeding or myelosuppression.

[b] Coagulation test should be performed if clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.1.

[c] 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. If results are positive, the patient is ineligible/must be discontinued from the study.

[d] Patients must be non-germline *BRCA* mutated to be enrolled into the study. Patients for whom their g*BRCA* status is already known should be consented to the study within 28 days prior to Day 1 of study treatment. Patients who do not know their mutation status will need *BRCA1/2* mutation screening (see Section 4.1.1 and Appendix F).

[e] Includes CA-125 measurement where required (Refer to Inclusion Criterion 6). RECIST assessment 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.

Note: MRI/ CT scan more than 28 days prior to Day 1 may be acceptable, please consult with AstraZeneca.

[f] These measurements may be repeated within the screening period if abnormalities are found which are the only reason for screen failing the patient and which can reasonably be expected to have return to the acceptable range

[g] All patients are required to submit either an archival tumour sample, or a fresh biopsy if an archival sample is not available, for retrospective testing of their genetic status. If archival tissue, the presence of adequate tissue needs to be confirmed prior to screening, but it will not be shipped to the central lab before Day1. If fresh, the biopsy should be taken after the baseline scan has been performed. Samples should be submitted as paraffin blocks, alternatively, sections mounted on glass slides prepared from the block can be provided. Please refer to the laboratory manual for further details regarding tissue collection, shipping and storage.

## Table 2 Study Plan Detailing the Procedures

| **Visit Number or type** | **2** | **3** | **Visit No. 4 and subsequent tumour assessment visits** | **Visit No. 5 and subsequent safety visits[a] (For the first 12 months only)** | **Study treatment discontinued** | **Follow up 30 days after last dose of study medication** | **Long-term follow up** |
|---|---|---|---|---|---|---|---|
| **Day** | 1 | 29 | On the first day of next visit period (V4 = Day 57 and thereafter every 8 weeks for the first 12 months; every 12 weeks thereafter[a]) | On the first day of next visit period **(V5=Day 85) and thereafter every 8 weeks)** | | | |
| **Visit Window** | **0** | **±3d** | **±7d** | **±3d** | **±7d** | **+7d** | |
| Physical examination [c] | X [b] | | | | | | |
| Vital signs, body weight (includes blood pressure, pulse and temperature) [c] | X [b] | | | | | | |
| ECOG performance status | X | | X | | X | | |
| Haematology / clinical chemistry [d] | X [b] | X | X | X | X | X | |
| Urinalysis [c] | X [b] | | | | | | |
| Pregnancy test [e] | X | X | X | X | | X | |
| Tumour assessment [f] | | | X | | | | |
| Blood sample for ctDNA | X | | | | X | | |
| Blood sample for restrospective g*BRCA* test[g] | X | | | | | | |
| AEs [h] | X | X | X | X | X | X | |
| FACT-O and EQ-5D-5L questionnaires | X | X | X | | X | X | |

| **Visit Number or type** | **2** | **3** | **Visit No. 4 and subsequent tumour assessment visits** | **Visit No. 5 and subsequent safety visits[a] (For the first 12 months only)** | **Study treatment discontinued** | **Follow up 30 days after last dose of study medication** | **Long-term follow up** |
|---|---|---|---|---|---|---|---|
| **Day** | 1 | 29 | On the first day of next visit period (V4 = Day 57 and thereafter every 8 weeks for the first 12 months; every 12 weeks thereafter[a]) | On the first day of next visit period **(V5=Day 85) and thereafter every 8 weeks)** | | | |
| **Visit Window** | **0** | **±3d** | **±7d** | **±3d** | **±7d** | **+7d** | |
| Concomitant medications including blood transfusions | X | X | X | X | X | X | |
| Olaparib dispensed/returned | X | X [j] | X [j] | | X | | |
| Subsequent cancer therapy following discontinuation of study treatment [k] | | | | | | X | X |
| Time to subsequent therapy and Survival[l] | | | | | | | X |

[a] From Visit 3 onwards, visits will take place on the first day of each 4-week visit period, relative to the date of the first olaparib dose (if the patient has not progressed and is still on treatment). Where the visit does not coincide with tumour assessment visits, these safety visits will only be for laboratory and pregnancy testing and recording of ECOG status, AEs and concomitant medication including transfusions. Where these visits coincide with tumour assessments, the assessment visit schedule will be performed

[b] If assessed within 7 days before first dose 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] All samples should be taken prior to first dose. Coagulation test should be performed if clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.1.

[e] Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, at the time points shown in Table 2 during study treatment and at the 30-day follow-up visit. If results are positive the patient is ineligible/must be discontinued from study treatment immediately.

[f] Visit 4 onwards: Subsequent tumour assessments will be conducted every 8 weeks (±7 days) for the first 12 months and then every 12 weeks (± 7 days) until documented disease progression.

[g] Unless patient was tested at Myriad as part of screening. All patients are required to provide a 9 ml blood sample for confirmation of g*BRCA* status. Please refer to the laboratory manual for further details regarding blood sample collection,shipping and storage.

[h] 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.

[j] +/- 2 days visit window allowed for the dispensing. 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 if required.

[k] Start date of the first anticancer treatments (including, but not limited to, chemotherapy and targeted agents), following discontinuation from study treatment must be recorded.

[l] Patient will be followed (can be by phone or email) regularly until start of subsequent therapy; survival will be followed at approximately 12 weekly intervals thereafter.

## 4.1 Screening/Enrolment Period

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.
Procedures will be performed according to Table 1 within 28 days prior to Day 1.

### 4.1.1 Testing for g*BRCA* mutations for patients with unknown g*BRCA* status

Under exceptional circumstances, g*BRCA* testing of potentially eligible patients whose g*BRCA* status is not yet known can be considered, but permission must be sought from the sponsor. Patients who do not know their mutation status, and who are being considered for this trial should be identified before screening so that the appropriate g*BRCA* mutation testing procedures can be put in place in a timely manner (Section 3.1). g*BRCA* testing will be conducted at a central laboratory (Myriad). Please refer to Appendix F for full instructions. Turnaround times at this laboratory should be no longer than 4 weeks.

## 4.2 Treatment Period

Descriptions of the procedures for this period are included in Table 2.

### 4.2.1 Visit 2 (Baseline Visit, Day 1)

Study procedures will be conducted on the scheduled day.

### 4.2.2 Visit 3 (Day 29)

Study procedures will be conducted on the scheduled day +/- 3 days (unless otherwise specified).
**All subsequent visits in the Treatment Period should be planned on the first day of each 4 week period relative to the date of the first olaparib dose. Visit 4 will therefore be on Day 57**

### 4.2.3 Visit 4 (Day 57) and subsequent on-treatment tumour assessment visits

Visit 4, (Day 57) is the first tumour assessment visit. Subsequent tumour assessment visits will take place on the first day of each 8 week visit period, relative to the date of the first olaparib dose, for the first 12 months, and subsequently each 12-week visit period, relative to the date of the first olaparib dose, until progression.
Study procedures will be conducted on the scheduled day +/- 3day, but radiological assessments can be conducted on the scheduled day ±7 days.

### 4.2.4 Visits 5 and Subsequent safety test visits

Visit 5 (Day 85) and subsequent 8 weekly visits which fall between on-treatment assessment visits will be for haematology, biochemistry and pregnancy testing, AEs and concomitant medication including transfusions. These safety-specific test visits will cease after the first 12 months and safety tests will then be conducted at the tumour assessment visits only.
Study procedures will be conducted on the scheduled day +/- 3days.

#### 4.2.5 Study treatment discontinued

Unused study treatment should be returned and study procedures for this visit should be conducted within 7 days of treatment discontinuation as shown in Table 2.

## 4.3 Follow-up Period

The start date of the subsequent anticancer treatment after discontinuation of study treatment needs to be recorded (including, but not limited to, chemotherapy and targeted agents).

#### 4.3.1 Follow up 30 days after last dose of study medication

30 days after last dose of study medication (+/- 7 days), study procedures should be conducted as shown in Table 2. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-day follow-up period after last dose of study medication must be followed to resolution.

#### 4.3.2 Long-term follow up beyond 30 days after last dose of study medication

Long-term follow up will be conducted until First Subsequent Treatment (or prior death), and for Overall Survival (by approximately 12 weekly contact with the patient after the 30 day visit described in 4.3.1). These assessments can be undertaken by phone or e-mail or mail, and do not require the patient to visit the Site.
Patients who discontinue study treatment in the absence of disease progression should continue to be followed for progression, after treatment discontinuation, as per the protocol schedule regardless of whether they start a subsequent therapy.

# 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 eCRFs as specified in the Clinical 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. The Investigator will sign the completed eCRFs. A copy of the completed electronic 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 eCRFs provided for this study. 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 Tumour evaluation

Following the screening assessment, subsequent tumour assessments will be conducted as per schedule up to disease progression regardless of whether study treatment is discontinued or delayed, protocol violations, or if the patient receives another anti-cancer therapy prior to progression, unless the patient withdraws consent.

## 5.2 Safety Assessments

### 5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in Table 1 and Table 2.
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 laboratory method used and routine practice at the site.The following laboratory variables will be measured:

**Table 3 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-Alanine transaminase (ALT) |
| B-Mean cell volume (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** total bilirubin ≥2 x ULN please refer to Appendix C, for further instructions.

#### 5.2.1.1 Coagulation

- Activated partial thromboplastin time (APTT) will be performed if clinically indicated

- Prothrombin time will be assessed and the international normalised ratio (INR) recorded at screening if clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that the INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Each coagulation test result will be recorded in the eCRF.

#### 5.2.1.2 Bone marrow or blood cytogenetic samples

In patients with prolonged haematological toxicities, bone marrow or blood cytogenetic samples may be indicated as defined in Section 6.8.1.3
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 the eCRF.

### 5.2.2 Physical examination and ECOG

ECOG status is performed at screening, baseline, at the start of each tumour assessment visit, and at the 30 day follow up. Physical examination, vital signs are performed at screening, baseline and as clinically indicated thereafter (see Table 1 and Table 2). ECOG performance status: refer to Appendix E.

#### 5.2.2.1 Vital signs and weight

Weight will be assessed at screening and baseline according to the Study Schedule (see Table 1 and Table 2) and as clinically indicated at any other time.
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.

#### 5.2.2.2 Pulse and blood pressure

Blood pressure and pulse will be assessed at screening and baseline according to the Study Schedule (see Table 1 and Table 2) and as clinically indicated at any other time.
Blood pressure and pulse rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size after 10 minutes rest.
The date of collection and measurement will be recorded on the appropriate eCRF.

#### 5.2.2.3 Body temperature

Body temperature will be measured in degrees Celsius according to local practice at screening, baseline and as clinically indicated (see Table 1 and Table 2).
The date of collection and measurement will be recorded on the appropriate eCRF.

### 5.2.3 Other safety assessments

#### 5.2.3.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, at the time points shown in Table 2 during study treatment and at the 30-day follow-up visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately.

## 5.3 Other Assessments

### 5.3.1 Patient Reported Outcomes (PRO: 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 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, Visit 4 (week 8), and then at every tumour assessment visit until progression. In addition, QoL questionnaires will be collected at the discontinuation of study treatment visit, and 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. 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. The endpoint for HRQoL analysis will be the FACT-O Trial Outcome Index (TOI). Other subscales will be considered as exploratory endpoints [redacted].

### 5.3.2 EQ-5D-5L

EuroQol five dimensions questionnaire (EQ-5D-5L) is a standardized instrument for measuring generic health status. The EQ-5D questionnaire is made up of two components; health state description and evaluation. In the description part, health status is measured in terms of five dimensions (5D); mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients will self-rate their level of severity for each dimension using a five-level scale (5L). In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS). The EQ-5D-5L questionnaire will be administered at the same time points as the FACT-O (5.3.1) [redacted].

## 5.4 Pharmacokinetics

Not applicable

## 5.5 Pharmacodynamics

Not applicable

## 5.6 Genetics

A blood sample for retrospective g*BRCA* testing (unless determined centrally at screening) and archival tumour sample for genetic analysis will be taken as per Table 1 and 2.

The effect of the following identifiable genetic subtypes will be examined through the impact of treatment on PFS in each group: -

1. somatic *BRCA* mutated and HRD scar positive;
2. HRD scar positive, non-*BRCA* mutated;
3. HRD scar negative, non-*BRCA* mutated

The tumour samples will be analysed for molecular sub-groups including mutations in Homologous recombination repair (HRR) genes, microsatellite instability (MSI) status, and tumour mutation load score. The following outcome measures will be explored:-

- PFS by molecular measures of HRR and genomic instability including:
    - MSI (positive vs negative)
    - HRR deleterious or suspected deleterious mutation (yes vs no)
    - TP53 deleterious or suspected deleterious mutation (yes vs no)
    - Tumour mutation load score
    - Loss of heterozygosity (yes vs no) for patients with a HRR mutation
- OS by TP53 mutation status (yes vs no).

## 5.7 Biomarker Analysis

Samples (about 20 mL whole blood to provide plasma) will be taken at Visit 2 and at treatment discontinuation to explore the feasibility of reliably identifying mutations in homologous recombination genes from circulating tumour DNA (ctDNA) by matching with results from tumour testing, and to enable future diagnostic development.

# 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.
Medical management of patient according to local practice is acceptable for AEs that are not SAEs and not adverse events of special interest (AESI), and that are grade 1 or 2 in severity.

## 6.1 Definition of Adverse Events

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

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

### 6.1.1 Olaparib adverse events of special interest

Adverse events of special interest [AESI] 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. AESIs for olaparib are the important potential risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.
AZ Safety will send a questionnaire to any investigator reporting an AESI, as an aid to provide further detailed information on the event. This information is separate from the eCRF. 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 Serious Adverse Event

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 or incapacity
- 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 Adverse Events

### 6.3.1 Time period for collection of adverse events

AEs/SAEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period (30 days after discontinuing IP except for AEs described in Section 6.3.1.1).
After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

#### 6.3.1.1 Adverse events after the 30-day follow-up period

For Pharmacovigilance purposes and characterisation, any SAE of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety regardless of the investigator's assessment of causality or knowledge of the treatment. Investigators will ask, during the regular follow up for overall survival, if the patient has developed MDS/AML or a new primary malignancy and must 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 data cut off and/or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.
Otherwise, after study treatment completion (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 adverse events

Any SAE or non-SAE 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 when the AE started and stopped
- Maximum intensity / intensity / changes in intensity will all be recorded for the following AE: nausea, vomiting, fatigue and anaemia. For all other AE, only intensity is required
- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP

- Outcome of the AE
- AE caused patient's withdrawal from study (yes or no)

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- 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 to other medication
- Description of AE

**Severity of adverse event**

For each episode of an AE, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.
It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in 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 4.0 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 web site (http://ctep.cancer.gov).

### 6.3.4 Causality collection

The Investigator will assess the causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'
For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.
A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

### 6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: e.g., '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 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarised in the clinical study report. 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 total bilirubin ≥ 2 x ULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on 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 IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the signs and symptoms of the cancer. 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 Disease under study

Symptoms of the disease under study are those which might be expected to occur as a direct result of metastatic ovarian cancer or procedures to diagnose or treat it. Events, which are unequivocally due to disease under study, should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

### 6.3.10 New cancers

The development of a new primary cancer should be reported as an AE (see Section 6.1.1 Olaparib Adverse Events of Special Interest) and would in most cases meet seriousness criteria (with the exception of some non-melanoma skin cancers). New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

### 6.3.11 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 the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

### 6.3.12 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day 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 may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

## 6.4 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.
If any SAE occurs in the course of the study, then Investigators or other site personnel inform 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.
For fatal or life-threatening AEs where important or relevant information is missing, active follow up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, 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 e-mail alert is sent to the designated AstraZeneca representative.
If the WBDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by SAE paper form. The AstraZeneca representative will advise the Investigator/study site staff on 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.
Olaparib 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 the AstraZeneca representative except iif the pregnancy is discovered before the study patient has received any study drug

### 6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, IP 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 IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) 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.

## 6.7 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.
A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were recognise that could have led to an error

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

- Drug name confusion
- Dispensing error, e.g., medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, e.g., kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

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

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.
If an medication error 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 completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

## 6.8 Management of Investigational Product Related Toxicities

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 twice daily as a first step

and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once dose is reduced, escalation is not permitted.

### 6.8.1 Management of haematological toxicity

#### 6.8.1.1 Management of anaemia

**Table 4 Management of Anaemia**

| Haemoglobin (Hb) | Action to be taken |
|---|---|
| **Hb < 10 *but* ≥ 8 g/dL (CTCAE grade 2)** | **First occurrence:**<br>Give appropriate supportive treatment and investigate causality.<br>Investigator judgement to continue olaparib with supportive treatment (eg transfusion) or interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl.<br>**Subsequent occurrences:**<br>If Hb < 10 but ≥ 9 g/dl investigator judgement to continue olaparib with supportive treatment (eg transfusion) or dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to 250 mg twice daily as a first step and to 200 mg twice daily as a second step).<br>If Hb < 9 but ≥ 8 g/dl, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to 250 mg twice daily as a first step and to 200 mg twice daily as a second step). |
| **Hb < 8 g/dL (CTCAE grade 3)** | Give appropriate supportive treatment (e.g., transfusion) and investigate causality.<br>Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dL.<br>Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease. |

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 CTC grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to Section 6.8.1.3 for the management of this.

#### 6.8.1.2 Management of neutropenia, leukopenia and thrombocytopenia

**Table 5 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 twice daily** as a first step and **200 mg twice daily** as a second step |

AE of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.
Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended; however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.
Platelet transfusions, if indicated, should be done according to local hospital guidelines.
For cases where patients develop prolonged haematological toxicity (≥2-week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 6.8.1.3.

#### 6.8.1.3 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 CTC grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x $10^9$/L)
- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets < 50 x $10^9$/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption.
Development of a confirmed MDS or other clonal blood disorder should be reported as a SAE and full reports must be provided by the Investigator to the AstraZeneca representative.

Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

### 6.8.2 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 twice daily as a first step and to 200 mg twice daily 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.

#### 6.8.2.1 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 HRCT scan) should be performed to exclude pneumonitis.
Following investigation, if no evidence of abnormality is observed on computed tomography (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.

#### 6.8.2.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In SOLO-2, nausea was reported in 78% of the olaparib treated patients and 33% of the placebo treated patients and vomiting was reported in 37% of the olaparib treated patients and 19% 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 of nausea and vomiting was reported in the first 3 months for 71 and 25% of patients respectively.
No routine prophylactic antiemetic treatment is required at the start of study treatment; however, patients should receive appropriate antiemetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e., two pieces of toast or a couple of biscuits).
As per international guidance on antiemetic 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.

#### 6.8.2.3 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 the AZ 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.

**Table 6 Dose Reductions for Study Treatment**

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

# 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

## 7.1 Identity of Investigational Product

| Investigational product [a] | Dosage form and strength |
|---|---|
| Olaparib | 100 mg and 150 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, olaparib tablets will be packed in high-density polyethylene bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib will be dispensed to patients as detailed in Table 2 until the patient completes the study, withdraws from the study or closure of the study.

Study treatment is available as film-coated tablets containing 100 mg or 150 mg of olaparib. Patients will be administered olaparib orally twice daily (300 mg twice daily) continually. Two x 150 mg olaparib tablets should be taken at the same times each day, approximately 12 hours apart with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

Dose reduction may be necessary to manage toxicity (doses down to 200mg twice daily, see Section 6.8), or because of the requirement to co-administer with CYP3A4 inhibitors (doses down to 100mg twice daily, see Section 7.7). Dose reductions can be managed in 50mg increments by combination of 150mg and 100mg tablets

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (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.

Patients will continue with olaparib until documented disease progression as assessed by the Investigator or unacceptable toxicity or for as long as they do not meet any other discontinuation criteria. Patients may continue to receive treatment beyond progression as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 3.9.

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

**Dose reductions**

For guidance on dose reductions for management of AEs refer to Section 6.8.

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 creatinine clearance (CrCl) falls below the threshold for study inclusion (≥ 51 mL/min), retesting should be performed promptly.

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

Each bottle/pack of investigational medicinal product (IMP) will have an IP label permanently affixed to the outside stating that the material is for clinical study/investigational use only and should be kept out of reach of children. The label will include a space for the enrolment code (E-code) to be completed at the time of dispensing.

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's 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 IP label on the bottle specifies the appropriate storage.

## 7.5 Compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the CRF.
Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer olaparib. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib 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 will be used only as directed in the Clinical 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 site staff 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 staff, if applicable, or the Clinical Research Organization (CRO) 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.

**Medications that may NOT be administered**

No other anticancer 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 olaparib to 100 mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards

- Moderate CYP3A inhibitors – reduce the dose of olaparib to 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards

- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

*Strong 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) 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 obvious change in the efficacy of study treatment.
*P-glycoprotein inhibitors*
It is possible that co-administration of P-glycoprotein (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 2B6.

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
- OATP1B1 – bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 – serum creatinine
- OAT3 – furosemide, methotrexate

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

**Anticoagulant therapy**

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

**Antiemetic/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 anticancer agents**

Patient must not receive any other concurrent anticancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or

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

**Subsequent therapies for cancer**

Details of first therapy for cancer after discontinuation of treatment will be collected.

### 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 eCRF.

## 7.8 Post Study Access to Study Treatment – Not Applicable

# 8. STATISTICAL ANALYSES BY ASTRAZENECA

## 8.1 Statistical Considerations

A comprehensive statistical analysis plan (SAP) will be prepared and finalised prior to the first analysis. All analyses will be performed by AstraZeneca or its representatives.

## 8.2 Sample Size Estimate

The primary endpoint is investigator assessed PFS using modified RECIST criteria version 1.1. A sample size of approximately 250 patients is proposed for this study in order to provide an adequate level of precision around the primary endpoint in the whole population. The primary analysis is planned at approximately 30 months after the first patient is enrolled, with an interim analysis after approximately 18 months. A supplementary analysis of OS will be performed when 135 OS events (~54% maturity) have been recorded, estimated to be approximately 36 months after the first subject is enrolled.
From published data (Study 19, Nova study) on non-g*BRCA* patients treated with a PARPi the median PFS ranges from 8 to 9 months compared to 4–5.5 months for those treated with placebo. Clinical trial simulations were performed assuming 250 patients enrolled over a 12 month period with 50% of patients enrolled after 8 months, a median PFS of 8.5 months and a piecewise exponential model for PFS. Across 500 simulations it is estimated that the mean number of PFS events is approximately 135 at 18 months (54% maturity) and 180 at 30 months (72% maturity), with corresponding mean 95% confidence interval (CI) widths of 3.87 and 3.27 months respectively.

## 8.3 Definitions of Analysis Sets

All efficacy analyses will be based on the full analysis set (all enrolled patients assigned to olaparib) with safety data summarised from the safety-analysis set (all enrolled patients who have received at least one dose of olaparib). 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 30-day follow up assessments).

## 8.4 Outcome Measures for Analyses

### 8.4.1 Calculation or derivation of efficacy variables

**Investigator RECIST based assessments**

From the investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

A visit response of PD is defined as at least a 20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) or an overall non-target lesion assessment of progression or a new lesion. For patients who are in complete response following chemotherapy or are enrolled with no evidence of disease, progression will be based on the presence of a new lesion. The earliest visit response of PD will be used to determine the date of disease progression.

Please refer to Appendix I for the definitions of Complete Response, Partial Response, Stable Disease and Progressive Disease by modified RECIST 1.1.

**Progression-free survival (PFS)**

PFS is defined as the time from the date of first dose until the earliest date of disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy, receives another anticancer therapy prior to progression or has notable increases in CA-125. 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 progression 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 progression assessment prior to the two missed visits. If the patient has no evaluable visits they will be censored at 1 day unless they die within two visits (17 weeks allowing for visit window) from baseline. The PFS time will always be derived based on scan/assessment dates not visit dates. Assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- When censoring a patient for PFS the patient will be censored at the latest of the dates contributing to a particular overall visit assessment

**Overall survival (OS)**

OS is defined as the time from the date of the first dose of olaparib to the date of death from any cause with patients censored on the last recorded date on which the patient was known to be alive.

**Time to first subsequent treatment or death (TFST)**

TFST is defined as the time from the date of the first dose of olaparib to the earliest of the date of death or commencement of first subsequent anticancer treatment. Patients who are alive and have not been recorded as taking a subsequent anticancer treatment will be censored at the last date their treatment status was recorded.

**Time to study treatment discontinuation or death (TDT)**

TDT is defined as the time from the date of the first dose olaparib to the earliest of the date of death or discontinuation of olaparib. Patients who are alive and are still receiving olaparib will be censored at the last date they are known to be alive.

**Chemotherapy Free Interval (CT-FI)**

CT-FI is defined as the time from the date of the last dose of platinum chemotherapy in the course immediately prior to enrolment in the study until the date of commencement of the first subsequent anticancer treatment (whether or not this is chemotherapy). Patients who are alive and have not been recorded as taking a subsequent anticancer treatment will be censored at the last date their treatment status was recorded. Patients who have died prior to the start of a subsequent anticancer treatment will be censored at their date of death.

### 8.4.2 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, deaths and laboratory data. These will be collected for all patients.

**Adverse events**

AEs (both in terms of the Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.
Any AE occurring before treatment with olaparib will be included in the data listings but will not be included in the summary tables of AEs.
Any AE occurring within 30 days of discontinuation of olaparib will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of olaparib) will be flagged in the data listings.

**Other significant adverse events**

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the clinical study report. A similar review of

laboratory/vital signs (pulse and blood pressure) data will be performed for identification of OAEs.
Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

### 8.4.3 Calculation or derivation of patient reported outcome variables

**Health-Related Quality of Life**
Patient-reported health-related quality of life (HRQoL) will be assessed using the FACT-O questionnaire (Basen-Enquist K et al 2001). The FACT-O is composed of the following subscales: physical, social/family, emotional, and functional well-being as well as the additional concerns scales consisting of specific ovarian cancer symptoms. The endpoint for health-related quality of life analysis will be the Trial Outcome Index (TOI), (Cella D et al 1993). Patients will be asked to report their health-related quality of life over the course of the previous 7 days.
The Trial Outcome Index (TOI) score will be derived from the sum of the scores of the 25 items included in the physical well-being (7 items), functional well-being (7 items), and ovarian cancer subscale (11 items) of the FACT-O questionnaire version 4. The total FACT-O score will also be calculated which is made up of the sum of the individual subscale scores: physical well-being (PWB), social well-being (SWB), emotional well being (EWB) and functional well-being (FWB).
The scores will be derived in accordance with the FACT-O Scoring Manual. A number of items are negatively stated and need to be reversed by subtracting the response from "4". The scoring manual identifies that the following items need to be reversed prior to summarizing: GP1-7, GE1, GE3-6, O1-3, C2, and B5. After reversing proper items, scores are multiplied by the number of items in the domain. For each subscale, if less than 50% of the subscale items are missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. If at least 50% of the items are missing, that subscale also will be treated as missing. The TOI score ranges from 0-100 and the FACT-O from 0-152. A higher score indicates a higher HRQoL.
The change from baseline in TOI score will be derived for each visit where there is available data. A change of at least 10 points in TOI score is considered as a clinically relevant or a minimally important difference (Osoba et al 2005). In this study the 10-point minimum clinically important difference will be applied only to deterioration.

**EQ-5D-5L**
The EQ-5D-5L index comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible five options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems).
A unique EQ-5D health state is referred to by a five digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the five dimensions. This data will be converted into a weighted health state index by applying scores from EQ5D value sets elicited from general population samples (the base case will be the UK valuation

set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. In addition to the descriptive system, respondents also assess their health today on a visual analogue scale (VAS), ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.
The change from baseline in EQ-5D-5L index score and VAS score will be calculated at each visit.

## 8.5 Methods for Statistical Analyses

The precision of all estimates will be presented using a 95% CI noting that the coverage of these intervals assume the patients recruited are a random sample of patients with the disease.

### 8.5.1 Analysis of the primary variable

PFS will be summarised using the Kaplan-Meier (KM) method, which will include a graph depicting the proportion of patients alive and without progression and estimates of median PFS and associated 95% CI. In addition, progression rates and 95% CIs at clinically important landmarks (such as 1 year and 18 months) will be estimated using the KM method. The standard error of the natural log of survival time will be used to calculate CIs. The CI for the median will be calculated by determining the earliest and latest survival times whose 95% CIs contain 0.5. If the 95% CI for survival at the largest event time contains 0.5 then the upper confidence limit will be described as Not Calculated.

**Sensitivity analyses**
A sensitivity analysis may be performed on PFS excluding any patients who did not have a negative *gBRCA* mutation status confirmed by the central Myriad test. Further details on any sensitivity analyses will be provided in the SAP.

**Comparison to historical controls**

In a post-hoc exploratory analysis, outcomes from this trial may be compared to historical data from published studies in a comparable patient population treated with placebo. Such an analysis does not form part of the formal study objectives.

**Subgroup analysis**

The primary endpoint will be summarised by HRD status in the following subgroups:

- HRD scar positive and somatic *BRCA* mutated
- HRD scar positive, non-*BRCA* mutated
- HRD scar negative, non-*BRCA* mutated

In exploratory analysis, PFS will also be summarised according to a range of molecular sub-groups including mutations in homologous recombination repair (HRR) genes, microsatellite instability (MSI) status, and tumour mutation load score (see Section 5.6).
In addition, PFS will be summarised according to important clinical characteristics, which will include:

- Best response to the last platinum regimen (CR or PR)

- Prior use of bevacizumab in combination with penultimate platinum regimen
- Number of prior platinum regimens (two vs. greater than two)
- Degree of sensitivity to the penultimate platinum chemotherapy: partial (6-12 months PFS) vs fully (≥12 months PFS) sensitive
- Histological subtype (HGSOC vs. high grade endometrioid ovarian cancer)

Pre-specified subgroup analyses will be further described in the SAP.

### 8.5.2 Analysis of the secondary/exploratory variables

**Overall Survival**

OS will be summarised using a KM plot to estimate the median and proportion of patients alive at clinically relevant time points such as 12, 24 and 30 months

**Other Time-to-event endpoints**

TFST, TDT and CT-FI will be summarised using a KM plot to estimate the median and event rates from clinically important landmarks such as 1 and 2 years.

**FACT-O**

Descriptive summary statistics and graphs will be reported for the TOI by visit as well as the change in TOI score from baseline.
The proportion of patients with any improvement from baseline in TOI score and the proportion of patients with at least a 10 point deterioration from baseline in TOI score will be estimated together with the exact 95% CI.
Additional analyses may be performed and will be described in the SAP.

**EQ-5D-5L**

Descriptive statistics will be calculated for each scheduled visit/time point in the study. Additionally summary statistics will be reported for the EQ-5D index score and the EQ-VAS score, and the change from baseline for the EQ-5D index score and the EQ-VAS score. Graphical plots of the mean EQ-5D index score and EQ-VAS score, including change from baseline, and associated 95% CI by scheduled visits/time points in the study will be produced. Additional analyses may be performed and will be described in the SAP.

### 8.5.3 Interim Analysis

An interim analysis of PFS will be performed approximately 18 months after the first patient is enrolled into the study, for internal planning purposes, and to provide ongoing data to external bodies. Based upon simulations (see Section 8.2) it is estimated that approximately 135 events will have occurred at the time of the interim analysis, equating to approximately 54% data maturity. Further details on the interim analysis will be provided in the SAP.

# 9. STUDY AND DATA MANAGEMENT

## 9.1 Training of Study Site Staff

Before the first patient is entered into the study, the CRO will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and train them in any study-specific procedures and any system(s) utilised.
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, the CRO 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 Clinical Study 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 CRO 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 Clinical Study Agreement for location of source data.

### 9.2.2 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Study Agreement with the Principal Investigator, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol (CSP) and the Study Agreement with Principal Investigator, the terms of CSP 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 Study Agreement with Principal Investigator shall prevail. Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or any patients are enrolled.
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

**Study files.** AstraZeneca will provide the Principal Investigator with a file in which to organise and retain all study-related documents. All study documents (including letters from AstraZeneca) should be retained in this file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by AstraZeneca's auditor, regulatory authorities, or IRB.
**Period of record retention**. The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (e.g., source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with AstraZeneca. However, this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and AstraZeneca. AstraZeneca should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site. The Investigator follows the principles outlined in the Clinical Study Agreement or the equivalent (e.g., site contract with CRO).

### 9.2.4 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organisation/structure of AstraZeneca, the name/department name of the study site, the address or phone number of the study site or AstraZeneca, the job title of the Investigator, and monitors).
The Investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons thereof to AstraZeneca and the head of study site, and retain a copy of the records.
The Investigator(s) may deviate from or make a change to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval, only in the event of a medical emergency, e.g., it is only way to avoid an immediate hazard to the patients. In such case, the Principal Investigator must notify details of the deviation or

change, the reason, and a proposed revision in the protocol if required, to AstraZeneca and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca should be obtained via the head of the study site.

## 9.3 Study Timetable and End of Study

Planned duration of the study:
Study period: from Q1 2018 (first patient enrolled) to Q1 2021 (last patient completes follow up).

Discontinuation or suspension of the whole study programme
If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator/Investigator, the head of the study site, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.
The Principal Investigator/Investigator will immediately notify the decision to the patients, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

**Completion of the study**

Upon terminating the study, the Principal Investigator/Investigator will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the study site's rules. The head of the study site, who is informed of the termination by the Investigator, will provide a written notification of the results to the IRB and AstraZeneca.
The end of the study is defined as 'the last visit of the last patient undergoing the study'.
The data cut-off for the primary analysis will be when all patients receiving olaparib have been followed for a minimum period of 18 months since the start of treatment. New data will be added to the clinical database after this time point to provide additional data maturity for the OS analysis. Patients are 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 olaparib. For patients who do continue to receive treatment beyond the time of this data cut-off, Investigators will continue to report all SAEs to the AstraZeneca representative until 30 days after study treatment is discontinued, in accordance with Section 6.4 (Reporting of Serious Adverse Events). 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 IP, the Investigator should notify the AstraZeneca representative. Additionally as stated in Section 6.3 (Recording of Adverse Events), any SAE or non-SAE that is ongoing at the time of this data cut-off, 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 Q1 2018 and to end by Q1 2021
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.

## 9.4 Data Management by Designated Clinical Research Organisation

Data management will be performed by a CRO according to the Data Management Plan.
If applicable, 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 of the MedDRA. Medications will be classified according to the World Health Organization (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, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

**Serious Adverse Event Reconciliation**

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

# 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 IRB may require direct access to parts of the hospital or practice source records relevant to the study, including patients' medical history

All data computer processed by AstraZeneca will be identified by study code and enrolment code (E-code).The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

## 10.3 Ethics and Regulatory Review

An Ethics Committee should approve the final Clinical 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 Clinical Study Protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final Clinical 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/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements. An IRB 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 head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca and the Principal Investigator before enrolment of any patient should into the study.

The IRB 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.

A valid contract between the study site and AstraZeneca should be signed before the Investigator can enrol any patient into the study. The protocol should be re-approved by the IRB annually.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the Principal Investigator with safety updates/reports according to local requirements.
The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

## 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.

If any new information on the study medication becomes available which may influence the decision of the patient to continue the study, the Investigator(s) should inform the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue the participation in the study. In addition, if the Investigator(s) deem it necessary to revise the Informed Consent Form, they should revise it immediately (Refer to Section 10.5). The Investigator(s) should re-explain to the patients using updated Informed Consent Form even if although the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

## 10.5 Changes to the Clinical Study 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 Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol 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 new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee, see Section 10.3.

If a change to a Clinical Study Protocol 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. Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

## 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 Clinical Study 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.

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

# 11. LIST OF REFERENCES

**Fong et al 2009**
Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med. 2009;361(2):123-34.

**Hay et al 2009**
Hay T1, Matthews JR, Pietzka L, Lau A, Cranston A, Nygren AO, Douglas-Jones A, Smith GC, Martin NM, O'Connor M, Clarke AR. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous *BRCA*2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Author information Cancer Res. 2009 May 1;69(9):3850-5. doi: 10.1158/0008-5472.CAN-08-2388. Epub 2009 Apr 21.
**[**PubMed PMC2579381]

**Helleday 2011**

The underlying mechanism for the PARP and *BRCA* synthetic lethality: clearing up the misunderstandings. Mol Oncol. 2011 Aug;5(4):387-93. doi: 10.1016/j.molonc.2011.07.001. Epub 2011 Jul 22. Review. [PubMed 21821475]

**Mirza et al 2016**
Mirza M, Monk B, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. NEJM. 2016 Oct 8; N Engl J Med 2016;375:2154-64.
DOI: 10.1056/NEJMoa1611310

**Murai et al 2012**
Junko Murai, Shar-yin N. Huang, Benu Brata Das, Amelie Renaud, Yiping Zhang, James H. Doroshow, Jiuping Ji, Shunichi Takeda, Yves Pommier. Differential trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res. Author manuscript; available in PMC 2013 Nov 1. Published in final edited form as: Cancer Res. 2012 Nov 1; 72(21): 5588–5599. doi: 10.1158/0008-5472.CAN-12-2753. [PubMed PMC3528345]

**Rottenberg et al 2008**
Rottenberg S1, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, Derksen PW, de Bruin M, Zevenhoven J, Lau A, Boulter R, Cranston A, O'Connor MJ, Martin NM, Borst P, Jonkers J. High sensitivity of *BRCA*1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci U S A. 2008 Nov 4;105(44):17079-84. doi: 10.1073/pnas.0806092105. Epub 2008 Oct 29. [PubMed PMC2579381]

# Appendix A Additional Safety Information

## Further Guidance on the Definition of a Serious Adverse Event

### Life-threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (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 serious adverse event (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 jeopardise 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 intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (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 (IATA) 6.2 Guidance Document

**Labelling and Shipment of Biohazard Samples**

International Airline Transportation Association (IATA) classifies biohazardous agents into three 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 are, 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, human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

- Are to be packed in accordance with UN3373 and IATA 650

**Exempt** – all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging

- 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

## 1. Introduction

This appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 6.3.7 of the Clinical Study Protocol.
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 adverse events (AEs) and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

## 2. Definitions

### Potential Hy's Law

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 x upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2 x ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (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.

## 3. Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 x ULN
- AST ≥ 3 x ULN
- TBL ≥ 2 x ULN

The Investigator will 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 case report form (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 Section 2 within this appendix for definition) by reviewing laboratory reports from all previous visits (local laboratory results)

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 within this appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

## 4. Follow up

### 4.1 Potential Hy's Law Criteria Not Met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

### 4.2 Potential Hy's Law Criteria Met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section 6)
- 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 aetiology 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.

**5. Review and Assessment of Potential Hy's Law Cases**

The instructions in this section should be followed for all cases where PHL criteria are met. 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 Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate. According to the outcome of the review and assessment, the Investigator will follow the instructions below.
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 a 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 amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

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

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.
At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patient' condition# compared with the last visit where PHL criteria were met[#]
  - If there is no significant change, no action is required
  - If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section 4.2 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.

**7. Actions Required for Repeat Episodes of Potential Hy's Law**

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.
The requirement to conduct follow up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.
The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, 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 Section 6 ?

If No: follow the process described in Section 4.2
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 4.2

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or 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 TWO highly effective forms of contraception in combination (as listed below). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).
Male subjects must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male subjects should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male subjects should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

**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 (for 3 months after last dose for male subjects). 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 transdermal system PLUS male condom

- Intrauterine system (IUS) device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom

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

# Appendix E ECOG Performance Status

| 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 Pre study germline *BRCA* Testing

Germline *BRCA* testing of potentially eligible patients whose gBRCA status is not yet known can be considered. Prior agreement of the sponsor is required.

In these cases the gBRCA test must be completed prior to patient enrolment, and before other screening procedures are undertaken. To ensure this, patients may be consented from the end of cycle 3 of their current chemotherapy if, in the opinion of the investigator, they are responding to treatment, and if it appears that the patient is likely to meet other eligibility requirements (see below).

In these cases, 28-day screening period will be considered to have started only after the availability of the gBRCA status report at the site, at the start of the screening procedures listed in Table 1, column 2.

Patients with unknown g*BRCA* status must consent to provide a blood sample for g*BRCA* testing and follow all local ethical procedures for genetic testing. The sample will be used to test for *BRCA* mutations using the current commercial Myriad BRACAnalysis® test prior to study entry. When the result from the Myriad test indicates the patient does NOT have a deleterious or suspected deleterious g*BRCA* mutation, the patient can be enrolled into the study (providing they have fulfilled all other screening requirements).

Prior to considering the patient for g*BRCA* testing, the following inclusion criteria must be met:

2. Patients must be ≥18 years of age

3. Female patients with histologically diagnosed relapsed HGSOC (including primary peritoneal and / or fallopian tube cancer) or high grade endometrioid ovarian cancer

5. Patients must have completed at least 2 previous courses of platinum containing therapy

Additionally the patient should not fall in any of the exclusion criteria marked with an asterisk in Section 3.2

If the patient enters the study, this test fulfils the requirement for a sample to be held for retrospective confirmation of g*BRCA* status, and an additional sample does not need to be sent

Patients found to be *BRCA* positive should have appropriate counselling according to local or institutional guidelines

The sample must be sent to Myriad Genetic Laboratories, 320 Wakara Way, Salt Lake City, UT 84108. Please refer to laboratory manual for further instructions.

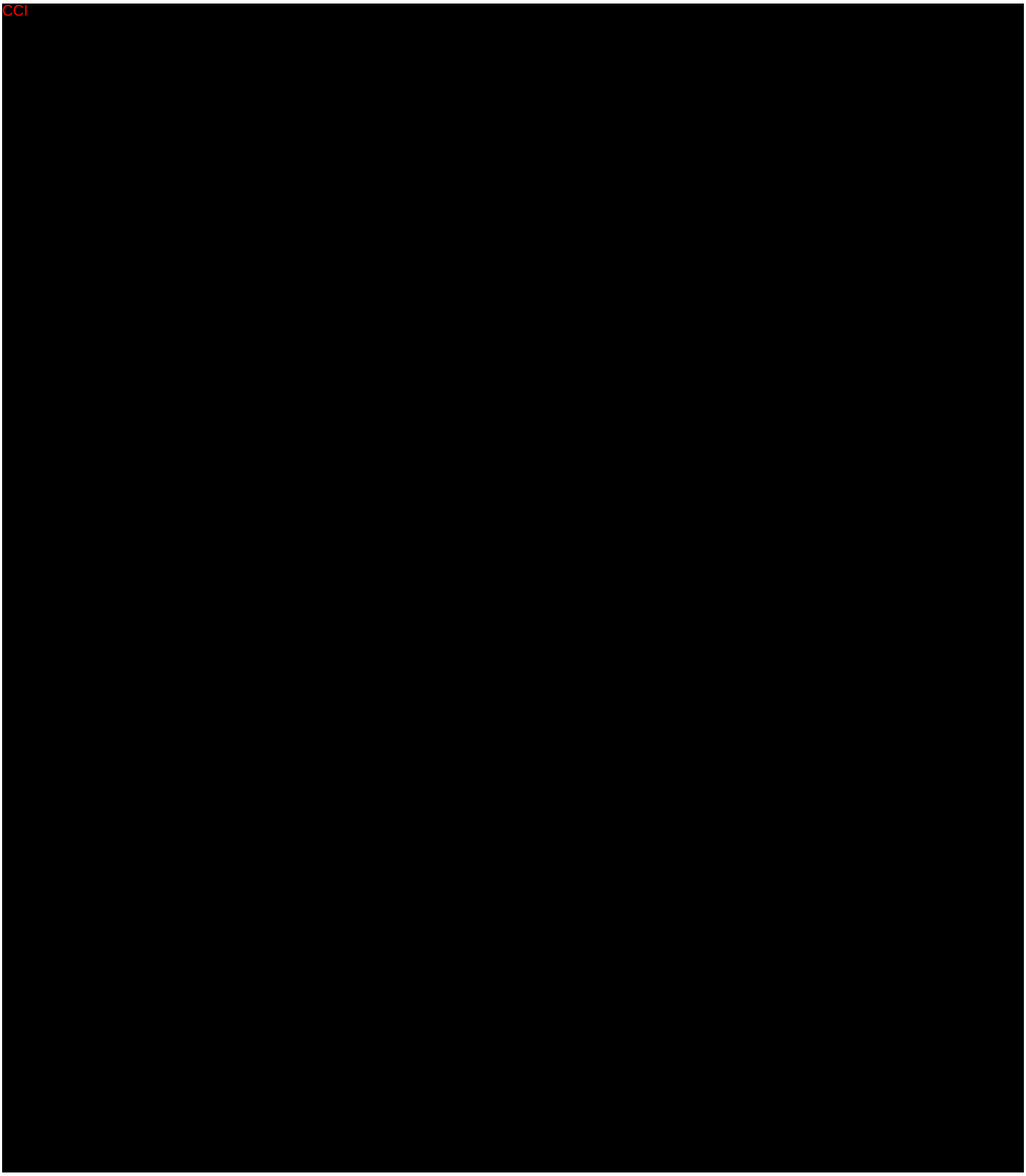
CCI

[redacted]

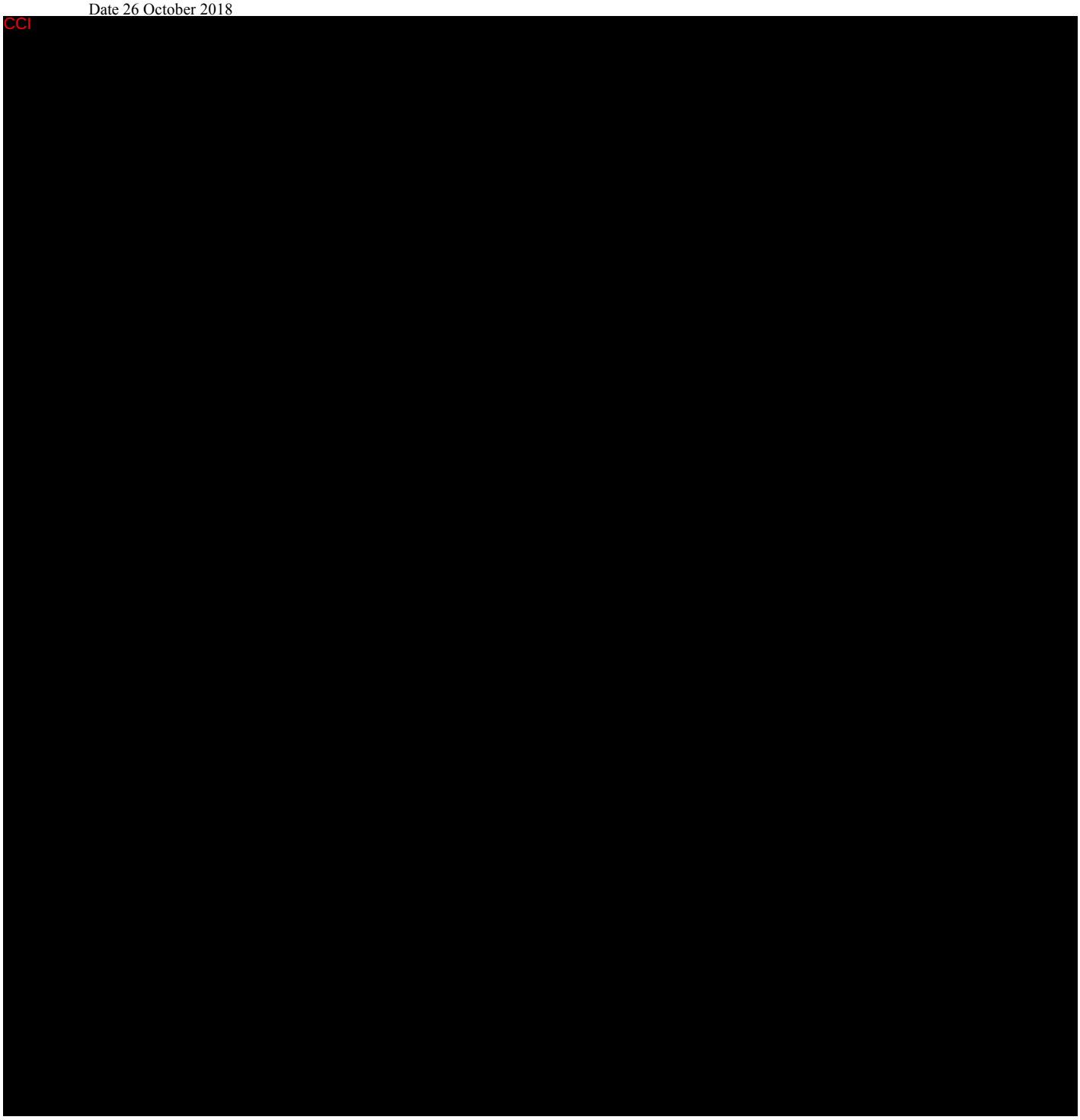
CCI

[redacted]

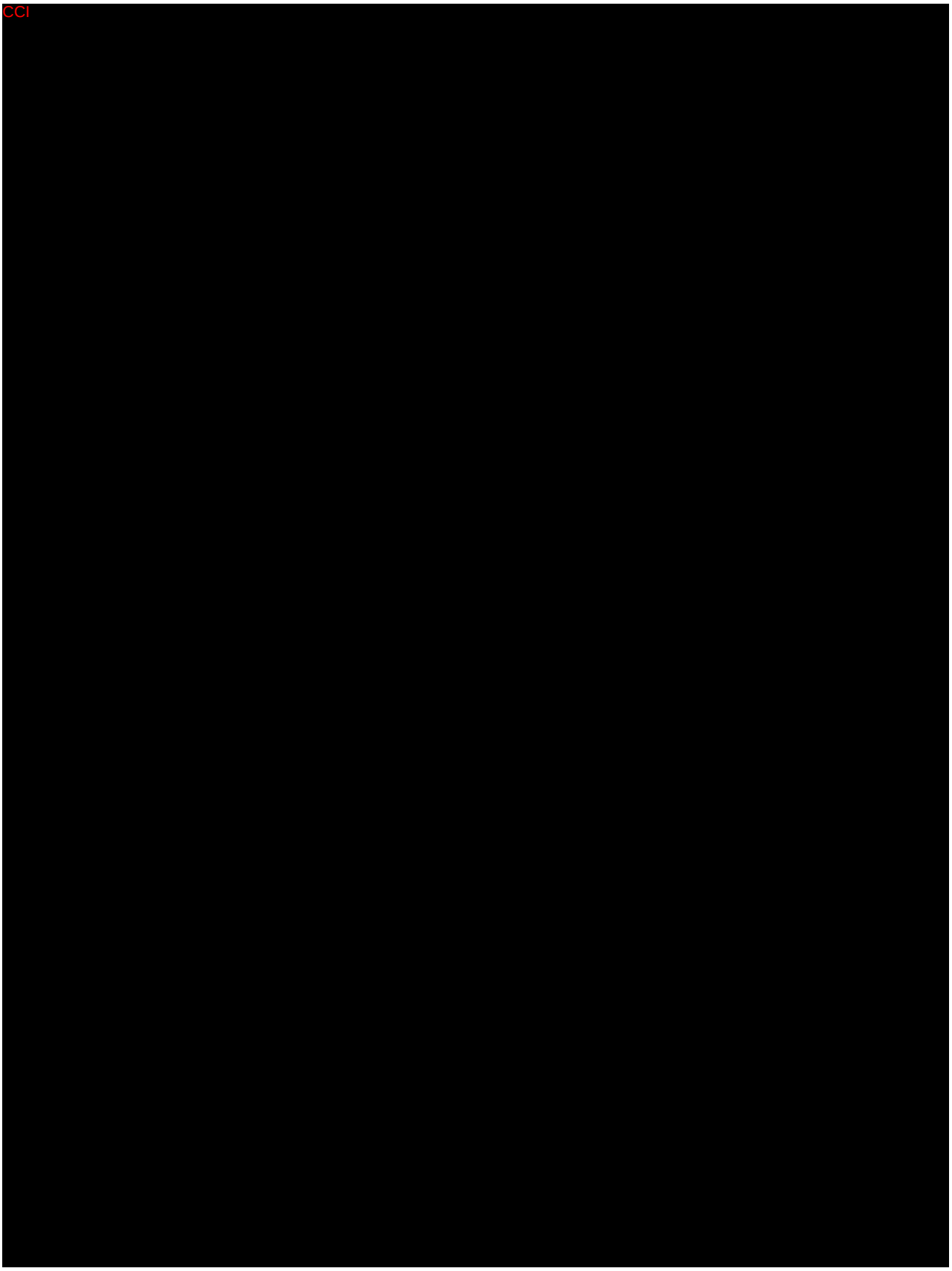
CCI

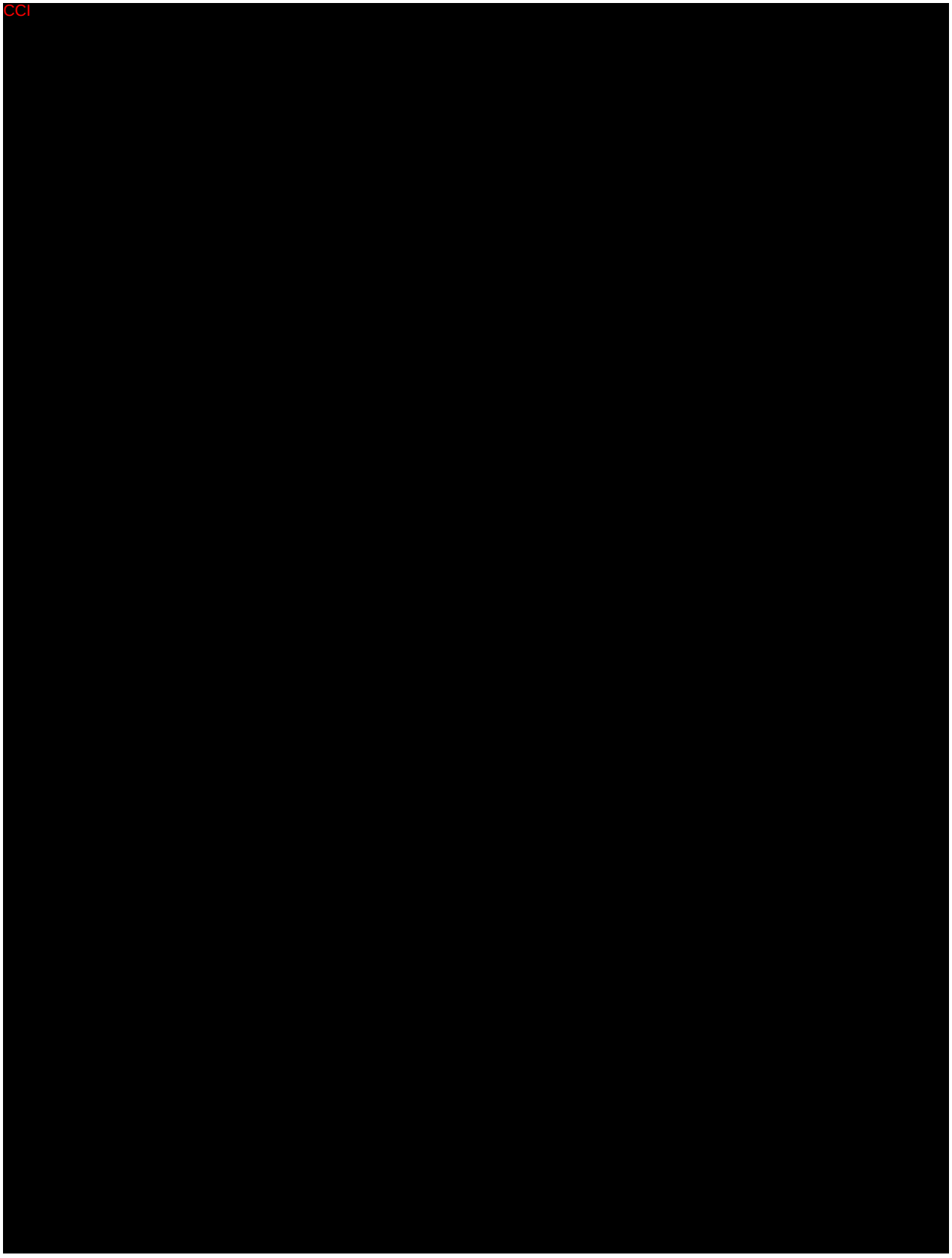


CCI



CCI




CCI

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

## Introduction

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 guidelines (**Eisenhauer et al 2009**) for the study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

## Definition of Measurable, Non-measurable, Target and Non-target Lesions

Patients with at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by computerised tomography (CT), or magnetic resonance imaging (MRI), or with no measureable disease, may be included in this study.

## Measurable lesions

A lesion, not previously irradiated, that can be measured accurately at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have a short axis ≥ 15 mm with CT or MRI) and which is suitable for accurate repeated measurements. CT slice thickness should be no greater than 5mm.

## Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline). Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)
- 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 are not measurable by CT or MRI
- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment
- Skin lesions assessed by clinical examination
- Brain metastases

## 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 non-cystic lesions should be selected as the target lesions (TLs).

### Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

### Non-target lesions

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

### Methods of Measurement

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

The methods to be used for RECIST assessment are summarised in **Table 7** and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

**Table 7 Summary of Methods of Assessment**

| Target Lesions | Non target lesions | New Lesions |
|---|---|---|
| CT (preferred) | CT (preferred) | CT (preferred) |
| MRI | MRI | MRI |
| | Plain X-ray (includes chest X-ray) | Plain X-ray (includes chest X-ray) |
| | Clinical examination | Clinical examination |
| | | Ultrasound |
| | | FDG-PET |

### CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.
In this study it is recommended that CT examinations will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

### Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients that also have other lesions assessable by CT, MRI and to identify the presence of new lesions.

## X-rays

### Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

### Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

### Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

### Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

### Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

### Cytology and histology

Histology will not be used as part of the tumour response assessment 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 the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

### FDG-PET scan

FDG-PET (fluorodeoxyglucose positron emission tomography) 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 (defined as when an uptake greater than twice that of the surrounding tissue is observed) 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.

## Tumour response evaluation

### Schedule of evaluation

Baseline tumour 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. Follow-up assessments should be performed according to the study schedule (Table 2) after the start of treatment until discontinuation of study treatment or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

### Target lesions

### Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.
The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

### Special cases:

- For TLs 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 TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 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 eg, radiotherapy, embolisation, surgery etc, during the study, the size of the TL should still be provided where possible

### Evaluation of target lesions

Table 8 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

**Table 8 Overall Visit Response for Target Lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm. |
| Partial Response (PR) | At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters. |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. |
| Progressive Disease (PD) | At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. |
| Not Evaluable (NE) | Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit.<br>Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response |

### Non-Target lesions

### Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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. Table 9 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

**Table 9 Overall Visit Response for Non-Target Lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis). |
| Non-CR/Non-PD | Persistence of one or more NTLs. |
| Progressive Disease (PD) | Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy |

| | |
|---|---|
| Not Evaluable (NE) | Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit.<br>Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met. |

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

**New Lesions**

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.
A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.
The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.
If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

**Symptomatic deterioration**

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.
Patients with 'symptomatic deterioration' requiring discontinuation of study treatment without objective evidence of disease progression at that time will undergo no further tumour assessments in this study. Tumour response data for such patients will be censored at the date of their last RECIST assessment.

**Evaluation of Overall Visit Response and Best Overall Response**

The overall visit response will be derived using the algorithm shown in **Table 10**

**Table 10 Overall Visit Response**

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

**Table 10 Overall Visit Response**

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no TLs/NTLs at baseline)

### Specifications for Radiological Imaging

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

### CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomical regions of interest.
The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

### Anatomic coverage

Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

### Intravenous contrast administration

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient.

It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.
If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations.

**Slice thickness and reconstruction material**

It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.
All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

**MRI Scan**

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.
For these reasons, CT is the imaging modality of choice.

## FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

## PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

## REFERENCES

**Eisenhauer et al 2009**
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247.

# Appendix J Signatures

## ASTRAZENECA SIGNATURE(S)

## OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

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

I agree to the terms of this study pr[redacted]

**AstraZeneca Representative**

PPD

01.11.2018

Date
(Day Month Year)

(DDR) Franchise, GMA
Academy House
136 Hills Road
Cambridge CB2 8PA, UK

## ASTRAZENECA SIGNATURE(S)

## OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

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

I agree to the terms of this study protocol.

**AstraZeneca Representative**

PPD

1. 11. 18

Date
(Day Month Year)

Da Vinci Building
Melbourne Science Park
Cambridge Rd, UK

## ASTRAZENECA SIGNATURE(S)

## OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

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

I agree to the terms of this study protocol.

**AstraZeneca Representative**

PPD

8 Nov 2018

Date
(Day Month Year)

Academy House
126 - 130 Hills Road,
Cambridge CB2 8PA, UK

# SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

## OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

**Signature:** PPD

5 NOV 18

Date
(Day Month Year)

INITIA ONCOLOGY
Hospital Quironsalud
Prof Severo Ochoa, 14
Planta Baja
46010 Valencia, Spain