LUCY - Lynparza Breast Cancer Real-World Utility, Clinical Effectiveness and Safety Study

A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Monotherapy in the Treatment of HER2-ve Metastatic Breast Cancer Patients with Germline or Somatic BRCA1/2 Mutations

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Clinical Study Protocol	
Drug Substance	Olaparib, AZD2281, KU-0059436
Study Code	D0816C00018
Version	4.0
Date	19 April 2021

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A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Monotherapy in the Treatment of HER2-ve Metastatic Breast Cancer Patients with Germline or Somatic *BRCA1/2* Mutations

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

Sponsor (Japan): ***AstraZeneca K.K., 3-1, Ofuka cho, Kita-ku Osaka 530-0011, Japan***

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VERSION HISTORY

Version 4.0, 19 April 2021
Amendment 3 Description of change: The second time point for statistical analysis has been extended to Q2/Q3 2021 due to longer than expected survival. Based on the current death event rate, at least ~130 deaths (~52% maturity) are predicted to have occurred by this date. Sections affected: Synopsis, Section 8.2 and Section 9.3 Description of change: In order to reduce the burden on patients in terms of schedule of assessments, the follow-up after data cut-off (DCO) was reduced. Patients still receiving treatment with olaparib will have the option of continuing to receive olaparib as part of the roll over ROSY-O study (NCT04421963). Section affected: Section 4 (including Table 2: Study Plan Detailing the Procedures) and Section 9.3 Description of change: acceptable non-hormonal and hormonal birth control methods were updated following Investigator Brochure update. Section affected: Appendix D In addition, minor formatting and editorial changes were made throughout the document.
Version 3.0, 22 October 2020
Amendment 2: Description of change: The contraceptive language was updated based on feedback from the Czech Republic regulatory authority. Sections affected: Section 3.1 Inclusion Criteria #11, Section 3.8.2 Contraception, and Appendix D. Description of change: Myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) were changed from important potential risks to important identified risks due to a change in risks related to olaparib. Section affected: Section 6.1.1 Olaparib adverse events of special interest. Description of change: Clarification of post study access in the form of transition to a roll-over study (ROSY-O), continuous supply within this trial, or switching to commercial drug.

Section affected: Section 7.8 Post Study Access to Study Treatment.

Description of change: Section 6.3.9 was removed as SAEs related to disease progression are not recorded.

Section affected: Section 6.3.9 Disease under study.

Description of change: Update of timelines to reflect the change in study completion period.

Sections affected: Synopsis and Section 9.3.

Description of change: Added details of the survival sweep to be performed for the final analysis to provide complete survival data.

Section affected: Section 8.4.1 Calculation or derivation of efficacy variables and Section 9.3 Study Timetable and End of Study.

Version 2.0, 27 April 2018
Amendment 1: CCI [redacted] Sections affected (by main headings): Study title, Synopsis, Exploratory Objectives, Section 1 Introduction, Section 3 Patient Selection (Inclusion Criteria #4), Section 4 Study Plan and Procedures (new text in subsections 4.1.1, 4.1.2, 4.1.3), Section 5.1 Efficacy Assessments, Section 7 IP and Other Treatments, Section 8 Statistical Analyses. Description of change: The following sections were revised per the olaparib standard protocol template effective 08 February 2018. Sections affected: Section 3.1 Inclusion Criteria #6, #8, Section 3.2 Exclusion Criteria #3, #7, #20, Section 3.8.1 Grapefruit juice, Section 6.8.1.1 Management of anaemia, Section 6.8.2.2 Management of nausea and vomiting, Section 6.8.2.4 Renal impairment, Section 7.2 Dose and Treatment Regimens, and Section 7.7 Concomitant Other Treatments. CCI [redacted] Sections affected: Synopsis, Section 2.4 Exploratory Objectives, Section 3.2 Exclusion Criteria #12, Section 8.4.1 Calculation or derivation of efficacy variables, and Section 8.5.2. Analysis of the secondary variables. Description of change: An optional consent to allow for samples collected for *BRCAm* to be available for additional biomarker testing outside the LUCY study. Sections affected: Section 4 Study Plan and Timing of Procedures, Section 5.7 Exploratory Biomarker Analysis

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

CLINICAL STUDY PROTOCOL SYNOPSIS

LUCY - Lynparza Breast Cancer Real-World Utility, Clinical Effectiveness and Safety Study

A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Monotherapy in the Treatment of HER2-ve Metastatic Breast Cancer Patients with Germline or Somatic *BRCA1/2* Mutations

International Coordinating Investigator

PPD

British Columbia Cancer Agency

PPD

Canada

Study sites and number of patients planned

The study will be conducted globally and an estimated 1400 patients will be screened at approximately 180 centres to recruit approximately 250 human epidermal growth factor receptor 2 negative (HER2-ve) metastatic breast cancer patients with germline and approximately 20 patients with somatic mutations in the breast cancer susceptibility genes (*BRCA1*, *BRCA2*).

Additional sites may be added depending on recruitment rates.

Study period	
Estimated date of first patient enrolled	Q1 2018
Estimated date of last patient completed	Q2/Q3 2021

Study design

This is a phase IIIb, single-arm, open-label, multicentre study to assess the clinical effectiveness in a real-world setting of single-agent olaparib treatment in HER2-ve metastatic breast cancer patients with germline or somatic *BRCA1/2* mutations. The target population is patients with HER2-ve metastatic breast cancer who have previously progressed after treatment with anthracycline or taxane-based chemotherapy. All patients must have a

confirmed genetic status for *BRCA1*, *BRCA2*. Tumour assessments will be conducted as per local practice at each patient visit, up to first disease progression. Tumour assessments are defined at a minimum as being clinical assessments as done in accordance with local practice, with documentation of the results on the eCRF; RECIST 1.1 must be used to assess tumour progression in somatic *BRCA* mutated patients. After first progression, assessments should be conducted in accordance with local practice and standard of care.

Objectives

Primary Objective:	**Outcome Measure:**
To evaluate the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting through assessment of progression-free survival in germline *BRCA* mutated patients	PFS, defined as the time from first dose of olaparib to the date of progression as determined by the Investigator (physician-defined progression*) or death from any cause (in the absence of progression)

*physician-defined progression can be radiological (e.g. RECIST) progression, symptomatic progression, or clear progression of non-measurable disease, as long as progression can be documented.

Secondary Objectives:	**Outcome Measures:**
To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of overall survival in germline *BRCA* mutated patients	Overall survival, defined as the time from first dose of olaparib to the date of death from any cause
To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of time to use of subsequent therapies, second progression, and study treatment discontinuation in germline *BRCA* mutated patients	• Time to first subsequent treatment or death, defined as the time from first dose of olaparib to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment • Time to second subsequent treatment or death, defined as the time from first dose of olaparib to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment • Time to study treatment discontinuation or death, defined as the time from first dose of olaparib to study treatment discontinuation or death if this occurs before discontinuation of study treatment

	• Time to second progression or death, defined as the time from first dose of olaparib to the earliest progression event subsequent to that used for the primary variable PFS or death from any cause
To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of clinical response rate and duration of clinical response in germline *BRCA* mutated patients	• Clinical response rate, defined as the proportion of patients assessed by the Investigator as responding (physician-defined clinical response, radiological [e.g. RECIST] or symptomatic) • Duration of clinical response, defined as the time from the date the Investigator first assessed the patient as responding to the date the Investigator assessed the patient as progressing or the date of death from any cause (in the absence of progression)

Safety Objective:	**Outcome Measures:**
To evaluate the safety and tolerability of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-word setting	Adverse events/serious adverse events Collection of clinical chemistry/haematology parameters

Exploratory Objectives:	**Outcome Measure:**
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

Screening

Based on the prevalence of *BRCA1/2* mutations in HER2-ve breast cancer patients, it is estimated that up to 1400 patients may require screening for enrolment into this study. In contrast to oestrogen receptor and/or progesterone receptor positive breast cancer patients, it is anticipated that a significant proportion of patients with triple-negative breast cancer may already have their *BRCA1/2* status documented, especially in the USA. There will not be a requirement for a repeat germline *BRCA1/2* genetic diagnostic test amongst this population.

Target patient population

Patients will be eligible if they have either triple-negative breast cancer or oestrogen receptor / progesterone receptor positive HER2-ve breast cancer.

All patients enrolled (enrolled patients are patients who fulfil eligibility criteria for receiving study treatment) in the study will be selected based on the following three principles:

- Genetic selection: Documented germline or somatic mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function; see Section 3.1). Patients with *BRCA1* and/or *BRCA2* mutations that are considered to be non-detrimental (e.g., "variants of uncertain clinical significance" or "variant of unknown significance" or "variant, favour polymorphism" or "benign polymorphism," etc.) may be reviewed by a diagnostics committee to determine whether or not the patient is eligible for the study.

- Treatment setting: All patients should have metastatic breast cancer and must have received treatment with anthracycline or taxane in either an adjuvant (may include neoadjuvant) or a metastatic setting. Patients should have received no more than 2 prior cytotoxic chemotherapy regimens in the metastatic setting.

- Phenotypic tumour selection: Patients can have either triple-negative breast cancer (defined as oestrogen receptor and progesterone receptor negative [immunohistochemistry nuclear staining <1%] and HER2-ve [immunohistochemistry 0, 1+ or 2+ and/or in situ hybridization non-amplified with ratio less than 2.0]) or oestrogen receptor / progesterone receptor positive breast cancer, as long as they are HER2-ve. Patients with oestrogen receptor and/or progesterone receptor positive breast cancer must have received and progressed on at least one line of endocrine therapy in either an adjuvant or a metastatic setting, including endocrine therapy in combination with a targeted agent such as a CDK4/6 or mTOR inhibitor. Patients are not considered suitable for further endocrine therapy.

Duration of treatment

Patients should continue to receive study treatment until documented physician-defined disease progression (see note below) as assessed by the Investigator or unacceptable toxicity, or for as long as they do not meet any other discontinuation criteria. Note: 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.

Once patients have been discontinued from study treatment, patients will be moved on to other treatment options or standard of care, as determined by their physician.

Investigational product, dosage and mode of administration

AstraZeneca's Pharmaceutical Development, Research and Development Supply Chain will supply olaparib to the Investigator as film-coated tablets.

Patients will be administered olaparib orally, twice daily at 300 mg. Two (2) 150 mg olaparib tablets should be taken at the same time each morning and evening of every day, approximately 12 hours apart, with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with a light meal. Dose reductions may be required in patients experiencing toxicities related to olaparib treatment (Section 6.8).

Statistical methods

The primary endpoint is progression-free survival. The statistical analyses will be performed at a minimum of two time points:

- The first when approximately 160 germline *BRCA* mutated patients have had a progression-free survival event

- The second after approximately 130 germline *BRCA* mutated patients have died, at which point the progression-free survival analysis will be updated

The somatic *BRCA* mutated patient cohort will also be assessed at these time points.

If germline *BRCA* mutated patients are recruited over 12 months, it is estimated that 160 progression-free survival events will have occurred by 19 months after the first germline *BRCA* mutated patient is entered; this is assuming exponentially distributed progression-free survival data with a median of 7 months and a recruitment function that assumes 25% of the germline *BRCA* mutated patients are recruited after 6 months. It is also estimated that approximately130 overall survival events will have occurred at 28 months if the median overall survival is 19 months.

In this study, disease progression in germline *BRCA* mutated patients will be based on Investigator assessment; RECIST 1.1 must be used to determine disease progression in somatic *BRCA* mutated patients. Tumour assessments will be conducted as per local practice at each patient visit, until first progression, then in accordance with local practice and standard of care. For patients with germline *BRCA* mutations, tumour assessments are defined at a minimum as being clinical assessments as done in accordance with local practice, with documentation of the results on the eCRF; for patients with somatic *BRCA* mutations, RECIST 1.1 must be used to assess tumour progression with documentation of results on the eCRF. Progression-free survival is defined as the time from the first dose of olaparib until the date of disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. The case report forms will capture each time a patient is assessed for progression regardless of the outcome of the assessment. 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.

Progression-free survival will be summarised using a Kaplan-Meier plot from which the median and its 95% confidence interval will be calculated together with the estimated progression rates and 95% confidence intervals at clinically important landmarks (such as 1 year).

Recruitment of 250 germline *BRCA* mutated patients will provide a sufficiently precise estimate of median progression-free survival. If the median progression-free survival observed is 7 months and analysed after 160 events, the 95% confidence interval for the median would be predicted to extend from 6.0 to 8.2 months (based on the formula of Collett). Similarly, at the overall survival follow up analysis, if the median overall survival observed is 19 months and data are analysed after 130 events, the 95% confidence interval for the median would be predicted to extend from 16.0 to 22.6 months.

Data from the germline and somatic *BRCA* mutated patient cohorts will be presented separately and combined.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse 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
BRCA1, BRCA2, BRCA1/2	Breast cancer susceptibility genes
BUN	Blood urea nitrogen
CE-IVD	Conformité Européenne (EU conformity) *in vitro* diagnostic
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CrCl	Creatinine clearance
CRF/eCRF	Case report form/ Electronic case report form
CRO	Clinical research organisation
CRR	Clinical response rate
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC(AE)	Common terminology criteria (for adverse event)
CYP	Cytochrome P450
DCIS	Ductal carcinoma in situ
DCO	Data cut-off
DCR	Disease control rate
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DoCR	Duration of clinical response
DSBs	DNA double strand breaks

Abbreviation or special term	Explanation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group; a performance status using scales and criteria to assess how a patient's disease is progressing
ESMO	European Society for Medical Oncology
gBRCA mutation	Germline *BRCA1/2* mutation
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HER2-ve	Human epidermal growth factor receptor 2 negative
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Homologous recombination
HRCT	High resolution computed tomography
HRD	Homologous recombination deficiency
IATA	International Airline Transportation Association
IB	Investigator brochure
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
INR	International normalised ratio
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally.
IP	Investigational product
IRB	Institutional Review Board, synonymous to Ethics Committee
IVRS/IWRS	Interactive Voice/Web Response System
KM	Kaplan-Meier
MATE	Multidrug and toxin extrusion (MATE1, MATE2K)
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging

Abbreviation or special term	Explanation
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OAE	Other significant adverse event
OAT3	Organic anion transporter 3
OATP1B1	Organic anion transporting polypeptide 1B1
OCT	Organic cation transporter (OCT1, OCT2)
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase
PFS	Progression-free survival
PFS2	Time to second progression or death
PHL	Potential Hy's Law
QT(c)	(Corrected) QT interval
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
sBRCA mutation	Somatic *BRCA1/2* mutation
SGOT	Serum glutamic oxaloacetic transaminase (also AST)
SGPT	Serum glutamic pyruvate transaminase (also ALT)
SSB	Single strand breaks
tBRCA mutation	Tumour *BRCA1/2* mutation (not yet known if s*BRCA* or g*BRCA*)
TBL	Total bilirubin
TDT	Time to study treatment discontinuation or death
TFST	Time from first dose to first subsequent treatment or death
TNBC	Triple-negative breast cancer
TSST	Time to second subsequent treatment or death
ULN	Upper limit of normal
USA	United States of America
WBDC	Web based data capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and Rationale for Conducting This Study

Research Hypothesis

Within the setting of breast cancer susceptibility gene (*BRCA1/2*)-mutated metastatic breast cancer in patients who are human epidermal growth factor receptor 2 negative (HER2-ve), olaparib monotherapy is a valid alternative to other cytotoxic treatments (Tutt et al 2010) that yield low clinical benefits to this group of patients and for which no evidence exists to support any one agent or combination over another (Mechetner et al 1998).

Predominantly, clinical data has been generated on germline *BRCA* mutations. Limited data exists for somatic *BRCA* mutations in the ovarian setting (Study 19; NCT00753545) but these data suggest patients with somatic mutations of the *BRCA* susceptibility gene may also benefit from PARP inhibition. The exploratory objectives in this protocol are aimed at generating supportive data for patients with somatic mutations in the breast cancer setting. The hypothesis is that since *BRCA* mutation drives efficacy via PARP inhibition, then germline or tumour mutations should not discriminate on the response seen.

In the present study, eligible patients must have progressed after previous treatment with anthracycline- or taxane-based chemotherapy in either the adjuvant (may include neoadjuvant) or metastatic setting. The time from first exposure to olaparib to the Investigator's assessment of disease progression (RECIST 1.1 must be used for s*BRCA*m patients) or death will be used as the primary measure of benefit.

Olaparib Mechanism of Action

Investigators should be familiar with the current olaparib (AZD2281, KU-0059436) Investigator brochure (IB).

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

PARP inhibition is a novel approach to targeting tumours with deficiencies in deoxyribonucleic acid (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 (Fong et al 2009). 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). As stated, 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 metastatic breast cancer patient population involved in this study falls under the advanced cancer, limited life expectancy definition outlined in International Council for Harmonisation (ICH) S9 guideline "Non-clinical Evaluation for Anticancer Pharmaceuticals" and meets the requirements outlined in the guideline.

1.2 Rationale for Study Design, Doses and Control Groups

Experience with Olaparib in Breast Cancer

The results from three phase II studies have demonstrated the potential benefit of olaparib as monotherapy treatment in breast cancer patients with germline *BRCA1/2* (*gBRCA*) mutations.

Study D0810C00008 (NCT00494234; EudraCT no. 2006-006458-91)

Study D0810C00008 was a proof-of-concept, open-label, single-arm multicentre study to assess the efficacy and safety of the capsule formulation of olaparib at two different doses in patients with advanced breast cancer (400 mg twice daily or 100 mg twice daily in 28-day cycles; n=27 in each group). Patients had a median of three previous chemotherapy regimens and approximately half of the patients had triple-negative breast cancer (TNBC). The objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (primary endpoint) was 41% at 400 mg twice daily, with responses in both TNBC and hormone receptor-positive HER2-ve patients. At 100 mg twice daily, a 22% ORR was observed. Responses were seen in both *gBRCA1* and *gBRCA2* carriers. The median time to progression was 5.3 months for the 400 mg twice daily group and 3.7 months for the 100 mg twice daily group. Toxicities were generally manageable. Treatment-related adverse events (AEs) were reported in 81% of patients and grade 3 or 4 events occurred in 24% of patients (Tutt et al 2010). Efficacy data from this study compare favourably with response rates in studies of single-agent cytotoxic agents (Livraghi and Garber 2015).

Study D0810C00042 (NCT01078662; EudraCT no. 2010-022278-15)

Study D0810C00042 was an open-label multicentre study investigating the efficacy and safety of olaparib in patients with a range of *BRCA1/2* mutation-associated advanced cancers. A total of 62 breast cancer patients were recruited, all of whom received at least three prior lines of therapy (with a median of six prior regimens). Eight (12.9%) of the breast cancer patients had an overall response and the median duration of response was 204 days. At 16 weeks,

disease control was observed in 23 patients (37.1%). The median progression-free survival (PFS) was 3.7 months. The median overall survival (OS) was 11.0 months and the survival rate was 74.6% at 6 months and 44.7% at 1 year (Kaufman et al 2015).

Study D0810C00020 (NCT00679783; EudraCT no. n/a)

Study D0810C00020 was an open-label study of olaparib in patients with known *gBRCA* or high-grade serous/undifferentiated ovarian cancer and patients with known *gBRCA* or TNBC. All patients received olaparib 400 mg twice daily. Tumour response data was analysed in 64 ovarian (*BRCA1/2* or serous ovarian) and 26 breast (*BRCA1/2* or triple negative) cancer patients. Germline *BRCA1/2* mutations were present in 11 out of the 26 breast cancer patients. The median number of prior chemotherapies in the breast cancer group was three. Over 70% of the breast cancer patients had received more than three previous lines of chemotherapy, with a median of 35.3 months from diagnosis to start of treatment with olaparib. None of the breast cancer patients achieved a RECIST response; however, 63% of the patients with *BRCA1/2* mutations had an overall best response of stable disease lasting 8 weeks or more. The median PFS period in this group was 3.6 months (Gelmon et al 2011).

Based on the phase II results, two phase III trials of olaparib monotherapy in patients with *gBRCA* mutated breast cancer were initiated: OlympiA (D081CC00006; NCT02032823; 2013-003839-30) and OlympiAD (D0819C00003; NCT02000622; 2013-005137-20). The OlympiA trial is a 12-month, multicentre, double-blind randomised controlled trial (RCT) comparing olaparib 300 mg twice daily to a placebo as adjuvant treatment in patients with HER2-ve breast cancer at high risk of recurring. OlympiAD is a randomised, open-label multicentre study comparing olaparib 300 mg twice daily to the Investigator's choice of a standard-of-care chemotherapy in patients with metastatic HER2-ve breast cancer.

Rationale for the LUCY study

There are limited data to help support and inform the health-care decisions on the effectiveness, benefits and potential harms in the use of olaparib monotherapy treatment for patients with metastatic breast cancer associated with g*BRCA1/2* mutations. It is the current practice to use monotherapy cytotoxic agents, but there is no evidence to support one over another, and all are associated with only moderate outcomes. This has led to a wide variation in the natural history of this disease subtype and the standard of care treatments used across different regions and countries. This can lead to uncertainty for payers, providers and other stakeholders in terms of the number of patients who might be available for future treatments with a PARP inhibitor, whether the treatments used in regulatory studies are applicable locally and what the prognostic outlook might be for this patient population.

The present study (known as LUCY) is a phase IIIb, single-arm, open-label study designed to evaluate the clinical response to olaparib monotherapy in a real-world setting, as assessed by the prescribing Investigator, in patients with proven g*BRCA* mutations. Patients with s*BRCA* mutations are permitted to enrol in an exploratory cohort. This study will generate additional, phase IIIb data to support other olaparib studies, which may help inform and guide clinical practice.

Based on the prevalence of g*BRCA1/2* mutations, it is estimated that up to 1400 patients may require screening in order to identify 250 patients with g*BRCA* mutations and approximately 20 patients with s*BRCA* mutations. In contrast to oestrogen receptor and/or progesterone receptor positive breast cancer patients, it is anticipated that a significant proportion of patients with TNBC may already have their *BRCA1/2* status documented, especially in the USA; there will not be a requirement for a repeat g*BRCA1/2* genetic diagnostic test amongst this population.

The dose of olaparib used in this study is 300 mg twice daily which is expected to be the approved dose.

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 metastatic breast cancer associated with germline or somatic *BRCA1/2* mutations, for whom clinical activity can be expected based on the results of phase II studies in this population. Therefore, a positive benefit/risk profile is expected and no ethical issues are identified from exposing patients 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.

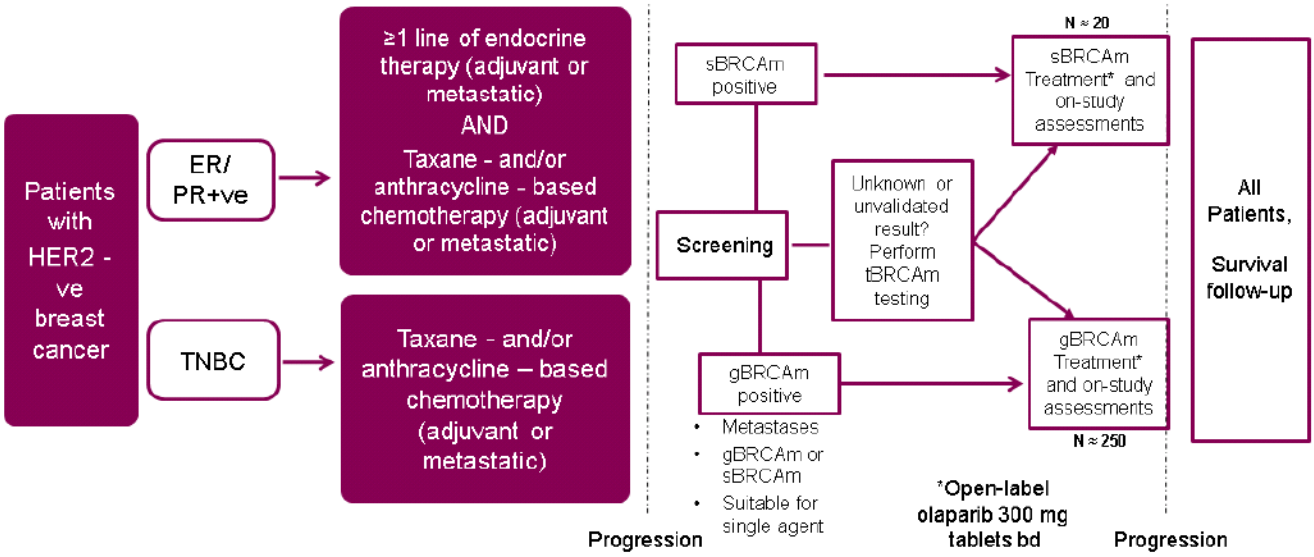
1.4 Study Design

This is a phase IIIb, open-label multicentre study to assess the clinical effectiveness of single-agent olaparib treatment in HER2-ve metastatic breast cancer patients with germline or somatic *BRCA1/2* mutations in a real-world setting. The target population is patients with HER2-ve metastatic breast cancer who have previously progressed after treatment with anthracycline- or taxane-based chemotherapy. All patients must have a confirmed genetic status for *BRCA1*, *BRCA2*.

Olaparib will be administered to all patients in this single-arm study (see Figure 1).

1.5 Study Governance and Oversight – Not Applicable

Figure 1 Study Flow Chart



*If patients discontinue olaparib treatment in the absence of progression, they should continue to be followed for progression as per the protocol schedule.

Abbreviations: +ve, positive; -ve, negative; bd, twice daily; *BRCAm*, *BRCA1/2* mutation; ER, oestrogen receptor; g*BRCA*m, germline *BRCA* mutation; PR, progesterone receptor; s*BRCA*m, somatic *BRCA* mutation; TNBC, triple negative breast cancer, t*BRCA*m, tumour *BRCA* mutation test

2. STUDY OBJECTIVES

2.1 Primary Objective

Primary Objective:	Outcome Measure:
To evaluate the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting through assessment of PFS in germline *BRCA* mutated patients	PFS, defined as the time from first dose of olaparib to the date of progression as determined by the Investigator (physician-defined progression) or death from any cause (in the absence of progression)

*physician-defined progression can be radiological (e.g. RECIST) progression, symptomatic progression, or clear progression of non-measurable disease, as long as progression can be documented.

2.2 Secondary Objectives

Secondary Objectives:	Outcome Measures:
To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of OS in germline *BRCA* mutated patients	OS, defined as the time from first dose of olaparib to the date of death from any cause
To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of time to use of subsequent therapies, second progression, and study treatment discontinuation in germline *BRCA* mutated patients	• Time to first subsequent treatment or death (TFST), defined as the time from first dose of olaparib to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment • Time to second subsequent treatment or death (TSST), defined as the time from first dose of olaparib to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment • Time to study treatment discontinuation or death (TDT), defined as the time from first dose of olaparib to study treatment discontinuation or death if this occurs before discontinuation of study treatment • Time to second progression or death (PFS2), defined as the time from first dose of olaparib to the earliest progression

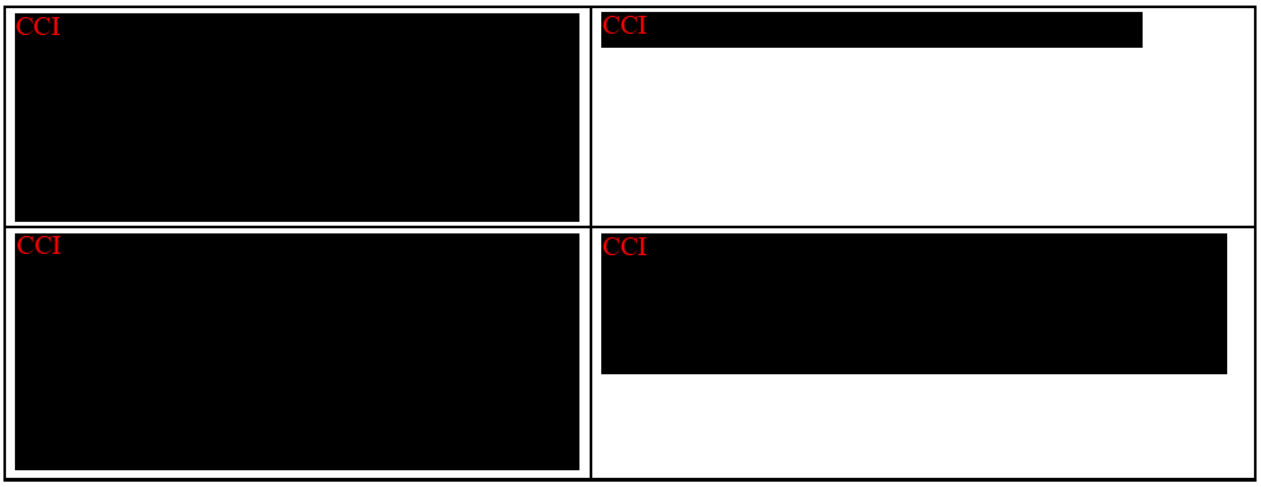
	event subsequent to that used for the primary variable PFS or death from any cause
To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of clinical response rate (CRR) and duration of clinical response (DoCR) in germline *BRCA* mutated patients	• CRR, defined as the proportion of patients assessed by the Investigator as responding (physician-defined response, radiological [e.g. RECIST] or symptomatic) • DoCR, defined as the time from the date the Investigator first assessed the patient as responding to the date the Investigator assessed the patient as progressing or the date of death from any cause (in the absence of progression)

2.3 Safety Objectives

Safety Objective:	**Outcome Measures:**
To evaluate the safety and tolerability of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting	AEs/serious adverse events (SAEs) Collection of clinical chemistry/haematology parameters

2.4 Exploratory Objectives

Exploratory Objectives:	**Outcome Measure:**
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]



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

Each patient must 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.

Patients who are being considered for this trial should be identified early so that the appropriate *BRCA1/2* mutation screening procedures can be put in place in a timely manner (see Section 4.1). Patients who do not know their *BRCA1/2* mutation status must first confirm all of the criteria marked with an asterisk (*) in Sections 3.1 and 3.2 prior to *BRCA1/2* mutation testing being carried out. After the *BRCA*1/2 mutation status is confirmed, all the inclusion and exclusion criteria, including the non-asterisk criteria, should now be addressed.

Prior to performing the *BRCA1/2* testing, an Investigator judgment of a patient's potential eligibility for the study should be made according to the timing and details of the screening tests within Table 1 and by reviewing the inclusion/exclusion criteria.

Where possible, g*BRCA* mutation testing will be conducted locally, unless it is confirmatory, based upon a positive tumour BRCA mutation assayed by Myriad, in which case it must be performed by Myriad.

3.1 Inclusion Criteria

All patients should fulfil the following criteria for inclusion in the study:

1. Provision of informed consent prior to any study specific procedures. For patients aged <20 years and screened in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.

2. Patients must be ≥18 years of age.

3. Histologically or cytologically confirmed HER2-ve breast cancer with evidence of metastatic disease. Patients can have either TNBC (defined as oestrogen receptor and progesterone receptor negative [immunohistochemistry nuclear staining <1%] and HER2-ve [immunohistochemistry 0, 1+ or 2+ and/or in situ hybridization non-amplified with ratio less than 2.0]) or oestrogen receptor / progesterone receptor positive breast cancer as long as they are HER2-ve.

4. Documented *BRCA1/2* status

   - To be regarded as *BRCA1/2* (+ve), the patient must have a mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental / lead to loss of function). Mutations that are not clearly pathogenic may be assessed by a committee of genetic specialists to adjudicate if the patient is eligible.

   - Patients with t*BRCA* mutations: must be confirmed by a validated method (e.g. results from a CLIA-certified laboratory or CE-IVD device)

5. Prior treatment with a taxane or an anthracycline in either an adjuvant (may include neoadjuvant) or metastatic breast cancer treatment setting

6. Patients should have received no more than two prior cytotoxic chemotherapy regimens in the metastatic setting. If a patient has oestrogen receptor and/or progesterone receptor positive HER2 negative metastatic breast cancer and has completed a prior line of hormonal treatment, then if the current or currently planned choice of treatment for the patient does not include a hormonal treatment then they would be a suitable patient to enter the study. Previous endocrine therapy could be in either an adjuvant or a metastatic setting and include endocrine therapy in combination with a targeted agent such as a CDK4/6 or mTOR inhibitor.

7. Be considered suitable, by the Investigator, for further treatment with single-agent chemotherapy for the metastatic disease

8. Patients must have normal organ and bone marrow function measured within 14 days prior to administration of study treatment as defined below:

   - Haemoglobin $\geq$ 10.0 g/dL with no blood transfusion in the past 28 days

   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L

   - Platelet count $\geq 100 \times 10^9$/L

   - Total bilirubin $\leq$ 1.5 x institutional upper limit of normal (ULN) unless the patient has documented Gilbert's Syndrome

- 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 ≤ 5x ULN

- Patients must have creatinine clearance (CrCl) estimated using the Cockcroft-Gault equation of ≥ 51 mL/min or 24 hour urine test may be done if standard of care:

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

[a] where F=0.85 for females and F=1 for males

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 (at least one criterion met):

    - amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments

    - luteinizing hormone and follicle stimulating hormone levels in the post-menopausal range for women under 50

    - radiation-induced oophorectomy with last menses >1 year ago

    - chemotherapy-induced menopause with >1 year interval since last menses

    - surgical sterilisation (bilateral oophorectomy or hysterectomy)

11. Women of childbearing potential, who are sexually active, must agree to the use of one highly effective form of contraception and their male partners must use a condom (as described in Appendix D) from the signing of the informed consent, throughout the period of taking study treatment and for at least 1 month after last dose of study drug, or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix D).

12. Male patients 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 patients should also use one highly effective form of contraception (see Appendix D for acceptable methods) if they are of childbearing potential.

13. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations for greater than 6 months

3.2 Exclusion Criteria

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

*Asterisk-marked criteria; refer to Section 3.

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. Exposure to an investigational product (IP) during the last 1 month or 5 half-lives (whichever is longer) prior to enrolment

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

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

6. 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.

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

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

10. *Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) 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.

    - Exception: Patients with adequately treated brain metastases documented by baseline CT or MRI scan that has not progressed since previous scans and that does not require corticosteroids (except ≤10 mg/day prednisone or equivalent for at least 14 continuous days prior to dosing) for management of CNS symptoms are eligible, provided that a repeat CT or MRI following the identification of CNS metastases (obtained at least 2 weeks after definitive therapy) must document adequately treated brain metastases.

13. Major surgery within 2 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. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high resolution computed tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

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

16. *Breastfeeding women

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

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)

20. Whole blood transfusions in the last 28 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criterion no. 8)

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

3.3 Patient Screening and Registration

Investigators should keep a record of the patient screening log, including 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 7-digit 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 his/her 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.

3.4 Procedures for Handling Incorrectly Enrolled Patients

Patients are considered enrolled once (1) it is confirmed that they meet all eligibility criteria (including *BRCA* mutation status) and (2) 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

It is prohibited to consume grapefruit juice while on olaparib therapy.

3.8.2 Contraception

Women of childbearing potential, who are sexually active, must agree to the use of one highly effective form of contraception and their male partners must use a condom (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, or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix D).

Male patients 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 patients should also use one highly effective form of contraception (as described in Appendix D) if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

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 (physician-defined progression can be radiological (e.g. RECIST) progression, symptomatic progression, or clear progression of non-measurable disease, as long as progression can be documented). Disease progression must be determined by RECIST 1.1 in s*BRCA*m patients.
- Unacceptable toxicity (patients can temporarily discontinue IP due to toxicity; IP can be re-started provided the disease has not progressed since discontinuation)
- AE
- 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 (or RECIST) 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

A patient who discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. The Principal Investigator/Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. They will also immediately inform AstraZeneca of the withdrawal. AEs will be followed up (See Section 6); 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), PFS2, OS, and subsequent therapies, 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 is based on the Investigator's assessment which could be radiological (e.g. RECIST) progression, symptomatic progression, or clear progression of non-measurable disease as long as progression can be documented. RECIST 1.1 must be used to determine tumour progression in s*BRCA*m patients. After discontinuation of study medication, the Principal Investigator/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the electronic case report form (eCRF) the date of discontinuation, the reasons, manifestation (e.g. if related to an AE, clinical manifestation of symptoms) and treatment at the time of discontinuation. If patients discontinue study treatment, the AstraZeneca monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Section 6.3.2). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to 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 up to the final analysis.

If a patient is withdrawn from the study, see Section 3.11.

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.
- Patient lost to follow up. (see Section 3.10.2)
- 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 a trial; this reason for study withdrawal is only valid for not enrolled patients).

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 7-digit IVRS unique 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:

- to further participation in the study including any further follow up (e.g., survival calls)
- withdrawal of consent to the use of their study generated data

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.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 3.11), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

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(s) is shown in Table 1. Please note the details of the screening visit(s) are dependent upon patient's *BRCA1/2* mutation status (known or unknown).

On-study assessments are shown in Table 2.

Table 1 Study Schedule – Screening (Visit 1; may be separate visits depending on *BRCA*1/2 testing)

Day	Visit 1a [c] Within 30* days of first dose	Visit 1b [c] Day -28 to -1
Informed consent	X	
Optional informed consent for additional exploratory research [j]	X	
IVRS/IWRS unique patient number obtained	X	
Known HER2, ER, PR result	X	
Demographics [a]	X	
Menopausal status	X	(X)
Medical and surgical history	X	(X)
Prior cancer therapies including radiotherapy, best response to prior chemotherapy regimen	X	(X)
History of blood transfusions [b]	X	(X)
Inclusion/exclusion criteria [c]	X	X
Patients with unknown *BRCAm* or *sBRCAm* result from an unaccredited lab: Blood (mandatory) and tumour tissue sample (optional) for *BRCA* testing [d]	X	(X)
Smoking status		X
Family history of any malignancies		X
Family history of hereditary *BRCA* syndrome with specification of type of germline *BRCA1/2* mutation if information is available		X
Physical examination		X
Vital signs (includes blood pressure, pulse and temperature), body weight		X
Haematology [e]		X [d]
Clinical chemistry / coagulation [f]		X [e]
Urinalysis [f]		X [e]
ECG [f,i]		X [e]
Pregnancy test for women of childbearing potential [g]		X
Patients with unknown *BRCA*m or s*BRCA*m: MRI/CT tumour assessment [h]		X

Day	Visit 1a [c] Within 30* days of first dose	Visit 1b [c] Day -28 to -1
AEs (from time of consent)		X
Concomitant medications	X	(X)

a Include date of birth (or, month and/or year of birth per local regulations), race/ethnicity per local regulations, education.

b Include history of blood transfusion within previous 28 days from start of study treatment and the reasons, e.g., bleeding or myelosuppression.

c Patients who are being considered for this trial should be identified early so that the appropriate *BRCA*1/2 mutation screening procedures can be put in place in a timely manner (see Section 4.1). Patients who do not know their *BRCA*1/2 mutation status must first confirm all of the criteria marked with an asterisk (*) in Sections 3.1 and 3.2 prior to *BRCA*1/2 mutation testing being carried out. After the *BRCA*1/2 mutation status is confirmed, all the inclusion and exclusion criteria, including the non-asterisk criteria, should now be addressed.

d Refer to Section 4.1 and subsections for *BRCAm* testing process. Patients must have a known deleterious or suspected deleterious *BRCA1/2* mutation to be enrolled into the study. Patients for whom their *gBRCA* status is already known should be consented to the study within 28 days prior to Day 1 of study treatment (see Section 4.1.2). Patients who do not know their mutation status will need *BRCA1/2* mutation screening (see Section 4.1.3). Please refer to the listed protocol sections for details on sample collection for each scenario.

e Haematology should be performed within 14 days of first dose, unless there is a known likelihood of the patient being at risk of anaemia (such as recent exposure within 3 weeks of chemotherapy from an earlier line of chemotherapy, or comorbidity) or other clinical need, per Investigator judgment. In the latter cases, haematology should be performed within 7 days of first dose. For a list of all required laboratory tests please refer to Section 5.2.1.

f Should be performed within 14 days of first dose, then as clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.1.

g 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. Details of the pregnancy tests must be recorded in the patient's medical records.

h Baseline RECIST for all eligible patients unless they are known *gBRCA*m positive Prior tumour assessment within 6 weeks is acceptable. Ideally, it should be performed as close as possible to the start of study treatment. Collect number and sites of metastases. Note, in the absence of a baseline scan then by protocol no RECIST diagnosis will be possible and radiological progression can only be defined as 'new metastasis'.

i Twelve-lead resting ECG should be performed.

j Once the details are decided, AstraZeneca will provide this optional consent form. The optional informed consent will allow patients the option of choosing whether or not to allow their *BRCA* mutation result to be collected within a database for potential use in future research. The actual research (not yet determined) will be done through a separate protocol from the LUCY protocol.

(X) Some tests may need to be redone to confirm no changes since visit 1a.

(*) Since it is anticipated results of *BRCA*m test may take longer than 2 weeks, the window for Visit 1a may be extended and performed within 60 days of first dose, at the discretion of the Investigator.

Table 2 Study Plan Detailing the Procedures

Visit Number	**2**	**3**	**Visit no. 4 onwards (subsequent on-treatment visits): [a] Visits to occur every 4 weeks up to week 12, then every 6 weeks up to week 48, and then every 12 weeks thereafter.**	**Study treatment discontinued**	**Follow up 30 days after last dose of study medication**	**Long-term follow up**	**Post-DCO**
Day	1	29	On the first day of next visit period (V4=Day 57; V5=Day 85; etc.)				
Visit Window	**0**	**±3d**	**±3d until 12 months/ ±7d after**	**+7d**	**+7d**		
Physical examination [b]	X [c]						
Vital signs, body weight (includes blood pressure, pulse and temperature) [b]	X [c]						
ECOG performance status [b]	X			X			
Haematology	X [d]	X	X	X	X		
Clinical chemistry [b]	X [c]			X	X		
Pregnancy test [e]	X	X	X [Pregnancy testing for women of childbearing potential should be conducted at regular intervals, e.g., monthly, but ideally aligned with the onsite visit schedule – to be determined by the Study Physician]		X		
Tumour assessment [f]		X	X [f]	X		X [f]	
AEs [g]	X	X	X	X	X		X [k]

Visit Number	**2**	**3**	**Visit no. 4 onwards (subsequent on-treatment visits): [a] Visits to occur every 4 weeks up to week 12, then every 6 weeks up to week 48, and then every 12 weeks thereafter.**	**Study treatment discontinued**	**Follow up 30 days after last dose of study medication**	**Long-term follow up**	**Post-DCO**
Day	1	29	On the first day of next visit period (V4=Day 57; V5=Day 85; etc.)				
Visit Window	**0**	**±3d**	**±3d until 12 months/ ±7d after**	**+7d**	**+7d**		
Concomitant medications including blood transfusions	X	X	X	X	X		
Olaparib dispensed/returned & IVRS dispensing call	X	X [h]	X [h]	X			
Patient IP compliance/Patient diary review		X [h]	X [h]	X			
Subsequent anticancer therapy(ies) following discontinuation of study treatment [i]					X	X	
Survival [j]						X	X [k]
Second progression						X	
Patients with stable brain metastases: MRI/CT [f]			Monitor per SOC and at week 24 (or progression, if earlier)				

[a] From Visit 4 onwards: Visits to occur every 4 weeks up to week 12, then every 6 weeks up to week 48, and then every 12 weeks thereafter.as long as the patient has not progressed and is still on treatment. Visits are relative to the date of the first olaparib dose.

[b] To be additionally performed if clinically indicated at any other time in alignment with standard of care.

[c] If assessed within 14 days before the first dose and meets the stated eligibility criteria (if applicable), it does not need to be repeated on Day 1 of study treatment, unless the Investigator believes that it is likely to have changed significantly. For a list of all required laboratory tests please refer to Section 5.2.1.

[d] If assessed within 14 days before the first dose and meets the stated eligibility criteria (if applicable), it does not need to be repeated on Day 1 of study treatment, unless the Investigator believes that it is likely to have changed significantly. 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. Details of the pregnancy tests must be recorded in the patient's medical records.

[f] Tumour assessment should be performed as per local practice at each patient visit. Tumour assessments are defined at a minimum as being clinical assessments as done in accordance with local practice, with documentation of the results on the eCRF, until documented disease progression. For g*BRCA*m patients, disease progression can be per Investigator (physician-defined, which can be radiological (e.g. RECIST) progression, symptomatic progression, or clear progression of non-measurable disease, as long as the progression is documented; RECIST 1.1 must be used to determine disease progression in s*BRCA*m patients. Long term follow up after first progression, assessments should be conducted in accordance with local practice and standard of care. Note, in the absence of a baseline scan then by protocol no RECIST diagnosis will be possible and radiological progression can only be defined as 'new metastasis'. Patients enrolled with stable brain metastases will have a scan at week 24 or at progression (whichever is earlier).

[g] 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.

[h] There is a ± 3 day 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 in accordance with local practice. Perform IP compliance review at each visit with drug dispensing.

[i] All anticancer treatments (including, but not limited to, chemotherapy and targeted agents), start and stop dates need to be recorded.

[j] During the long-term follow up period, patients should continue to be followed up for survival in accordance with local practice in alignment with standard of care.

[k] Patients who have completed treatment will be followed up until the survival sweep following the DCO. Patients for whom treatment with olaparib is ongoing at the time of DCO, and who would like to continue to receive study treatment, will be able to continue receiving olaparib as part of the roll-over ROSY-O study if, in the opinion of the Investigator, they are continuing to receive benefit from study treatment. Only safety and survival data will be collected post DCO and until ROSY-O roll over.

4.1 Screening/Enrolment Period

At screening, consenting patients are assessed to ensure that they meet eligibility criteria listed in Section 3. Patients who do not meet these criteria must not be enrolled in the study.

All screening assessments listed in Table 1 must be performed. Wherever possible, all screening assessments should be performed on the same date/same visit. The timing and number of screening visits will depend on whether or not the patient's *BRCA 1/2* mutation status is known at the Screening visit. It is anticipated that Visit 1a will be conducted within 30 days prior to first dose; however, it is anticipated *BRCA*m testing may take longer than 2 weeks so, up to 60 days prior to first dose is permitted at the discretion of the Investigator if they feel the timing would not adversely affect their patient's care.

Perform the tests in Table 1 under Visit 1a (can be confirmed per local practice as standard of care) prior to any *BRCA*1/2 test. These tests should confirm all of the criteria marked with an asterisk (*) in Sections 3.1 and 3.2.

To be regarded as *BRCA1/2* (+ve), the patient must have a mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental / lead to loss of function. Patients with *BRCA1* and/or *BRCA2* mutations that are considered to be non-detrimental (e.g., "variants of uncertain clinical significance" or "variant of unknown significance" or "variant, favour polymorphism" or "benign polymorphism," etc.) may be reviewed by a diagnostics committee to determine whether or not the patient is eligible for the study.

4.1.1 BRCAm testing for known gBRCAm positive patients

If the patient has a known positive *gBRCAm*, no retesting is needed. No blood or tumour tissue sample is needed.

4.1.2 BRCAm testing for known sBRCAm positive patients

If the patient has a known positive s*BRCA*m:

- If the s*BRCA*m testing was done by a validated method (e.g. results from a CLIA-certified laboratory or CE-IVD device), no retesting is needed.
- If s*BRCA*m testing was done in an unaccredited laboratory, then blood sample and tumour sample (if consented) will be sent to Myriad for testing.

After the *BRCA*1/2 mutation status is confirmed, all the inclusion and exclusion criteria, including the non-asterisk criteria, should now be addressed.

4.1.3 BRCAm testing for patients with unknown BRCA1/2 status

In the absence of a known *BRCA* mutation, blood (mandatory) and tumour sample (optional) will be collected:

- Where a tumour sample is available (and consented to), this sample should be sent to Myriad for t*BRCA*m testing first. If a tumour sample cannot be obtained and shipped **within 10 days,** the Investigator may proceed with sending the blood sample for g*BRCA*m testing, to mitigate the risk of delaying trial entry for a potentially positive g*BRCA*m patient. In this case, g*BRCA*m test may be performed locally.

- Positive t*BRCA*m results would enable trial entry and dosing for that patient. This will be followed by a confirmatory g*BRCA*m test performed by Myriad. To ensure a high quality g*BRCA* sample is sent for testing, this sample should be taken once a positive t*BRCA*m result is obtained, i.e. Visit 1b or Visit 2. Test result must be known prior to the next scheduled tumour assessment for s*BRCA*m patients (Visit 3). As long as a patient has positive t*BRCA*m result they may receive their first dose of olaparib without delay even as they are awaiting confirmatory test results.

After the *BRCA*1/2 mutation status is confirmed, all the inclusion and exclusion criteria, including the non-asterisk criteria, should now be addressed.

4.2 Treatment Period

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

4.2.1 Visits 2 and 3 inclusive

These visits will take place in the first 4 weeks (29 days) of treatment.

Excluding Visit 2 (Day 1), study procedures will be conducted on the scheduled day ± 3 days (unless otherwise specified) and there will be a ± 3-day visit window allowed for dispensing olaparib tablets.

4.2.2 Visit 4 and subsequent on-treatment visits

After the first 29 days, visits to occur every 4 weeks up to week 12, then every 6 weeks up to week 48, and then every 12 weeks thereafter, as long as the patient has not progressed and is still on treatment. Visits are relative to the date of the first olaparib dose treatment.

Study procedures will be conducted on the scheduled day ± 3 days up to week 48, then ± 7 days thereafter. The same windows are allowed for dispensing olaparib tablets.

4.2.3 Study treatment discontinued

If the patient discontinues study treatment for any reason (see Section 3.9), unused study treatment should be returned and study procedures should be conducted within 7 days of treatment discontinuation as shown in Table 2.

4.3 Follow up Period

All subsequent anticancer treatments after discontinuation of study treatment need to be recorded (including, but not limited to, chemotherapy and targeted agents); start and stop dates; and the date of progression must also be recorded.

4.3.1 Follow up 30 days after last dose of study medication

Study procedures should be conducted 30 days after last dose of study medication (+ 7 days), 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 include recording subsequent anticancer therapy(ies), tumour progression and survival calls. Long-term assessments to second progression and beyond to be done as per local practice and in alignment with standard of care.

Patients who discontinue study treatment in the absence of disease progression should continue to be followed for progression, after treatment discontinuation, as per local practice and standard of care.

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 electronic CRFs 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 (or applicable information, in Japan). The Investigator will sign the completed electronic CRFs. 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 electronic CRFs provided by AstraZeneca. 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 local practice at each patient visit per Table 2. Tumour assessments are defined at a minimum as being clinical assessments as done in accordance with local practice, with documentation of the results on the eCRF.

Tumour assessments are performed up to the first physician-defined disease progression for g*BRCA*m patients, or RECIST-defined disease progression for s*BRCA*m patients, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

Physician-defined progression can be radiological (e.g. RECIST) progression, symptomatic progression, or clear progression of non-measurable disease, as long as progression can be documented. Note, in the absence of a baseline scan then by protocol no RECIST diagnosis will be possible and radiological progression can only be defined as 'new metastasis'. For s*BRCA*m patients, tumour progression must be determined by RECIST 1.1.

After first progression, tumour assessments should be performed in accordance with local practice and standard of care.

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.

Haematology should be performed within 14 days of first dose, unless there is a known likelihood of the patient being at risk of anaemia (such as recent exposure within 3 weeks of chemotherapy from an earlier line of chemotherapy, or comorbidity) or other clinical need, per Investigator judgment. In the latter cases, haematology should be performed within 7 days of first dose.

Haematology does not need to be repeated on Day 1 of study treatment if assessed within 14 days before starting study treatment, unless the Investigator believes that it is likely to have changed significantly. After Day 1, it should be performed every 4 weeks up to week 12, then every 6 weeks up to week 48, and then every 12 weeks thereafter per the schedule in Table 2, as long as the patient has not progressed and is still on treatment.

Clinical chemistry, urinalysis and coagulation should be performed within 14 days before starting study treatment.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

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)	Urinalysis (dipstick)
B-Haemoglobin (Hb)	S/P-Creatinine	U-Hb/ Erythrocytes/Blood
B-Leukocyte count	S/P-Bilirubin, total	U-Protein/Albumin
B-Absolute neutrophil count	S/P-Alkaline phosphatase (ALP)	U-Glucose
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	
	S/P-Sodium	
	S/P-Urea or Blood Urea Nitrogen (BUN)	
	S/P-Total Protein	

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 at screening and 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

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as part of standard of care, defined in Section 6.8.1.

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

5.2.2 Physical examination and ECOG performance status

Physical exam is performed at screening and baseline. ECOG PS is performed at baseline (ECOG scale, refer to Appendix E). Tests may be repeated at any other time as clinically indicated in alignment with standard of care.

5.2.3 ECG

5.2.3.1 Resting 12-lead electrocardiogram

ECGs will be assessed at screening and as clinically indicated in alignment with standard of care.

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

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

5.2.4 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 in alignment with standard of care.

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.

5.2.4.1 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 in alignment with standard of care.

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.

5.2.4.2 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) in alignment with standard of care.

The date of collection and measurement will be recorded on the appropriate eCRF.

5.2.5 Other safety assessments

5.2.5.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for 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. Details of the pregnancy tests must be recorded in the patient's medical records.

5.3 Other Assessments – Not Applicable

5.4 Pharmacokinetics – Not Applicable

5.5 Pharmacodynamics – Not Applicable

5.6 Samples for *BRCA* testing

Patients with unknown *BRCAm*, or whose *sBRCAm* result is from an unaccredited laboratory, will provide a mandatory blood sample at screening. The collection of tumour sample is optional. The tumour sample may be a historical tumour tissue paraffin block from resection or a core biopsy from the primary tumour or metastases. The portion of tumour within the block should be 20% at a minimum. This sample will have been collected at diagnosis but prior to study entry. Alternatively, sections mounted on glass slides prepared from the block can be provided.

Please refer to the laboratory manual for further details of the collection, shipping and storage of the blood sample and optional tumour sample for *BRCAm* testing.

5.7 Exploratory Biomarker Analysis

CCI

CCI [redacted]

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

Medical management of patients 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

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

A questionnaire will be sent to any Investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESI 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 case 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 arm. Investigators will be asked during the regular follow up for OS if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the IP, 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 collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome
- 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 $\geq$ 3 x ULN together with total bilirubin $\geq$ 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 New cancers

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

6.3.10 Lack of efficacy

When there is deterioration in the cancer, for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless 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.

6.3.11 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post study follow up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

- Deaths with an unknown cause should always be reported as a SAE. A post-mortem 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 telephone. 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 for:

- If 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.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.

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.

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

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:** Give appropriate supportive treatment and investigate causality. Investigator judgment to continue study treatment with supportive treatment (e.g., transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dL. **Subsequent occurrences:** If Hb**< 10 *but* ≥ 9 g/dL** investigator judgement to continue study treatment with supportive treatment (e.g. transfusion) *or* dose interrupt (for maximum 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). If Hb**< 9 *but* ≥ 8 g/dL**, dose interrupt (for maximum 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. Interrupt study treatment for a maximum of 4 weeks until improved to Hb ≥ 9 g/dL. 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 judgment 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 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 $< 50 \times 10^9$/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 study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of

treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic 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

In the case of co-administration with CYP3A inhibitors, refer to Section 7.7.

6.8.2.4 Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test 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 (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

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 on Day 1 and then at each visit per 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.

When dose reduction is necessary (see below, Section 6.8 and Section 7.7), patients will take one 150 mg tablet and one 100 mg tablet (250 mg twice daily), or two 100 mg tablets (200 mg twice daily).

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 (can be radiological [e.g. RECIST] progression, symptomatic progression, or clear progression of non-measurable disease, as long as progression can be documented) or unacceptable toxicity or for as long as they do not meet any other discontinuation criteria. RECIST 1.1 must be used to determine disease progression in s*BRCA*m patients.

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

For guidance on dose reductions for management of AEs (including renal impairment) refer to Section 6.8.2.4.

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 7-digit IVRS unique 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, and overdoses, 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.

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

It is the Investigator/institution's responsibility to establish a system for handling study treatments, including IPs, so as to ensure that:

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

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

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the Investigator. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist, and copies retained in the Investigator site file. Dispensing and accountability records will continue to be collected for as long as patients continue to receive study treatment, although they will not be entered on the database after the database has closed. Study site personnel, if applicable, and the AstraZeneca or 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.

Sites may destroy unused IP locally per institutional practices.

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

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

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.

Medications that may NOT be administered

Table 7 Prohibited medications

Prohibited medication/class of drug:	
Anticancer therapy: Chemotherapy Immunotherapy Hormonal therapy* Radiotherapy (except palliative) Biological therapy Other novel agents	Not permitted while the patient is receiving study medication
Live virus vaccines Live bacterial vaccines	Not permitted while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

*Hormone Replacement Therapy (HRT) is acceptable

Restricted concomitant medications

Table 8 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
(a) Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of *olaparib* to 100 mg 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 inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib.
Moderate CYP3A inducers: bosentan, efavirenz and modafinil	If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy olaparib.

Table 8 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1 substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
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.

Table 8 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before the study and they were started at least 2 weeks prior to beginning study treatment.

Subsequent therapies for cancer

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

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

Patients may still continue to receive olaparib after progression if the investigator feels the patient is still deriving clinical benefit.

The provision of study drug at study completion may include, but is not be limited to, transition to a roll-over study (ROSY-O), continuous supply within this trial (e.g., in countries where regulatory approval is not obtained for a roll-over study) or switching to commercial drug as permitted by local regulations.

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 of this study is PFS. The statistical analyses will be performed at a minimum of two time points:

- The first when approximately 160 germline *BRCA* mutated patients have had a PFS event
- The second after approximately 130 germline *BRCA* mutated patients have died, at which point the PFS analysis will be updated

The somatic *BRCA* mutated patient cohort will also be assessed at these time points.

If germline *BRCA* mutated patients are recruited over 12 months, it is estimated that 160 PFS events will have occurred by 19 months after the first germline *BRCA* mutated patient is entered; this is assuming exponentially distributed PFS data with a median of 7 months and a recruitment function that assumes 25% of the germline *BRCA* mutated patients are recruited after 6 months. It is also estimated that approximately 130 OS events will have occurred at 28 months if the median OS is 19 months.

Recruitment of 250 germline *BRCA* mutated patients will provide a sufficiently precise estimate of median PFS. If the median PFS observed is 7 months and analysed after 160 events, the 95% confidence interval (CI) for the median would be predicted to extend from 6.0 to 8.2 months (based on the formula of Collett). Similarly, at the OS follow up analysis, if the median OS observed is 19 months and data are analysed after 130 events, the 95% CI for the median would be predicted to extend from 16.0 to 22.6 months.

8.3 Definitions of Analysis Sets

The full analysis set will include all patients who receive at least one dose of olaparib. The full analysis set will be used for all efficacy and safety analyses.

Data from the germline and somatic *BRCA* mutated patient cohorts will be presented separately and combined.

8.4 Outcome Measures for Analyses

8.4.1 Calculation or derivation of efficacy variables

Progression-free survival (PFS)

In this study, disease progression in g*BRCA*m patients will be based on Investigator assessment, i.e. radiological (e.g. RECIST) progression, symptomatic progression, or clear progression of non-measurable disease, as long as progression can be documented; disease progression in s*BRCA*m patients must be determined by RECIST 1.1. PFS is defined as the time from the date of the first dose of olaparib until the date of disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. The CRFs will capture

each time a patient is assessed for progression regardless of the outcome of the assessment. 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. If the patient has no evaluable visits they will be censored at 1 day.

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

Clinical response rate (CRR)

Response in g*BRCA*m patients will be based on the Investigator's assessment; response in s*BRCA*m patients must be based on RECIST 1.1. The CRR is defined as the proportion of patients with at least one visit in which the Investigator assessed the patient as responding. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of CRR. However, any responses, which occurred after a further anticancer therapy was received, will not be included in the numerator for the CRR calculation.

Duration of clinical response (DoCR)

CCI

[redacted]

CCI

[redacted]

Overall survival (OS)

OS will be 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.

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

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 second subsequent treatment or death (TSST)

TSST is defined as the time from the date of the first dose olaparib to the earliest of the date of death or commencement of the second subsequent anticancer treatment. Patients who are alive and have not been recorded as taking two subsequent anticancer treatments 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 their treatment was recorded as being administered.

Time to second progression or death (PFS2)

PFS2 is defined as the time from the date of the first dose olaparib to the earliest of the date of death or the progression event subsequent to that used for the primary variable PFS. Patients alive and for whom a second disease progression has not been observed will be censored at the last time known to be alive and without a second disease progression.

Disease control rate (DCR) at week 24:

Among the subset of patients with brain metastases at baseline, DCR is defined as no evidence of progression at or prior to week 24 as assessed by an MRI or CT scan.

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 judgment, 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.

Nausea and vomiting

Rates and severity of nausea/vomiting will be summarised over time and also according to whether the patient received antiemetic therapy taking into account the severity of nausea/vomiting at the time of administration.

8.5 Methods for Statistical Analyses

Data will be summarised using descriptive statistics as appropriate. Continuous variables will be summarised by the number of observations (n), mean, standard deviation, median, quartiles, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. The precision of estimates will be presented using a 95% CI when appropriate.

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 survival curve and estimates of median survival and associated 95% CI. In addition, progression rates and 95% CIs at clinically important landmarks (such as 1 year) 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".

Subgroup analysis

The primary endpoint will be summarised according to important clinical characteristics, which will include:

- Line of therapy
- Prior exposure to platinum-containing therapy

- Hormone status and other important patient and disease characteristics, as described in the SAP

8.5.2 Analysis of the secondary variables

Time-to-event endpoints

OS, DoCR, TFST, TSST, TDT and PFS2 will be summarised using a KM plot to estimate the median and event rates from clinically important landmarks such as 1 and 2 years. Subgroup analyses may also be performed on the secondary variables if appropriate.

Clinical response rate (CRR)

CRR will be summarised as the proportion of patients assessed by the Investigator as having a response using the number of patients exposed to olaparib as the denominator. Exact binomial CIs will be calculated.

Disease control rate (DCR)

CCI [redacted]

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 (if applicable) 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 Direct access to source data in Japan

The Head of the study site and the Principal Investigator/ Investigator will cooperate for monitoring and audit by AstraZeneca, and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the CRFs against source data before the Principal Investigator signs the CRFs to ensure accuracy and completeness of documentation, and assure that the Principal Investigator has submitted the CRFs to AstraZeneca. If the Investigator wishes to amend the collected CRFs, the monitor will ensure that the Principal Investigator has recorded the amendment with signature and date and provided this to AstraZeneca.

9.2.3 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 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.

9.2.4 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.

9.2.5 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 the 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

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

Data observed after final DCO will not feature in the final clinical study report (CSR) except those data from the survival sweep and for end of treatment/study. After the final DCO patients who have completed study treatment will no longer be required to have follow-up visits and patients ongoing on study treatment will be treated as per standard of care. Patients for whom treatment with olaparib is ongoing at the time of DCO, and who would like to continue to receive study treatment, will be given the option to continue receiving olaparib as part of the roll over to ROSY-O study if in the opinion of the Investigator, they are continuing to receive benefit from study treatment.

. For patients who do continue to receive treatment beyond the time of this DCO, Investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after study treatment is discontinued, in accordance with Section 6.4 (Reporting of Serious AEs). If an Investigator learns of any AEs or SAEs, including death, at any time after the DCO until the end of the study, and he/she considers there is a reasonable possibility that the event is causally related to the study treatment, the Investigator should notify AstraZeneca, Patient Safety. Additionally as stated in Section 6.3 (Recording of AEs), any SAE or non-serious AE that is ongoing at the time of this DCO, must be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve, or the patient is lost to follow-up.

The study is expected to start in Q1 2018 and to end by Q2/Q3 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.

When all data have been coded, validated, signed and locked, a clean file will be declared and the database will be locked.

Serious Adverse Event Reconciliation

SAE reconciliation reports are produced and reconciled with the AstraZeneca Patient Safety database.

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.

The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

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 7-digit IVRS unique code.

10.3 Ethics and Regulatory Review

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 screening of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, 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.

Japan only:

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 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 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.

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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 judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, 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 judgment 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 subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix 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.

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) $\geq$ 3 x upper limit of normal (ULN) **together with** total bilirubin (TBL) $\geq$ 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 $\geq$ 3 x ULN **together with** TBL $\geq$ 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 $\geq$ 3 x ULN

- AST ≥ 3 x ULN
- TBL ≥ 2 x ULN

When a patient meets any of the identification criteria, in isolation or in combination, the local laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

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

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the local laboratory
- Complete the appropriate unscheduled laboratory 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 who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

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

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, who are sexually active, must agree to the use of one highly effective form of contraception and their male partner must use a condom (as listed below). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Male patients 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 patients should also use one highly effective form of contraception if they are of childbearing potential (as listed below). Male patients 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:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month (for female patients) or at least 3 months (for male patients), after the last dose of study treatment. 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 (provided coils are copper-banded) PLUS male condom.

Acceptable hormonal methods:

- Mini pill PLUS male condom: Progesterone-based oral contraceptive pill using desogestrel. Cerazette® (Merck Sharp & Dohme) is currently the only highly efficacious progesterone-based pill available.
- Combined pill PLUS male condom: Normal and low-dose combined oral pills.
- Injection PLUS male condom: Medroxyprogesterone injection (e.g., Depo-Provera® [Pfizer]).
- Implants PLUS male condom: Etonogestrel-releasing implants (e.g., Nexplanon® [Merck Sharp & Dohme]).

- Patch PLUS male condom: Norelgestromin/ethinyl estradiol transdermal system (e.g., Xulane®).

- Intravaginal device (e.g., ethinyl estradiol-/etonogestrel-releasing intravaginal devices such as NuvaRing® [Merck Sharp & Dohme]) PLUS male condom.

- Levonorgestrel-releasing intrauterine system (e.g., Mirena® [Bayer]) 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 Signatures

AstraZeneca Representative

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