**Revised Clinical Study Protocol**

Drug Substance: Olaparib

Study Code: D0819C00003

[redacted]

# A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to assess the efficacy and safety of Olaparib Monotherapy versus Physician's Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients with germline *BRCA1/2* Mutations

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

[redacted]



**The following Amendment(s) and Administrative Changes are included in this revised protocol:**

| Amendment No. | Date of Amendment | Local Amendment No. | Date of local Amendment |
|---|---|---|---|
| [redacted] | | | |

| Administrative change No. | Date of Administrative Change | Local Administrative change No. | Date of local Administrative Change |
|---|---|---|---|
| [redacted] | | | |

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# PROTOCOL SYNOPSIS

## A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to assess the efficacy and safety of Olaparib Monotherapy versus Physician's Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients with germline *BRCA1/2* Mutations


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**Study location and number of patients planned**

The study will be conducted globally, and approximately 310 patients will be randomised to the study.

For the Pharmacokinetic (PK) part of the study, approximately 50 patients randomised to olaparib, at those sites that have confirmed that they are able to take the PK assessment samples.

| Study period | | Phase of development |
|---|---|---|
| Estimated date of first patient enrolled | [redacted] | III |
| Estimated date of last patient completed | [redacted] | |

**Objectives**

**Primary Objective**

To determine the efficacy of single agent olaparib vs physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by progression-free survival (PFS) using blinded independent central review (BICR) data assessed by Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

## Safety Objective

To assess the safety and tolerability of single agent olaparib vs physician's choice chemotherapy (capecitabine, vinorelbine or eribulin)

## Secondary Objectives

1. To compare the efficacy of single agent olaparib versus physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by assessment of overall survival, time to second progression or death (PFS2) and objective response rate (ORR) using BICR data assessed by RECIST 1.1.

2. To assess the effect of olaparib on the Health-related Quality of Life (HRQoL) as measured by EORTC QLQ-C30 global QoL scale.

3. To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future *BRCA* mutation assays (gene sequencing and large rearrangement analysis).

4. To determine the exposure to olaparib in patients receiving olaparib monotherapy

## Exploratory Objectives

The exploratory objectives of this study are:

1. To explore the impact of olaparib on symptoms and HRQoL as measured by the EORTC QLQ-C30 disease related multi-item symptom and functional scales.

2. To explore patients' treatment satisfaction (as measured by the Satisfaction with Therapy scale of the CTSQ and the other sub-scales and items of the CTSQ) on Olaparib, compared to physician's choice chemotherapy

3. To investigate the health economic impact of treatment and the disease on hospital related resource use.

4. To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents

5. To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour (mandatory if available), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional).

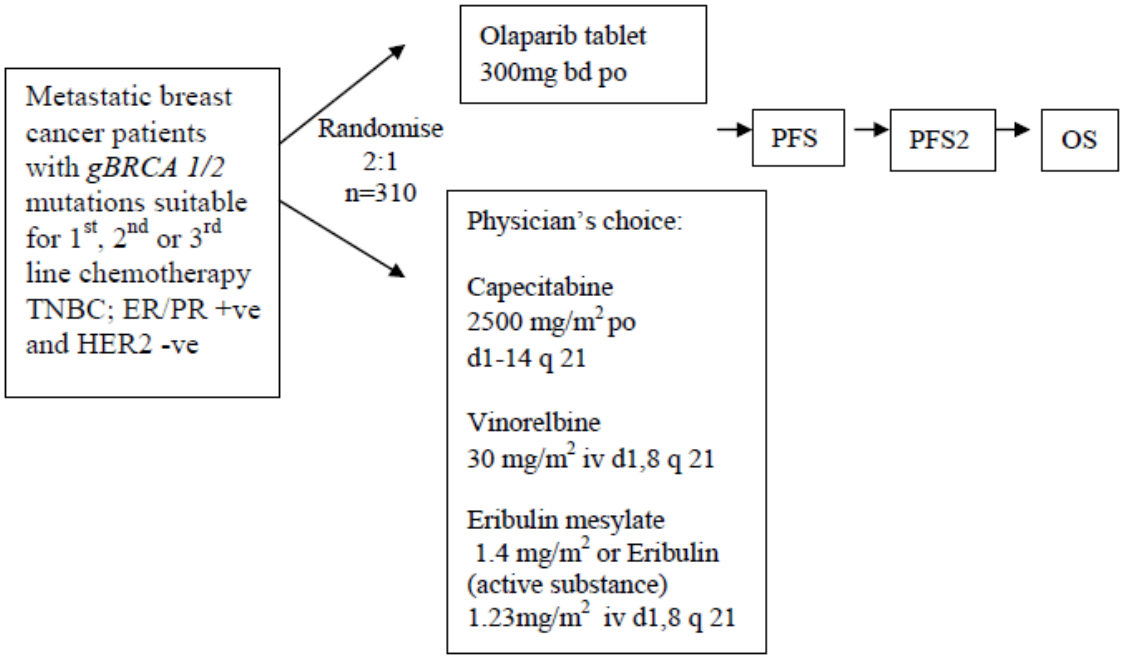
6. To determine the frequency of and describe the nature of *BRCA* mutation/s in tumour samples and to compare this with germline *BRCA* mutation status.

7. Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (mandatory if available), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional).

8. To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional).

The exploratory analyses may not be reported in the main clinical study report (CSR). If not, they will be reported separately.

**Study design**




This open label, randomised, controlled, multi-centre phase III study will assess the efficacy and safety of single agent olaparib vs standard of care based on physician's choice of capecitabine, vinorelbine or eribulin in metastatic breast cancer patients with *gBRCA 1/2* mutations. Due to different routes and schedules of administration of the treatment options on the control arm as well as their different toxicity profiles, the study cannot be blinded. Given the open label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with a primary analysis of PFS based on blinded independent central review (BICR) of all patient scans. Secondary endpoints will

include overall survival, ORR based on BICR, PFS2 (defined as objective radiological or symptomatic progression or death), safety assessments and health related quality of life.

Approximately 310 patients will be randomised 2:1 (olaparib:chemotherapy) into the trial. The treatment groups include olaparib 300 mg po bid daily tablet continuous, or physician's choice of chemotherapy. The investigator must declare prior to randomisation their choice of chemotherapy i.e. capecitabine or vinorelbine or eribulin.

The randomisation scheme will be stratified based on:

- Received prior chemotherapy regimens for metastatic breast cancer (yes/no)
- ER and/or PgR positive vs ER and PgR negative
- Prior platinum for breast cancer (yes/no)

**Target patient population**

All patients randomised in the study will be selected based on the following 3 principles:

- **Genetic selection**: Documented germline mutation in *BRCA*1 or *BRCA*2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Patients with *BRCA*1 and/or *BRCA*2 mutations that are considered to be non detrimental (eg, "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism," etc) will not be eligible for the study.
- **Treatment setting**: All patients should have metastatic breast cancer and must have received treatment with anthracycline unless contraindicated and taxane in either adjuvant or metastatic setting. No more than 2 prior lines of cytotoxic chemotherapy for metastatic disease are allowed which means that to be eligible, patients should be suitable for single agent chemotherapy in either 1$^{st}$, 2$^{nd}$ or 3$^{rd}$ line setting. Prior therapy with platinum for metastatic breast cancer is allowed provided there has been no evidence of disease progression during platinum treatment. In addition, patients may have received prior platinum as potentially curative treatment for a prior non-breast cancer (eg ovarian cancer) with no evidence of disease for $\geq$ 5 years prior to study entry or as adjuvant/neoadjuvant treatment for breast cancer provided at least 12 months have elapsed between the last dose of platinum-based treatment and randomization
- **Phenotypic tumor selection**: Patients can have either triple-negative breast cancer (defined as ER and PgR negative (IHC nuclear staining <1%) and HER2 negative (IHC 0, 1+ or 2+ and/or ISH non-amplified with ratio less than 2.0)) or ER/PgR positive breast cancer, as long as they are HER2 negative. Patients with ER and/or PgR positive breast cancer must have received and progressed on at least one line of

endocrine therapy either in adjuvant or metastatic setting or are not considered appropriate for endocrine treatment.

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

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib to the investigator as green film-coated tablets.

Patients will be administered olaparib orally twice daily (bid) at 300 mg. Two (2) x 150 mg olaparib tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL 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 will be managed with 100 mg tablets.

**Comparator, dosage and mode of administration**

Investigators will declare prior to randomisation in the IVRS their choice of one of the following regimens:

- Capecitabine 2500 mg/m$^2$ po daily (divided in 2 doses) x 14 days, repeat every 21 days
- Vinorelbine 30 mg/m$^2$ IV Day 1 and Day 8, repeat every 21 days
- Eribulin mesylate 1.4 mg/m$^2$ or Eribulin (active substance) 1.23mg/m$^2$ IV Day 1 and Day 8, repeat every 21 days

**Duration of treatment**

Patients will be randomised (using an IVRS/IWRS) in a 2:1 ratio to the treatments as specified below:

- Olaparib tablets po. 300 mg twice daily
- Physician's choice of chemotherapy (capecitabine, vinorelbine or eribulin)

Patients should continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 as assessed by the investigator or unacceptable toxicity and they do not meet any other discontinuation criteria. Patients who are determined to have progressed according to RECIST 1.1 criteria by the Investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled RECIST visit. Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator. Within this study, patients on chemotherapy will not be provided olaparib post discontinuation of study treatment.

All patients should continue RECIST assessments until documented evidence of objective radiological progression in accordance with RECIST 1.1, irrespective of treatment decisions

(i.e RECIST follow up until progression even if a patient discontinues study treatment prior to progression and/or receives a subsequent therapy prior to progression).

**Outcome variable(s):**

- Primary outcome variable
  - Progression Free Survival by BICR using RECIST 1.1.
- Safety outcome variables
  - Adverse Events (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology
- Secondary outcome variables
  - Overall Survival
  - Time from randomisation to second progression, defined as objective radiological or symptomatic progression or death (PFS2)
  - Objective Response Rate by BICR using RECIST 1.1
  - PFS, PFS2 and OS based on patients with *gBRCA* mutations confirmed by the central test (only required if population differs from the ITT population)
  - Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire
  - Pharmacokinetic sampling
- Exploratory outcome variables
  - Potential retrospective biomarker research
  - Mean change from baseline in EORTC QLQ-C30 disease related multi-item symptom and functional scales
  - Treatment satisfaction score (as measured by the Satisfaction with Therapy scale and the other sub-scales and items of the Cancer Therapy Satisfaction Questionnaire (CTSQ-16)
  - Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay.

- Adjusted overall survival estimates (if appropriate, to support reimbursement appraisals)

**Statistical methods**

Approximately 310 patients will be randomised (2:1 ratio of olaparib:chemotherapy) and the primary PFS analysis will occur once approximately 230 PFS events (confirmed via a central review) have occurred.

With 230 PFS events the study has 90% power to show a statistically significant difference in

PFS at the two-sided 5% level if the assumed true treatment effect is a HR 0.635;
this translates to an approximate 2 month improvement in median PFS over an assumed 4 month median PFS on chemotherapy, assuming PFS is exponentially distributed.
It is estimated that the study recruitment period will be approximately 18 months and that 230 progression events will have occurred approximately 2 years after the first patient is randomised in the study.

An initial OS and PFS2 analysis will be performed at the same time as the primary analysis of PFS and will use the same methodology and model as PFS.

The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of randomised treatment (olaparib or chemotherapy). The safety data will be summarised descriptively and will not be formally analysed.

PFS will be analysed using a log rank test stratified by the stratification factors. The HR together with its 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour olaparib). This analysis will be performed when approximately 230 progression events have occurred. The primary analysis will be based on a blinded independent central review (BICR) of disease progression by RECIST 1.1; however, a sensitivity analysis will be performed using the investigator-recorded assessment.

Subgroup analyses will be conducted to assess consistency of treatment effect across potential or expected prognostic factors (see Section 12.2.2 for all predefined subgroups). An analysis will not be performed if there are too few events available for a meaningful analysis of a particular subgroup (i.e., if there are less than 20 events in a subgroup)..

A further analysis of OS and PFS2 will be performed when the OS data are approximately 60% mature (~190 events) and a multiplicity adjustment will be made to account for the different analyses.

Supportive analyses of time to subsequent therapy or death, and time to second subsequent therapy or death will be provided, using the same methodology as specified for the primary

analyses of PFS; however no multiplicity adjustment will be applied as these are viewed as supportive endpoints.

Objective tumour response rates (based on central review) will be summarised for the two treatment arms. In addition, the investigator reported response rates will also be summarised.

Exploratory analyses of OS which attempt to adjust for any potential confounding impact of subsequent use of PARP inhibitors on the control arm may be performed if an appropriate proportion of patient's on the control arm receive such treatments and sufficient information is collected on subsequent therapy use. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), Inverse Probability of Censoring Weighting (IPCW) (Robins 1993) and other methods in development will be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Other subsequent therapies may also be considered such as platinum therapies if important imbalances are reported across the treatment arms. Details will be pre-specified in the SAP or Payer Analysis Plan as this analysis is intended to support reimbursement appraisals.

**Analysis of Patient Reported Outcomes (PRO) endpoints**

Descriptive statistics will include means, standard deviations, medians, and ranges for each continuous or ordinal scale/subscale/item by arm at each time point. Descriptive graphical techniques will include mean plots by arm for each continuous or ordinal scale/subscale/item. Relative frequencies of responses for each ordinal item will also be generated at each time point by arm.

Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire from a mixed model repeated measures analysis will be presented over time by treatment group.

The exploratory analyses will examine:

- Descriptive summaries of EORTC QLQ-C30 disease related multi-item symptom and functional scales, visit response and best overall response, by treatment arm.

- Descriptive summaries of treatment satisfaction (as measured by the Satisfaction with Therapy scale and the other sub-scales and items of the CTSQ-16), by treatment arm.

Additional descriptive summaries will be presented for all other PRO sub-scales by treatment arm over time.

**Biomarkers**

Appropriate summaries of exploratory outcome variables and data listings will be produced and compared across the two treatment arms. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.

**Pharmacokinetic analysis**

The plasma concentration-time data will be analysed by non-linear mixed effects modelling in order to evaluate the pharmacokinetic characteristics of olaparib, quantify variability in the pharmacokinetics, identify demographic or pathophysiological covariates which may explain the observed variability and explore exposure-response relationships.

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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 (see definition in Section 6.4.1) |
| ALP | Alkaline phophatase |
| ALT | Alanine aminotransferase |
| AML | Acute myeloid leukaemia |
| ANC | Absolute neutrophil count |
| APTT | Activated Partial Thromboblastin Time |
| AST | Aspartate aminotransferase |
| BICR | Blinded Independent Central Review |
| bd | Twice a day |
| BoR | Best overall Response |
| BP | Blood pressure |
| *BRCA* | Breast cancer susceptibility gene |
| BUN | Blood Urea Nitrogen |
| CHO | Chinese hamster ovary |
| CI | Confidence interval |
| CR | Complete Response |
| CRF | Case Report Form (electronic/paper) |
| CSA | Clinical Study Agreement |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Event |
| CTSQ-16 | Cancer Therapy Satisfaction Questionnaire |
| DAE | Discontinuation of Investigational Product due to Adverse Event |
| DCIS | Ductal carcinoma *in situ* |
| DNA | Deoxyribonucleic acid |
| DSB | Double strand break |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group: a performance status using scales and criteria to assess how a patient's disease is progressing |
| EFR | Evaluable for response |

| Abbreviation or special term | Explanation |
|---|---|
| EORTC QLQ-C30 | Quality of life questionnaire |
| ER | Estrogen receptor |
| ISH | *in-situ* hybridisation |
| *gBRCA* mutation or *gBRCAm* | The term "*gBRCA* mutation" is used to refer to a germline *BRCA1* or *BRCA2* mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte colony stimulating factor |
| GGT | Gamma Glutamyltransferase |
| HR | Hazard ratio |
| HER-2 | Human Epidermal Growth Factor Receptor 2 |
| HRD | Homologous Recombination Deficiency |
| HRQoL | Health Related Quality of Life |
| ICH | International Conference on Harmonisation |
| IHC | Immuno histochemistry |
| International Co-ordinating investigator | If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally |
| INR | International Normalised Ratio |
| IPCW | Inverse Probability of Censoring Weighting |
| IV | Intravenously |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| KM | Kaplan-Meier |
| LIMS | Laboratory Information Management System |
| Mg | milligram |
| mL | millilitre |
| MCHC | Mean Cell Haemoglobin Concentration |
| MCV | Mean Cell volume |
| MDS | Myelodysplastic syndrome |
| MTP | Multiple testing procedure |
| NE | Not Evaluable |
| OAE | Other Significant Adverse Event (see definition in Section 11.2.1) |
| ORR | Objective response rate |

| Abbreviation or special term | Explanation |
|---|---|
| OS | Overall survival |
| PARP | Polyadenosine 5'diphosphoribase [poly (ADP ribose)] polymerise |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| PFS2 | Time from randomisation to second progression or death |
| PgR | Progesterone receptor |
| PGx | Pharmacogenetic research |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| po | *Per os* (by mouth) |
| PP | Per Protocol |
| PR | Partial response |
| RECIST | Response Evaluation Criteria in Solid tumours. This study will use RECIST version 1.1. |
| RPSFT | Rank Preserving Structural Failure Time |
| SAE | Serious adverse event (see definition in Section 6.4.2) |
| SAP | Statistical analysis plan |
| SD | Stable Disease |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SSB | Single strand breaks |
| TFST | Time to First Subsequent Therapy |
| TL | Target Lesion |
| TNBC | Triple negative breast cancer |
| ULN | Upper limit of normal |
| WBC | White Blood Cell |
| WBDC | Web Based Data Capture |

# 1. INTRODUCTION

## 1.1 Background

### 1.1.1 Breast cancer and its treatment

Breast cancer is a life-threatening disease and is the second leading cause of cancer death among women. In 2013, it is estimated that there will be 232,340 newly diagnosed breast cancer cases in the US, and approximately 39,620 women will die from breast cancer (American Cancer Society 2013). In the European Community, the estimated age adjusted annual incidence in 2008 was 88.4/ 100 000 and the mortality 24.3/100 000 (Aebi S et al 2011).

Approximately 5% of breast cancers are associated with a mutation in the *BRCA1* and/or *BRCA2* gene with approximately 3% associated with the *BRCA1* gene (generally TNBC), and approximately 2% associated with the *BRCA2* gene (generally hormone receptor positive [ER+]). In the general population, *BRCA* mutation carriers have an increased relative risk of breast cancer. The presence of *BRCA1* mutations is associated with lifetime risk of breast cancer of 60 to 70% and a lifetime risk of ovarian cancer of 20 to 45% (Antoniou et al 2003). *BRCA2* mutations are associated with lifetime risk of breast cancer of 40 to 60% in women and 5 to 10% in men and a lifetime risk of ovarian cancer of 10 to 20%. Rare individuals carry deleterious mutations in both *BRCA1* and *BRCA2* genes.

In breast cancer, there are differences between *BRCA1* and *BRCA2* mutation carriers. Approximately 70% of *BRCA1* mutated breast cancer present as triple negative breast cancer (TNBC). In contrast, breast cancer patients carrying mutations in the *BRCA2* gene are more likely to be positive for expression of the estrogen receptor and approximately 20% are triple negative (Mavaddat N et al 2012).

Although there are phenotypic differences in breast cancers resulting from *BRCA1* or *BRCA2* mutations, their important commonality is that mutations in either gene result in tumours that are deficient in homologous recombination, making both appropriate for treatment with PARP inhibitors whereby the process of synthetic lethality can be exploited. In a previous AstraZeneca sponsored Phase II proof of concept study in patients with breast cancer carrying *BRCA* mutations (Study D0810C00008), approximately 60% of patients had *BRCA1* mutations (the other 40% had *BRCA2* mutations) with 55% of tumours overall triple negative in phenotype. In this study, anti-tumour activity was seen in patients with either *BRCA1* or *BRCA2* mutations (Tutt A et al 2010).

Given the small size of the *BRCA* subpopulation in breast cancer, information comparing the outcome from this subpopulation with the overall breast cancer population is based on reports from a number of small studies (Robson et al 2004, Rennert et al 2007, Bordeleau et al 2011, Goodwin et al 2012), and firm conclusions cannot be drawn. The overall body of evidence suggests that once baseline prognostic factors (such as hormone receptor and HER2 status) and treatment are taken into account, patients with *BRCA* mutations have a similar outcome to their sporadic counterparts. This is in contrast to patients with *BRCA1*/*BRCA2*-related ovarian

cancer who have an improved survival compared with non-carriers, particularly if they receive platinum-based therapy.

There are no approved treatments for patients with germline *BRCA1/2* mutations and these patients are treated according to their hormone receptor and HER2 status.

### 1.1.2 Chemotherapy use in advanced breast cancer

Recurrent or metastatic breast cancer is an incurable malignancy with a median survival of 20 to 24 months in unselected populations (Hortobagyi 1998), which has not changed significantly over the last decade. Because of the increased use of anthracyclines and taxanes as therapy for early-stage breast cancer, many patients' tumors become resistant to these agents by the time of disease recurrence, thereby reducing the number of treatment options for metastatic breast cancer. Moreover, even when these agents can be used to treat metastatic breast cancer, treatment failure occurs in most cases; as a result, the 5-year survival rate of patients with metastatic breast cancer is only 27% (Moreno-Aspitia and Perez 2009).

The first International Consensus Guidelines for Advanced Breast Cancer advise that both combination and sequential single agent chemotherapy are reasonable options for treating metastatic breast cancer patients (Cardoso et al 2012). Based on the available data, in patients pre-treated with anthracycline and taxane (in the adjuvant or metastatic setting) who do not need combination chemotherapy (e.g. life-threatening visceral metastases, need for rapid clinical response or symptom control), capecitabine single agent is the preferred choice. Established other chemotherapy options include vinorelbine and eribulin. Recently, there is an increased interest in the role of platinum in TNBC and particularly the *BRCA* mutated subset of those patients. Despite significant efficacy seen with platinum in a small single arm trial in *BRCA1* mutated advanced breast cancer patients (Byrski et al 2012), in order for the results to be generalised, these data need to be confirmed in a randomised control trial. Presently there is insufficient data to recommend platinum agents use over standard chemotherapy in advanced breast cancer.

### 1.1.3 PARP inhibition as a target for *BRCA* mutation positive breast cancer

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) 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 anti-cancer agents.

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumours with homologous recombination deficiencies (HRD), such as ovarian

cancers in patients with *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

*BRCA1* and *BRCA2* defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fong et al 2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011, Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous 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* knockout models, either as a stand-alone treatment or in combination with established chemotherapies.

### 1.1.4 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib IB.

### 1.1.5 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies e.g., dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of olaparib. *Ex vivo* studies have confirmed that olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test *in vitro*. When dosed orally, olaparib also induced micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that olaparib can have adverse effects on embryofoetal survival and development at dose levels that do not induce significant maternal toxicity.

Further information can be found in the current version of the olaparib IB.

### 1.1.6 Clinical experience

As of 2 October 2013, an estimated 2103 patients with ovarian, breast, gastric, pancreatic, and a variety of other solid tumours are estimated to have received treatment with olaparib across the dose range 10 mg od to 600 mg bd in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other chemotherapy/anti-cancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing. The

majority of patients to date have received the capsule formulation of olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the olaparib development programme. Approximately 248 patients with advanced breast cancer have been treated with olaparib.

Below is an outline of the monotherapy olaparib studies conducted in breast cancer patients.

#### 1.1.6.1 Olaparib monotherapy studies in breast cancer patients

**Study D0810C00002**

Study D0810C00002 was a Phase I open-label, dose escalation and cohort expansion study in 98 patients with solid tumours. Patients in the dose-escalation cohort received olaparib at doses ranging from 10 mg daily to 600 mg twice daily; whereas all patients in the dose-expansion cohort received olaparib at 200 mg twice daily after the MTD was identified as 400 mg bid. The main tumours by type were ovarian (54 [55.1%]), breast, (13 [13.3%]); large intestine (5 [5.1%]), prostate (4 [4.1%]) and skin cancers (4 [4.1%]). Overall 23 patients were *BRCA* mutation carriers; of these, 19 patients had *BRCA* mutated ovarian, breast, or prostate cancer and were evaluable for response. Forty-seven percent (9/19) of the patients had a RECIST defined objective response and 63% (12/19) had stable disease for at least 4 months (Fong et al 2009).

**Study D0810C00008**

Study D0810C00008 was a Phase II proof-of-concept study initiated as an open-label, single-arm, international, multicenter study to assess the efficacy and safety of olaparib given orally bid in patients with advanced breast cancer. Patients had a median of 3 previous chemotherapy regimens. Approximately half of the patients had TNBC. The primary objective was to assess the efficacy of the capsule formulation at 2 different doses of olaparib in terms of ORR in patients with advanced breast cancer. Patients received olaparib at a dose of 400 mg bid or 100 mg bid continuously in 28-day cycles, for multiple cycles, until no further clinical benefit was apparent or the patient was withdrawn from the study. The cohorts were conducted in sequence, the 400 mg bid group first (n=27) followed by the 100 mg bid group (n=27). In the ITT analysis set, the confirmed Response Evaluation Criteria in Solid Tumors (RECIST) ORR overall was 11/27 (41%) at 400 mg bid and 6/27 (22%) at 100 mg bid. Responses were seen in both *gBRCA1* and *gBRCA2* carriers. Median time to progression was 5.3 months for the 400 mg bid group and 3.7 months for the 100 mg bid group (Tutt A et al 2010).

**Study D0810C00020**

Study D0810C00020 was a Phase II open-label, non-randomised 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 bid until disease progression or until the investigator believed it was in the best interest of the patient to stop treatment. Tumour response data was analysed in 64 ovarian (*BRCA* or serous ovarian) and 26 breast (*BRCA* or triple negative) cancer patients who received olaparib 400 mg bid. Germline *BRCA*

mutations were present in 11 out of the 26 breast cancer patients. Median number of prior chemotherapies in the breast cancer group was 3 (range: 1 to 7). Over 70% of the breast cancer patients had received more than 3 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 *BRCA* mutations had an overall best response of SD lasting 8 weeks or more. The median PFS in this group was 3.6 months (Gelmon K et al 2011).

**Study D0810C00042**

Study D0810C00042 was a Phase II, open label, nonrandomised, noncomparative, multicenter study in patients with advanced cancers who had confirmed genetic *BRCA1* and/or *BRCA2* mutations. A total of 62 breast cancer patients were recruited, all of whom received at least 3 prior lines of therapy (with a median of 6 prior regimens). Eight (12.9%) of the breast cancer patients had an OR and the median duration of response was 204 days. At 16 weeks, disease control was observed in 23 (37.1%) patients. The median PFS was 3.68 months. The median OS was 11.01 months; the survival rate at 6 months was 74.6%, and at 1 year was 44.7% (Kaufman B et al 2013).

The details on the pivotal phase II data in ovarian cancer patients as well as olaparib combination with chemotherapy are presented in the Investigator Brochure.

## 1.2 Research hypothesis

Single agent olaparib tablet 300 mg bid has superior efficacy and acceptable tolerability profile as compared with physician's choice of cytotoxic chemotherapy (capecitabine, vinorelbine or eribulin) in patients with deleterious or suspected deleterious germline mutation in *BRCA1* and/or *BRCA2* and metastatic breast cancer that has been treated with an anthracycline and a taxane. The efficacy in this study will be assessed by the primary analysis of PFS defined as the time from randomisation until the date of objective radiological disease progression according to RECIST1.1 or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to disease progression. To reduce bias, primary analysis of PFS will be based on blinded, independent central review of RECIST scans. Secondary endpoints include overall survival, PFS2, safety assessments and Health related Quality of life.

## 1.3 Rationale for conducting this study

Mutations in *BRCA1* and *BRCA2* are the most common definable cause of inherited breast cancer. Cells that lack *BRCA1/2* function, such as cancer cells from patients with germline mutations in these genes, are deficient in the ability to repair double-strand DNA breaks through homologous recombination (HR) (Roy et al 2012). This deficiency is presumed to underlie the observation that *BRCA1/2*-deficient cells are sensitive to interventions that promote double strand DNA breaks or cross-links, such as ionizing radiation and platinum-based chemotherapeutic agents. It is also presumed to underlie the observation that *BRCA1/2*-deficient cells are sensitive to treatment with inhibitors of poly-(ADP-ribose)-polymerases

(PARP inhibitors) (Bryant et al 2005, Farmer et al 2005) which are presumed to force repair of single-strand breaks towards the homologous repair pathway rather than the pathways that usually address single-strand breaks. Phase I and proof-of-concept phase II studies have shown that PARP inhibitors have significant activity with limited toxicity when used as single agents in the treatment of *BRCA1/2* mutation-associated breast and ovarian cancer. (Audeh et al 2010, Fong et al 2009, Tutt A et al 2010) In patients with breast cancer that has progressed after anthracycline and taxane therapy, there are a number of potential cytotoxic treatments, with none offering a clear advantage over the others. The present trial is an important step in defining the role of olaparib as a PARP inhibitor in metastatic *BRCA1/2* mutated breast cancer patients. The study will assess the efficacy of olaparib relative to single agent conventional chemotherapy. If the trial is successful it will give patients a relatively non-toxic oral therapeutic option as an alternative to conventional cytotoxic chemotherapy.

### 1.3.1 Rationale for using Myriad Genetics

The FDA has indicated that the BRCA1 and BRCA2 mutation assay will need to be approved as a companion diagnostic in the US.

Myriad Genetics has been chosen as a partner in developing a companion diagnostic for *BRCA1* and *BRCA2* testing because it has extensive experience of *BRCA1* and *BRCA2* mutation detection. Myriad keeps a comprehensive database on *BRCA1* and *BRCA2* gene mutations and their clinical relevance. Furthermore, Myriad has an established laboratory infrastructure, which supports high volume testing with turnaround times that can meet the needs of a clinical trial.

## 1.4 Risk/benefit and ethical assessment

As of 2nd of October 2013, an estimated 2103 patients with ovarian, breast, gastric, pancreatic, and a variety of other solid tumours are estimated to have received treatment with olaparib across the dose range 10 mg od to 600 mg bid in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other chemotherapy/anti-cancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing. The majority of patients to date have received the capsule formulation of olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the olaparib development programme.

An analysis of monotherapy data across 12 AstraZeneca sponsored monotherapy studies in 975 patients who have been given olaparib capsule estimated that 16.1% (157/975) of patients had been exposed to olaparib capsulefor ≥12 months at the time of database closure for the 12 studies. Furthermore, 41/ 975 patients received treatment for >24 months (longest duration was 44 months). From the available data to date, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure.

Olaparib as monotherapy at doses up to 400 mg bid capsule is generally well tolerated, with most common AEs including nausea, fatigue, vomiting, anaemia mainly mild-to-moderate

(CTCAE Grade ≤ 2) in severity. In addition, in a small number of patients MDS/AML or pneumonitis have been observed and identified as important risks.

**Important potential risks**

**Myelodysplastic syndrome/acute myeloid leukaemia**

There have been 16 reports of myelodysplastic syndrome (MDS) and/or acute myeloid leukaemia (AML) in patients treated with olaparib as of Oct 2013; 11 cases in olaparib monotherapy trials and 5 cases in olaparib combination studies with carboplatin and paclitaxel (n=4) or cediranib (n=1). A total of 2103 patients are estimated to have received olaparib, giving a cumulative incidence of 0.76% for MDS/AML, similar to the cumulative incidence reported from control arms of olaparib randomised studies 0.7% (2/304 patients). All 16 patients had primary ovarian or peritoneal cancer and 12 of them were *BRCA1/2* positive (3 cases *BRCA* status unknown; 1 case negative). It has been hypothesised that a deficiency in the expression of *BRCA* genes may leave patients more vulnerable to the adverse effects of chemotherapy, and therefore, at an increased risk of MDS/AML as a result of cancer treatment (Cole and Strair 2010). Most patients had been treated with extensive previous chemotherapy ranging from 6 to 95 cycles over periods of 3.5 months to 15 years, including platinum agents, topoisomerase II inhibitors, alkylating agents and taxanes. The median time from diagnosis of cancer to onset of MDS was 5.3 yrs (range 2.9 -12.7). The median time from start of olaparib treatment to onset of MDS was 0.9 years (0.1 to 4.8 years). The reported events of MDS/AML occurred post discontinuation of olaparib treatment in 8 of the 16 patients following a median of 0.1 years post treatment discontinuation (range: 0.1 to 1 years). Half of the patients (n=8) had received olaparib for ≤ 12 months (5 patients had ≤ 6 months exposure) and the other 8 cases occurred following longer than 12 month olaparib exposure (3 patients following 12-18 months exposure and 5 patients following >2 years exposure to olaparib).

Since bone marrow is known to be a target organ for olaparib toxicity, a risk of MDS/AML with long-term exposure to olaparib cannot be excluded, but there is insufficient data at present to evaluate the strength, if any, of this relationship. Moreover, while non-clinical data suggest bone marrow progenitor cell populations are reduced temporarily following olaparib treatment, there is no evidence to date linking olaparib treatment to the generation of abnormal bone marrow precursors. Furthermore, all patients who developed MDS/AML had extensive prior chemotherapy and while it is not possible to exclude the contribution of olaparib, it is also considered that there were other potential contributing factors in all cases. Preclinical data also suggest potential benefit with PARP inhibitors in MDS/AML and clinical trials are now underway to assess this effect (Gaymes et al 2008).

To ensure robust safety monitoring, patients in this clinical trial will have weekly safety assessments during the first cycle and then safety assessments every 3 weeks during the rest of the treatment period. Clinical guideline of managing bone marrow toxicity and use of G-CSF is implemented as the safety management plan.

**Pneumonitis**

As of 2nd of Oct 2013, 10 patients out of a total of 2103 patients are estimated to have received olaparib have reported pneumonitis, giving a cumulative incidence of 0.5% for pneumonitis. Pneumonitis was also reported for 2 patients (0.7%) of 304 patients that received placebo or comparator in the olaparib trial programme (1 patient on placebo in Study 19 and 1 patient on paclitaxel in Study 39. The patients were treated with olaparib for breast cancer (n=2), ovarian cancer (n=2), non-small cell lung cancer (n=2), small cell lung cancer (n=1), pancreatic cancer (n=1), gastric cancer (n=1) and thymic cancer (n=1). Five of the 10 patients had a history of tobacco smoking. The majority of patients had received prior radiotherapy and/or chemotherapy. The majority of patients had relevant medical histories including pneumonitis, interstitial lung fibrosis, dyspnoea, haemoptysis, chest infection, allergic asthma, pleural effusion, and pleural metastases.

Investigation of any new or worsening pulmonary symptoms has been implemented as a safety management plan (section 5.5.7.2).

**New Primary Malignancies**

Overall, the number of reports of new primary malignancies is low, with 21 events (in 19 patients) being reported to date in 2103 olaparib treated patients (0.9%) and one event (bladder cancer) reported in the placebo arm of the double-blind Study 19. In randomised controlled studies, 5 events of new primary malignancies have been reported in four olaparib treated patients and one event in a placebo treated patient:

In the double blind maintenance Study 19, two events of new primary malignancies have been reported in olaparib treated patients and one event in a placebo treated patient. In the open label *gBRCA* ovarian monotherapy dose-finding Study 12, three events were reported in two olaparib treated patients.

Of the 21 reported events in olaparib treated patients, in ten the events were non-melanoma skin cancers. There was one report of malignant melanoma. The other 10 events of new primary malignancies were breast cancer (n=2), breast cancer *in situ*, gastric cancer, lung neoplasm (plus event of recurrence of the lung carcinoma), plasma cell myeloma, colon cancer, malignant muscle neoplasm (lesion present pre-olaparib treatment) and one fatal event of T-lymphoblastic lymphoma/leukaemia.

Of the 19 olaparib treated patients subsequently diagnosed with a new primary malignancy, the majority were reported whilst receiving olaparib treatment (16 patients). In 3 patients the event was reported after olaparib discontinuation

The duration of olaparib treatment for the 19 patients was:

- <6 months for 3 patients
- 6 to 12 months for 6 patients

- 12 to 18 months for 2 patients
- 18 to 24 months for 2 patients
- >2 years for 6 patients.

The type of new primary cancers reported were generally in line with secondary cancers observed in ovarian and breast cancer populations reported in the literature (Bergfeldt et al 1995, Fowble et al 2001, Wesolowski et al 2007), or were cancers such as skin cancer, known to be the most common cancer in the general population and associated with high cure rates.

Ovarian cancer patients have been reported to have an increased risk of developing second primary malignancies. Patients with *gBRCA* mutations are at risk of developing other primary cancers notably breast cancer. Ginsburg et al 2010 reported higher rates of skin cancers in patients with *BRCA1* (1.6%) and *BRCA2* (3.0%) mutations.

There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all 19 olaparib treated patients. All patients had previously received various chemotherapy agents including multiple cycles of DNA damaging platinum containing chemotherapies, taxanes, anthracyclines and other alkylating and DNA damaging agents. Four patients were reported to have had prior radiotherapy. Seven of the 19 patients had previous medical histories of cancer (ovarian, cervix, breast, peritoneal) and 3 patients with skin cancers had either had previous basal cell carcinoma reported or had skin lesions evident prior to study treatment) prior to the cancer under investigation in the olaparib studies.

There is insufficient evidence for an association between olaparib treatment and the development of new primary malignancies in the clinical trial programme to date.

**Potential benefit**

Phase II clinical studies have investigated the effect of olaparib either as monotherapy or in combination with other chemotherapy agents in cancer patients. In patients carrying germline *BRCA* mutations, monotherapy studies in patients with heavily pre-treated breast cancer have reported an objective response rate (ORR) of up to 41%. Further details on olaparib breast cancer trials provided in Section 1.1.6.1.

In ovarian cancer patients, the pivotal phase II study D0810C00019, a double-blind, randomised study assessed the efficacy of olaparib 400 mg bid capsules as a maintenance treatment following platinum-based chemotherapy in patients with platinum sensitive relapsed high grade serous ovarian cancer. The progression-free survival (PFS) following olaparib maintenance therapy was significantly longer compared with the placebo group (HR 0.35; 95% CI: 0.25, 0.49; p<0.00001) in the overall population. In the subgroup of patients with *BRCA* mutant ovarian cancer, the effect was even greater with a PFS HR of 0.18 (95% CI: 0.11, 0.31; p<0.00001; median 11.2 versus 4.3 months). An interim analysis of OS was performed at 58% maturity. In the overall population, the analysis demonstrated a non-statistically significant numerical advantage for olaparib-treated patients (OS HR 0.88; 95%

CI 0.64-1.21; p=0.43808) and there was again a greater effect in the *BRCA*-mutated subgroup: the OS HR was 0.74 (95% CI 0.46 to 1.19; p=0.20813) with a numerical advantage in median overall survival observed with olaparib (median 34.9 months versus 31.9 months with placebo). Among the 62 placebo-treated patients with *BRCA* mutations, 14 switched to a PARP inhibitor post progression.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

To determine the efficacy of single agent olaparib vs physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by progression-free survival (PFS) using blinded independent central review (BICR) data assessed by Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

## 2.2 Secondary objectives

The secondary objectives of this study are:

1. To compare the efficacy of single agent olaparib versus physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by assessment of overall survival, time to second progression or death (PFS2) and objective response rate (ORR) using BICR data assessed by RECIST 1.1.

2. To assess the effect of olaparib on the Health-related Quality of Life (HRQoL) as measured by EORTC QLQ-C30 global QoL scale.

3. To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future *BRCA* mutation assays (gene sequencing and large rearrangement analysis).

4. To determine the exposure to olaparib in patients receiving olaparib monotherapy

## 2.3 Safety objective

1. To assess the safety and tolerability of single agent olaparib vs physician's choice chemotherapy (capecitabine, vinorelbine or eribulin).

## 2.4 Exploratory objectives

The exploratory objectives of this study are:

1. To explore the impact of olaparib on symptoms and HRQoL as measured by the EORTC QLQ-C30 disease related multi-item symptom and functional scales.

2. To explore patients' treatment satisfaction (as measured by the Satisfaction with Therapy scale of the CTSQ and the other sub-scales and items of the CTSQ) on Olaparib, compared to physician's choice chemotherapy.

3. To investigate the health economic impact of treatment and the disease on hospital related resource use.

4. To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents.

5. To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour (mandatory if available), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional).

6. To determine the frequency of and describe the nature of *BRCA* mutation/s in tumour samples and to compare this with germline *BRCA* mutation status.

7. Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (mandatory if available), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional).

8. To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional).

The exploratory analyses may not be reported in the clinical study report (CSR). If not, they will be reported separately.

# 3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

## 3.1 Overall study design and flow chart

This open label, randomised, controlled, multi-centre phase III study will assess the efficacy and safety of single agent olaparib vs standard of care based on physician's choice of capecitabine, vinorelbine or eribulin in metastatic breast cancer patients with *gBRCA1/2* mutatations. Due to different routes and schedules of administration of the treatment options

on the control arm as well as their different toxicity profiles, the study cannot be blinded. Given the open label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with a primary analysis of PFS based on blinded independent central review (BICR) of all patient scans. Secondary endpoints will include overall survival, PFS2, ORR by BICR, safety assessments and health related quality of life.

Approximately 310 patients will be randomised 2:1 (olaparib:chemotherapy) into the trial. The treatment groups include olaparib 300 mg po bid daily tablet continuous, or physician's choice of chemotherapy from one of the following regimens. The investigator must declare prior to randomisation their choice of chemotherapy i.e. capecitabine or vinorelbine or eribulin.

- Capecitabine 2500 mg/m$^2$ po daily (divided in 2 doses) x 14 days, repeat every 21 days
- Vinorelbine 30 mg/m$^2$ IV Day 1 and Day 8, repeat every 21 days
- Eribulin mesylate 1.4 mg/m$^2$ or Eribulin (active substance) 1.23mg/m$^2$ IV Day 1 and Day 8, repeat every 21 days

The randomisation scheme will be stratified based on:

- Received prior chemotherapy regimens for metastatic breast cancer (yes/no)
- ER and/or PgR positive vs ER and PgR negative
- Prior platinum for breast cancer (yes/no)

**Target patient population**

All patients recruited in the study will be selected based on the following 3 principles:

- **Genetic selection**: Documented germline 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). Patients with *BRCA1* and/or *BRCA2* mutations that are considered to be non detrimental (eg. "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism," etc) will not be eligible for the study.
- **Treatment setting**: All patients should have metastatic breast cancer and must have received treatment with anthracycline unless contraindicated and taxane in either adjuvant or metastatic setting. No more than 2 prior lines of cytotoxic chemotherapy for metastatic disease are allowed which means that to be eligible, patients should be suitable for single agent chemotherapy in either 1st, 2nd or 3rd line setting. Prior therapy with platinum for metastatic breast cancer is allowed provided there has been no evidence of disease progression during platinum

treatment. In addition, patients may have received prior platinum as potentially curative treatment for a prior non-breast cancer (eg. ovarian cancer) with no evidence of disease for ≥ 5 years prior to study entry or as adjuvant/neoadjuvant treatment for breast cancer provided at least 12 months have elapsed between the last dose of platinum-based treatment and randomization

- **Phenotypic tumor selection**: Patients can have either triple-negative breast cancer (defined as ER and PgR negative (IHC nuclear staining <1%) and HER2 negative (IHC 0, 1+ or 2+ and/or ISH non-amplified with ratio less than 2.0)) or ER/PgR positive breast cancer, as long as they are HER2 negative. Patients with ER and/or PgR positive breast cancer must have received and progressed on at least one line of endocrine therapy either in adjuvant or metastatic setting or are not considered appropriate for endocrine treatment.

All patients must have a known deleterious or suspected deleterious *BRCA* mutation to be randomised; this may have been determined prior to enrolment into the study or may be assessed as part of the enrolment procedure for the study (via centrally provided Myriad test).

Patients known to have germline BRCA mutation/s prior to randomisation can enter the study based on this result provided they meet all other eligibility criteria. The type of BRCA1/2 mutation must be reported in the eCRF. In addition the patients must consent to give 2 blood samples, one for a confirmatory Myriad gBRCA test post randomisation and the second for assessment of current and future BRCA mutation assays. These are needed in order to ensure sufficient information is collected in the study to justify the approval of the Myriad germline BRCA test as a companion diagnostic for olaparib in the USA.

Patients with unknown BRCA status must consent to provide 2 blood samples for germline BRCA testing and follow all local ethical procedures for such genetic testing. One sample will be used to test for BRCA mutations using the current commercial Myriad BRCA analysis test prior to study entry. The second blood sample from all tested patients (including those who do not have a BRCA mutation) is required for a bridging study to validate the companion diagnostic test for olaparib and/or assessment of current and future BRCA mutation assay(s). When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious germline BRCA mutation and the patient meets all other eligibility criteria, the patient can be randomised into the study.

After confirmation of eligibility patients will be randomised 2:1 to receive either:

- Arm A; olaparib 300 mg po twice daily

- Arm B; Physicians choice of chemotherapy (capecitabine, vinorelbine or eribulin)

Following randomisation patients in both treatment arms will attend clinic visits weekly for the first 3 weeks of treatment (Days 1, 8 and 15). Patients will then attend clinic visits every 3 weeks while receiving study treatment. Patients should continue to receive study treatment until objective radiological disease progression as per RECIST as assessed by the investigator,

unacceptable toxicity or as long as they do not meet any other discontinuation criteria as outlined in Section 5.8.

Patients will have RECIST assessments until evidence of objective disease progression irrespective of treatment decisions (i.e even if they discontinue study treatment and/or receive a subsequent therapy prior to progression). RECIST assessments will be scheduled every 6 weeks (+/- 1 week) from randomisation for the first 24 weeks and then every 12 weeks (+/- 1 week) thereafter.

All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. All treatment decisions will be based on site assessment of scans. Patients who are determined to have progressed according to RECIST 1.1 criteria by the Investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled RECIST visit.

Patients who discontinue treatment and/or receive a subsequent therapy prior to disease progression should continue to have RECIST assessments as per the study schedule. Failure to do so may result in bias to the study results.

Following objective disease progression, further treatment options will be at the discretion of the investigator. Patients may be allowed to continue study treatment if the investigator believes, and AZ Study Physician concurs, that the patient could continue to receive benefit, the patient is not experiencing serious toxicity, and there is no available better alternative treatment that could benefit the patient.

Once a patient has progressed the patient will be followed every 8 weeks for second progression (PFS2), defined as objective radiological or symptomatic progression, or death, and vital status (OS).

Start and stop date of subsequent systemic anticancer treatment will be collected. Information on any further systemic anti-cancer treatments will be collected until death, loss to follow-up or withdrawal of consent.

After the primary Progression Free Survival (PFS) analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Ongoing collection of site review tumour assessment is required and must be recorded in the electronic case report form (eCRF).

A primary PFS analysis will be performed when approximately 230 PFS events based on the BICR have occurred. The primary PFS analysis will be based on a blinded independent central review (BICR) of disease progression by RECIST;
however, a sensitivity analysis will be performed using the investigator-recorded assessment. All efficacy variables including overall survival will be analysed at the time of the primary PFS analysis (providing sufficient events are available to make the analysis meaningful).

**Figure 1 Study Flow Chart**

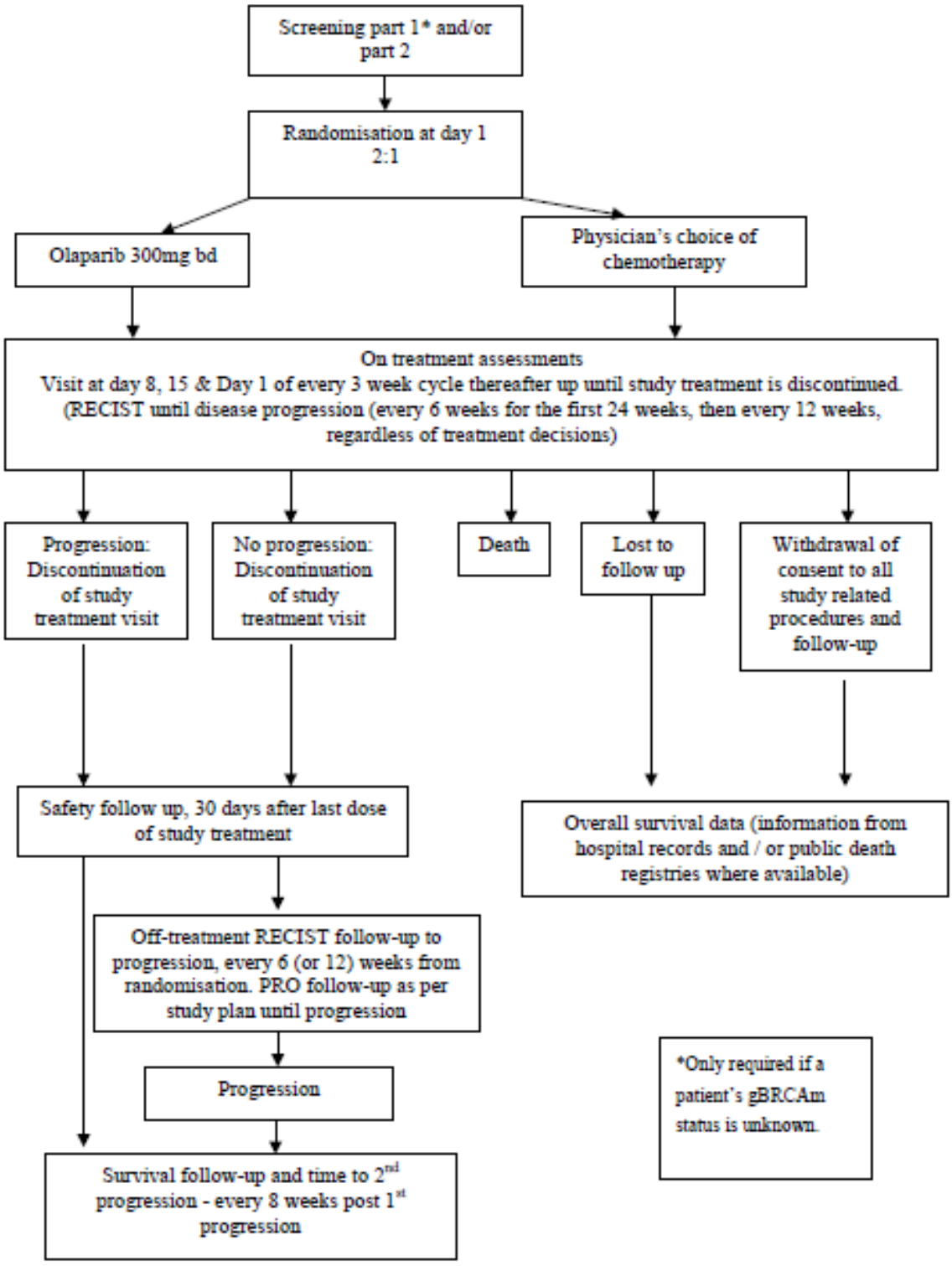

**Table 1 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up**

| **Visit Number** | **Screen PART 1** (Pt with UNKNOWN *BRCA* status only) | **Screen PART 2** (ALL patients) | **On treatment Cycle 1** | | | **On treatment visits every 3 weeks** | **Study treatment discontinued** | **30-Day follow-up** | **Survival follow-up** |
|---|---|---|---|---|---|---|---|---|---|
| **Day** | | **-28 to 0** | **1** | **8** | **15** | **Cycle X Day 1** | | | **Every 8 weeks** |
| **Visit Window** | | | | **±3d** | **±3d** | **±3d** | **±7d** | **±7d** | **±7d** |
| Informed consent | X | X | | | | | | | |
| Randomisation | | | X [c] | | | | | | |
| Demographics | X | X | | | | | | | |
| Medical and surgical history [b] | | X | | | | | | | |
| Family history of cancer | | X | | | | | | | |
| Prior cancer therapies | | X | | | | | | | |
| Inclusion/exclusion criteria | X (all * criteria)[a] | X | | | | | | | |
| ECOG Performance Status | | X | | | | | X | | X |
| Vital signs | | X | X [d] | | | X (every 12 weeks) | X | X | |
| Haematology / clinical chemistry | | X | X [e] | X | X | X | X | X | |
| Physical examination [f] | | X | X | | | X | X | X | |
| Tumour Assessment (RECIST 1.1) | | X [g] | | | | X [g] | | | |
| ECG [h] | | X | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| **Day** | | **-28 to 0** | **1** | **8** | **15** | **Cycle X Day 1** | | | **Every 8 weeks** |
| **Visit Window** | | | | **±3d** | **±3d** | **±3d** | **±7d** | **±7d** | **±7d** |
| Urinalysis [i] | | X | | | | | | | |
| Pregnancy test [j] | X | X | X | | | | | | |
| Blood samples *BRCA* status [k] | X | | X [l] | | | | | | |
| Adverse Events | X[m] | X | X | X | X | X | X | X | |
| Concomitant medications including blood transfusions | | X | X | X | X | X | X | X | |
| EORTC QLQ-C30 | | X [Λ] | | | | X [n] (every 6 weeks until progression) | | | |
| CTSQ-16 | | | | | | X (every 6 weeks until discontinuation of study treatment) | X | | |
| Healthcare Resource Use[o] | | | X | X | X | X | X | X | |
| Pharmacogenetic blood sample (optional) | | | X | | | | | | |
| Archival tumour (mandatory if available) [t] | | X | | | | | | | |

**Table 1 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up**

| **Visit Number** | **Screen PART 1** (Pt with UNKNOWN *BRCA* status only) | **Screen PART 2** (ALL patients) | **On treatment Cycle 1** | | | **On treatment visits every 3 weeks** | **Study treatment discontinued** | **30-Day follow-up** | **Survival follow-up** |
|---|---|---|---|---|---|---|---|---|---|
| **Day** | | **-28 to 0** | **1** | **8** | **15** | **Cycle X Day 1** | | | **Every 8 weeks** |
| **Visit Window** | | | | **±3d** | **±3d** | **±3d** | **±7d** | **±7d** | **±7d** |
| Tumour biopsy (optional) [p] | | X | | | | X Only at progression | | | |
| Blood sample for PK analysis (Subset of patients) [μ] | | | | | | X | | | |
| Blood samples for biomarker analysis (mandatory) [q] | | | X | | | X Only at progression | | | |
| Olaparib dosing [u] | | | ← Continuous twice daily dosing → | | | | | | |
| Eribulin dosing [v] | | | X | X | | X | | | |
| Vinorelbine dosing [w] | | | X | X | | X | | | |
| Capecitabine dosing [x] | | | ← Days 1-14 only → | | | X | | | |
| Subsequent cancer therapy [r] | | | | | | | | X | X |
| Second progression assessment | | | | | | | | | X |
| Survival [s] | | | | | | | | | X |
| Olaparib dispensed/returned | | | X | | | X | X | | |

[a] These screening assessments do not need capturing on the eCRF, but they must be recorded in the patient's notes.

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

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

[d] If vital signs assessed within 7 days before starting study treatment, it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

[e] Safety blood samples do not need to be repeated on Day 1 of study treatment if they have been assessed within 7 days before starting study treatment and which must have been 3 weeks after last dose of chemotherapy, unless the investigator believes that it is likely to have changed significantly. Coagulation analysis only required at baseline.

[f] Physical examination should be performed according to the schedule, after the baseline assessment it is not necessary to record the details on the eCRF, any clinically significant changes not unequivocally related to disease progression, should be reported as adverse events.

[g] Baseline RECIST assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed no more than 28 days before the start of study treatment and as close as possible to the start of study treatment and prior to randomisation. RECIST follow-up assessments will be performed every 6 weeks (±1 week) for the first 24 weeks, then every 12 weeks (±1 week) after randomisation until objective disease progression as defined by RECIST 1.1, irrespective of treatment decisions. Follow-up assessment will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Prior to primary analysis for PFS, all scans will be submitted for independent review. If progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled visit. Following disease progression further RECIST assessments will not be performed and assessment of disease will be as per local clinical practice.

[h] ECG assessments to be completed within 7 days before starting treatment. After screening, ECGs will only be required if clinically indicated.

[i] Urinalysis should be performed at screening. After screening, urinalysis will only be required if clinically indicated

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

[k] Any patient who consents to study related Myriad *gBRCA* status testing, must also have a blood sample taken at the same time for the purpose of developing and validating a future diagnostic test(s) for *BRCA* mutations

[l] Samples to be taken on Day1 only for patients with known *BRCA* mutation who have not completed PART 1 screening

[m] Adverse events must be captured from time of consent. However, in Screening PART 1 of the study only SAEs related to study procedures will be collected.

[n] EORTC QLQ-C30 questionnaires to be completed every 6 weeks until disease progression.

[o] Healthcare Resource Use should be collected up to disease progression or treatment discontinuation (and 30 day follow-up), whichever is the latter.

[p] Optional tumour biopsies to be taken during screening and at disease progression. Sample will only be submitted to the study biobank once the patient has been randomised.

[q] Mandatory blood samples to be taken prior to dosing on Day 1 and at disease progression

[r] Details of all anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents) post discontinuation of study treatment need to be recorded

[s] In addition to their regular 8 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see section 5.9).

[t] Sample will only be submitted to the study biobank once the patient has been randomised.

[u] Continuous Olaparib 300mg twice daily dosing. 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

[v] Eribulin mesylate 1.4 mg/m2 or Eribulin (active substance) 1.23mg/m2 IV Day 1 and Day 8, repeat every 21 days

[w] Vinorelbine 30 mg/$m^2$ IV on day 1 and day 8, repeat every 21 days

[x] Capecitabine 2500 mg/$m^2$ orally (divided in 2 doses) for 14 days, repeat every 21 days

[Λ] Baseline EORTC QLQ-C30 should be completed prior to randomisation once eligibility is confirmed

[µ] PK sampling to be performed in a subset of patients. Sampling times: Cycle 2 Day 1 pre-dose, post dose 0-0.5 hour, 0.5-1.5 hours, 3-6 hours and 6-12 hours (see Section 6.9)

For patients who discontinue study treatment prior to disease progression RECIST assessments will continue until objective disease progression (every 6 weeks for the first 24 weeks, then every 12 weeks). Subsequent therapy will be collected for these patients from the time of treatment discontinuation.

## 3.2 Rationale for study design, doses and control groups

### 3.2.1 Rationale for study design

The proposed Phase III study is designed to determine the efficacy and safety of single agent olaparib vs physician's choice of chemotherapy (capecitabine, vinorelbine or eribulin) for the treatment of metastatic breast cancer patients with *gBRCA1/2* mutations, previously treated with anthracycline and taxane. Since there is no single standard of treatment in patients with metastatic breast cancer who have previously failed anthracycline and taxanes and in line with the first International Consensus Guidelines for Advanced Breast Cancer ABC1 (Cardoso et al 2012) and common clinical practice, a physician's choice of chemotherapy is provided for the control arm of the study consisting of capecitabine, vinorelbine or eribulin. None of these agents has shown a clear advantage over the others in this setting.

Due to different ways and schedules of administration of the chemotherapies on the control arm as well as their different tolerability profiles, the study cannot be blinded. Given the open label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with a primary analysis of PFS based on blinded independent central review (BICR) of all patient scans. A number of secondary endpoints will provide further support for the clinical benefit of olaparib in this patient population, and will include overall survival, PFS2 (time from randomisation to second progression), ORR by BICR, safety assessments and health related quality of life.

### 3.2.2 Rationale for study treatment dose

It should be noted that the safety and efficacy of olaparib has been demonstrated in the clinical program using the capsule formulation (400 mg - 8 capsules - twice daily); however, an improved more patient friendly tablet formulation (2 tablets twice daily) has been developed and will be used in this study. The tablet dose of olaparib that will be investigated is 300 mg bid which is considered similar to the capsule 400 mg bid dose. This tablet dose has been chosen based on data from Study D0810C00024. Since it has been shown that the capsule and tablet formulations are not bioequivalent, a formulation switch based on bioequivalence has not been possible. The tablet dose of 300 mg bid is considered to have similar efficacy in terms of tumour shrinkage in *BRCA* mutated ovarian cancer patients to the 400 mg bid capsule. The 300 mg bid tablet dose matches or exceeds the exposure of the 400 mg capsule in terms of AUC, $C_{maxss}$, and $C_{minss}$. The tolerability profile of the 300 mg bid tablet dose in Study D0810C00024 was considered similar to the 400 mg bid capsule formulation. The most common AEs were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue, and anaemia. Further information is provided in the olaparib Investigator's Brochure.

### 3.2.3 Rationale for patient reported outcomes

The assessment of patient-reported outcomes (PROs) in clinical research provides important insight into how therapies impact the daily lives of patients. Patient reports regarding health-related quality of life have proven more comprehensive than provider-collected data in breast cancer patients (Oberguggenberger et al 2011). Because olaparib is a new drug about which

little is known regarding toxicity and impact on quality of life, we will use questionnaires to assess overall quality of life, treatment satisfaction and tolerability symptoms in each of the two study arms.

### 3.2.4 Rationale for health economic data

The assessment of health economic resource use data will provide important information for payers and will be used within economic evaluations of olaparib.

### 3.2.5 Study Population

Approximately 310 metastatic breast cancer patients with *gBRCA1/2* mutations will be randomised into the study.

All patients recruited in the study will be selected based on the following principle:

- Genetic selection: Documented germline 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). Patients with *BRCA1* and/or *BRCA2* mutations that are considered to be non-detrimental (eg, "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favour polymorphism" or "benign polymorphism," etc) will not be eligible for the study.

In terms of *BRCA* mutation status, the following scenarios are considered:

- Status known: for patients already known to have a germline *BRCA* loss of function mutation (known as deleterious or suspected deleterious) the exact sequence variant must be recorded on the screening CRF and a copy of the genetic diagnosis available at site. These patients may be randomised into the study based on the known status, however, re-confirmation of the loss of function mutation from a blood sample will be undertaken by a central laboratory, Myriad Genetic Labs Inc.

- Status unknown: The germline *BRCA* mutation status must be determined prior to randomisation as a loss of function mutation i.e. a known deleterious or suspected deleterious mutation

# 4. PATIENT SELECTION CRITERIA

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

Patients with unknown *BRCA* mutation status who are being considered for this trial should be identified early so that the appropriate *BRCA* mutation screening procedures can be put in place in a timely manner. These patients must fulfil all of the criteria marked with an asterisk below prior to *BRCA* mutation testing being carried out.

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

## 4.1 Inclusion criteria

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

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

2. *Patients must be male or female ≥18 years of age

3. *Histologically or cytologically confirmed breast cancer with evidence of metastatic disease

4. Documented 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)

5. *Patients must have received treatment with an anthracycline (e.g. doxorubicin, epirubicin) unless contraindicated and a taxane (e.g. paclitaxel, docetaxel) in either a neo-adjuvant / adjuvant or metastatic setting.

6. *Patients who have received platinum (cisplatin or carboplatin, either as monotherapy or in combination) for advanced breast cancer are eligible to enter the study provided there has been no evidence of disease progression during the platinum chemotherapy

7. Patients who have received prior platinum based chemotherapy are eligible if platinum was given either as potentially curative treatment for a prior non-breast cancer (eg ovarian cancer) with no evidence of disease for ≥ 5 years prior to study entry or as adjuvant/neoadjuvant treatment for breast cancer provided at least 12 months have elapsed between the last dose of platinum-based treatment and randomization

8. Patients with estrogen and/or progesterone receptor-positive disease must have received and progressed on at least one endocrine therapy (adjuvant or metastatic), or have disease that the treating physician believes to be inappropriate for endocrine therapy

9. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT (MRI where CT is contraindicated) and is suitable for repeated assessment as per RECIST 1.1.

10. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

- Haemoglobin ≥ 10.0 g/dL with no blood transfusions (packed red blood cells and platelet transfusions) in the past 28 days
- Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L
- Platelet count ≥ 100 x $10^9$/L
- Total bilirubin ≤ 1.5 x institutional upper limit of normal
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN
- Serum or plasma creatinine ≤ 1.5 x institutional upper limit of normal (ULN)

11. *ECOG performance status 0-1 within 21 days of randomisation

12. * Postmenopausal or hysterectomized; women of childbearing potential are eligible with a negative urine or serum pregnancy test documenting evidence of non-childbearing status.

    Postmenopausal is defined as any of the following:

    - Age ≥ 60 years
    - Age < 60 years and amenorrheic for 1 year or more in the absence of chemotherapy and/or hormonal treatment
    - luteinising hormone (LH), follicle stimulating hormone (FSH) and plasma oestradiol levels in the postmenopausal range for women under 60 years of age
    - radiation-induced oophorectomy with last menses >1 year ago
    - or surgical sterilisation (bilateral oophorectomy)

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

14. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary tumour if available

    For inclusion in

(a) the optional exploratory genetic research and/or

(b) the optional tumour biopsy research,

patients must fulfil the following criteria:

- Provision of informed consent for genetic research
- Provision of informed consent for tumour biopsy research

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

## 4.2 Exclusion criteria

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

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

2. *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.).

3. Cytotoxic chemotherapy or non-hormonal targeted therapy within 21 days of Cycle 1 Day 1 is not permitted. Endocrine therapy must have been discontinued 7 or more days before Cycle 1 Day 1. Palliative radiotherapy must have been completed 14 or more days before Cycle 1 Day 1. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 5 days prior to study treatment.

4. *Patients with HER2-positive disease (3+ by IHC or ISH amplified ≥ 2.0).

5. *Previous randomisation in the present study.

6. Exposure to an investigational product within 30 days or 5 half lives (whichever is longer) prior to randomisation

7. *Any previous treatment with a PARP inhibitor, including olaparib.

8. *Patients with second primary cancer, EXCEPTIONS: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, Ductal Carcinoma in Situ (DCIS), stage 1 grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years prior to study entry.

9. Resting ECG with QTc > 470 msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTc >470 msec, patient will be eligible only if repeat ECG demonstrates QTc ≤470 msec.

10. *Patients cannot have received more than 2 prior lines of cytotoxic chemotherapy for metastatic disease. Prior treatments with hormonal therapy and non-hormonal targeted therapy are allowed and not counted as a prior line of cytotoxic chemotherapy. For the purposes of this protocol, the combination of an aromatase inhibitor and everolimus is not considered cytotoxic chemotherapy.

11. *Concomitant use of known potent CYP3A inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. For further detail refer to Appendix I.

12. Persistent toxicities (≥CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy.

13. *Patients with myelodysplastic syndrome/treatment related acute myeloid leukaemia.

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

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

16. *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 bilateral lung disease on High Resolution Computed Tomography scan or any psychiatric disorder that would limit ability to comply with study procedures, and any other medical condition that, in the opinion of the investigator, places the patient at unacceptable risk of toxicity.

17. *Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria: Disease outside the CNS is present. No clinical evidence of progression since completion of CNS-directed therapy. Minimum of 2 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥3) acute toxicity with no ongoing requirement for > 10mg of prednisone per day or an equivalent dose of other corticosteroid.

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

19. Pregnant or breast feeding women.

20. *Previous allogeneic bone marrow transplant.

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

22. *Whole blood transfusions in the last 120 days prior to enrolment to the study which may interfere with *gBRCA* testing (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.10)

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

# 5. STUDY CONDUCT

## 5.1 Restrictions during the study

### 5.1.1 Contraception

Female patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 1 month after last dose of study drug.

Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination, throughout the period of taking study treatment and for 3 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm. Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drug(s).

For details please refer to Appendix F Acceptable Birth Control Method.

### 5.1.2 Olaparib and CYP3A

Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A enzyme activity (see Section 5.6.1) from the time they enter the screening period until 30 days after the last dose of study medication.

## 5.2 Patient enrolment and randomisation and initiation of study treatment

The Principal Investigator will:

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

2. Patients will be assigned a unique patient identifier which should be used to identify the patient on the eCRFs and any other trial-related communications (Ecode).

3. Determine patient eligibility. See Sections 4.1 and 4.2.

4. Randomise the patient using the randomisation system which is available for this trial, answering all questions which are asked by the system including questions relative to the stratification factors.

5. The randomisation system will randomly assign treatment (olaparib or chemotherapy) and this information will be made available to the site personnel.

As patients are screened for the study, they must be allocated an enrolment code (E-code). The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (e.g., the first patient screened at centre number 0001 would be assigned the E-code E0001001, the second patient screened would be E0001002 and so on). This number is the patient unique identifier and is used to identify the patient on the eCRFs.

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

### 5.2.1 Procedures for randomisation

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the IVRS/IWRS Centralised Randomisation Centre for allocation of randomised therapy. The investigator must declare prior to randomisation their choice of chemotherapy i.e. capecitabine or vinorelbine or eribulin.

The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the (IVRS/IWRS) database. The randomisation scheme will be produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers.

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

The randomisation scheme will be stratified based on:

- Received prior chemotherapy regimens for metastatic breast cancer (yes/no)
- ER and/or PgR positive vs ER and PgR negative
- Prior platinum for breast cancer (yes/no)

For the purpose of stratification, a patient is considered to have received a chemotherapy regimen if he or she received at least 1 cycle of chemotherapy (at least 3 infusions if weekly regimen), or if he or she progressed clinically before completing a full cycle.

Patients will be identified to the Centralised Randomisation Centre using patient E-code and date of birth.

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

Eligible patients will be randomised in a 2:1 ratio as specified below:

- olaparib tablets po 300 mg twice daily
- physician's choice of chemotherapy
  - Capecitabine 2500 mg/m$^2$ po daily (divided in 2 doses) x 14 days, repeat every 21 days
  - Vinorelbine 30 mg/m$^2$ IV Day 1 and Day 8, repeat every 21 days
  - Eribulin mesylate 1.4 mg/m2 or Eribulin (active substance) 1.23mg/m$^2$ IV Day 1 and Day 8, repeat every 21 days

It is recommended that patients commence study treatment as soon as possible after randomisation, and ideally within 3 days.

## 5.3 Procedures for handling patients incorrectly enrolled or randomised or initiated on study treatment

**Patients who fail to meet the inclusion/exclusion criteria** should not, under any circumstances, be enrolled or receive study treatment. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Team Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. Once a decision is made, Investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review.

The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped and be withdrawn from the study.

## 5.4 Blinding and procedures for unblinding the study – Not Applicable

## 5.5 Treatments

### 5.5.1 Identity of study treatment(s)

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib to the Investigator as green film-coated tablets as shown in Table 2 below.

**Table 2 Identity of investigational product**

| Investigational product | Dosage form and strength |
|---|---|
| Olaparib* | Tablet –100mg |
| Olaparib* | Tablet – 150mg |

* Descriptive information for olaparib can be found in the Investigator's Brochure

Capecitabine, vinorelbine and eribulin will be sourced locally. Only under exceptional circumstances when this isn't feasible these chemotherapies will be supplied through AstraZeneca. Descriptive information for capecitabine, vinorelbine and eribulin can be found in the local package inserts supplied with the drug.

### 5.5.2 Doses and treatment regimens

### 5.5.3 Olaparib

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

For all centres, olaparib will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. The randomised study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. The planned dose of 300 mg bid will be made up of two (2) x 150 mg tablets bid with 100 mg tablets used to manage dose reductions. Tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL 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/snack (e.g., two pieces of toast or a couple of biscuits).

No switch to olaparib will be provided in this study (i.e. chemotherapy patients will not be offered olaparib following their chemotherapy).

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.

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

#### 5.5.3.1 Chemotherapy

Dosing and treatment regimen information for capecitabine, vinorelbine and eribulin can be found in the local package inserts supplied with the drug. Please follow the prescribing information for toxicity management and dose reduction.

Standard or reduced dose of capecitabine can be used after the first cycle as per standard clinical practice.

### 5.5.4 Additional study drug- Not applicable

### 5.5.5 Labelling

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

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

The patient emergency contact details will not be on the label, unless it is a country-specific regulatory requirement, 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.

### 5.5.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the olaparib bottle specifies the appropriate storage. Storage conditions for chemotherapy can be found in the local package inserts supplied with the drug.

### 5.5.7 Management of toxicity of olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted.

#### 5.5.7.1 Management of haematological toxicity

**Management of anaemia**

**Table 3 Management of anaemia**

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

Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to dedicated section "Management of prolonged haematological toxicities while on study treatment" for the management of these cases.

**Management of neutropenia, leukopenia and thrombocytopenia**

**Table 4 Management of neutropenia, leukopenia and throbocytopenia**

| *Toxicity* | *Study treatment dose adjustment* |
|---|---|
| CTCAE gr 1-2 | Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation |
| CTCAE gr 3-4 | Dose interruption until recovered to CTCAE gr 1 for a maximum of 4 weeks, and dose reduction to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step |

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if required.

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 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

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

Study treatment can be interrupted for CTCAE grade 1 /2 neutropenia or thrombocytopenia as per investigator's judgement. In case of CTCAE grade 3/4 neutropenia, leukopenia or thrombocytopenia, study treatment should be interrupted for a maximum of 4 weeks. Study treatment can be restarted at the same dose if an adverse event of neutropenia, leukopenia or thrombocytopenia have been recovered up to CTCAE grade 1 or less. Any subsequent interruptions will require study treatment dose reductions to 250 mg twice daily as a first step and to 200 mg twice daily as a second step.

**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 (Platelets < 50 x $10^9$/L)

Weekly differential blood counts including reticulocytes and peripheral blood smear should be performed. 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.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety.

### 5.5.7.2 Management of non-haematological toxicity

**Management of new or worsening pulmonary symptoms**

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in study treatment dosing is recommended and a diagnostic workup (including

a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

**Management of nausea and vomiting**

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They 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 with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines, dexamethasone.

**Interruptions for intercurrent non-toxicity related events**

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with 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 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.

### 5.5.8 Management of toxicity of chemotherapy

Information on dosing and management of toxicity of capecitabine, vinorelbine and eribulin can be found in the local package inserts supplied with the drug. The use of any marketed comparator should be according to the local label.

Hypokalemia or hypomagnesemia should be corrected prior to initiating eribulin and these electrolytes should be monitored periodically during therapy.

## 5.6 Concomitant and post-study treatment(s)

Any medications (with the detailed exceptions) which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the investigator, providing the medications, the doses, dates and reasons for administration are recorded.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded. This includes any blood transfusions.

The reasons for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate sections of the eCRF.

All medications (prescriptions or over the counter medications) continued at the start of study or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

### 5.6.1 CYP3A restrictions for olaparib arm

The use of any natural/herbal products or other "folk remedies" should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded.

Olaparib produced little/no direct inhibition in vitro of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 but inhibition of CYP3A4 was seen when olaparib was tested at high concentrations, suggesting that olaparib has the potential to cause clinically relevant interactions with other CYP3A substrates in the liver or gastrointestinal tract. Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro, with CYP3A4 being most likely to be induced to a clinically relevant extent. Since olaparib may reduce exposure to substrates of CYP3A through enzyme induction, the efficacy of hormonal contraceptives may be reduced if co-administered with olaparib. In vitro data have also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4/5 and in vivo data have shown that co-administration with itraconazole (a known CYP3A inhibitor) increases olaparib AUC by an average of 2.7-fold. Consequently, to ensure patient safety, the following potent inhibitors of CYP3A must not be used during this study for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

For patients taking any of the above, the required wash-out periods prior to starting study treatment is one week.

In addition, in vivo data have shown that co-administration with rifampicin (a known CYP inducer) reduces olaparib AUC by an average of 87%. Therefore, to avoid potential reductions in exposure due to drug interactions, the following CYP3A inducers should be avoided:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*)

For patients taking any of the above, the required wash-out periods prior to starting study treatment are phenobarbitone 5 weeks, and for any of the others, 3 weeks.

After randomisation if the use of any potent inducers or inhibitors of CYP3A are considered necessary for the patient's safety and welfare, the investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

### 5.6.2 Effect of olaparib on other drugs

Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 and UGT1A1 substrates in the liver or GI tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP3A4 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and Pgp is unknown. It cannot be excluded that olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.

In vitro, olaparib has been shown to be an inhibitor of Pgp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and is a weak inhibitor of BRCP. It cannot be excluded that olaparib may increase the exposure to substrates of Pgp (eg, statins, digoxin, dabigatran, colchicine), OATP1B1 (eg, bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (eg, metformin), OCT2 (eg, serum creatinine), OAT3, MATE1 and MATE2K. In particular, caution should be exercised if olaparib is administered in combination with any statin.

### 5.6.3 Interaction of olaparib and specific co-medications

Preliminary data suggest that there is no clinically meaningful drug-drug interaction between anti-hormonal agents, tamoxifen (20 mg), anastrozole (1 mg) or letrozole (2.5 mg) when given in combination with olaparib (300 mg tablet), at steady state.

### 5.6.4 Anti-emetics/ Anti-diarrhoeals

Should a patient develop nausea, vomiting and/or diarrhoea, then these symptoms should be reported as AEs (see section 6.4.3) and appropriate treatment of the event given.

### 5.6.5 Anticoagulant Therapy

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

### 5.6.6 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment.

Treatment with bisphosphonates or RANKL inhibitor for the prevention of skeletal related events in patients with bone metastasis is permitted and must be started at least 5 days prior to randomisation.

### 5.6.7 Subsequent therapies for cancer

Details of first and subsequent therapies for cancer after discontinuation of treatment, will be collected.

The choice of subsequent systemic anticancer treatment will be entirely at the discretion of the investigator.

### 5.6.8 Live virus and bacterial vaccines

Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30-day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

## 5.7 Treatment compliance

The administration of all study drugs (including olaparib and chemotherapy) should be recorded in the appropriate sections of the eCRF.

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

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

Chemotherapy will be administered at the study site as per standard practise and dose delays and modifications recorded in the eCRF.

### 5.7.1 Accountability

The study treatment provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed and returned.

Study site personnel, will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed. Any discrepancies must be accounted for on the appropriate forms.

## 5.8 Discontinuation of study treatment

Patients may discontinue study treatment in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Objective radiological disease progression
- Adverse Event
- Severe non-compliance to study protocol
- Death

### 5.8.1 Procedures for discontinuation of a patient from study treatment

A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); questionnaires and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 5.9.

Any patient discontinuing study treatment should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study treatment, 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 eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study treatment 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 Sections 6.4.3 and 6.4.4). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4.4) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study treatment to collect and / or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment should also be reported as an AE.

All patients must be followed for survival and PFS2, up to the final analysis.

## 5.9 Withdrawal from study

Patients are at any time free to withdraw from study (study treatment and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); questionnaires and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

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

*If a patient decides at any point in the trial that they do not wish to continue with the full study schedule of assessments but are still willing to provide important study information (e.g. disease recurrence information and/or survival status information) then the patient should continue in the study and information should continue to be collected on the clinical database. However if a patient does not wish to have any further data collected, only then should they be considered as withdrawing consent from the study. To minimise the number of cases of early withdrawal the investigator should discuss the options with the patient in case they would still be willing to undergo reduced assessments and/or reduced data collection, in which case they would remain in the study.

If a patient withdraws consent (ie no further assessment or collection of their data) they will be specifically asked if they are also withdrawing consent to the use of any of their samples (tumour and blood) taken during the trial (see section 6.6 and 6.7).

Data obtained prior to withdrawal of consent will be maintained in the clinical database and used in the study reporting.

The status of ongoing, withdrawn (from the study) and 'lost to follow up' patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to collection of further 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.

# 6. COLLECTION OF STUDY VARIABLES

## 6.1 Recording of data

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

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

## 6.2 Study procedures

A study initiation visit must be conducted at the centre prior to the commencement of any study activities requiring informed consent. A schedule for the tests and evaluations to be conducted in this study is contained in this section and in Table 1.

### 6.2.1 Screening procedures

The following assessments and procedures should be performed during screening Part 1 and Part 2 as per Figure 1 and Table 1.

For details of the schedule and nature of assessments see below:

- Date of birth, sex, race and ethnicity
- Medical and surgical history including previous cancer and radiotherapy and history of blood transfusions in previous 120 days

- Family history of cancer
- Current and concomitant medications including previous cancer therapies
- ECOG Performance Status
- Vital signs (supine blood pressure and pulse; body temperature), body weight, height
- Haematology /Clinical chemistry/Urinalysis
- Physical examination
- CT (or MRI if CT is contraindicated) of chest, abdomen and pelvis
- ECG (within 7 days prior to the start of the study treatment)
- Menopausal status; serum or urine pregnancy test for women of childbearing potential. The pregnancy test should be prior to performing the *BRCA* blood test during screening part 1, within 28 days prior to the start of study treatment and confirmed on day 1 prior to dosing
- For patients with **unknown** BRCA status: *BRCA1/2* mutation status. 2 blood samples: One blood sample to test for *BRCA* mutations using the current commercial Myriad *BRCA*nalysis test, and the second blood sample for a bridging study to validate the companion diagnostic test for olaparib.
- Adverse events must be captured from time of consent. However, in Screening Part 1 of the study only SAEs related to study procedures will be collected. In Screening Part 2 all AEs/SAEs will be collected
- Archival paraffin embedded tumour tissue sample, if available
- Tumour biopsy (optional)
- EORTC QLQ-C30 should be completed prior to randomisation once eligibility is confirmed

The Principal Investigator/Sub-Investigator should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

### 6.2.2 **On treatment procedures**

The visit schedule is based on 21-day cycles.

Patients will attend the clinic weekly on days 1 (1st day of treatment), 8 and 15, following the commencement of study treatment and then every 3 weeks (day 1 of every cycle) until discontinuation of treatment.

The following assessments will be performed at time points specified in the study schedule (see Table 1):

- Vital signs. Body weight is only required at day 1 of 1st day of study treatment, if it has not been assessed within 7 days of randomisation. Any other time as clinically indicated
- Haematology and clinical chemistry: Safety blood samples do not need to be repeated on Day 1 of study treatment if there have been separate assessments within 7 days before starting study treatment and which must have been 3 weeks after last dose of chemotherapy based therapy, unless the investigator believes that it is likely to have changed significantly
- Physical examination (assessments post Day 1 are not required to be captured on an eCRF, however any significant changes from baseline must be reported as an AE)
- CT of chest, abdomen and pelvis (or MRI if CT is contraindicated) performed until objective disease progression. RECIST assessments to be scheduled every 6 weeks (±1 week) from randomisation for the first 24 weeks and then every 12 weeks (±1 week). If progression is not confirmed by BICR an additional scan will be requested at the next scheduled visit. CT/MRI of chest, abdomen and pelvis to be performed until objective disease progression.
- ECG any time if clinically indicated
- Urinalysis any time if clinically indicated
- Serum or urine pregnancy test for women of childbearing potential (prior to treatment on day 1 of 1st day of study treatment). If the test is positive then a confirmatory test should be performed
- For patients with **known** BRCA status: *BRCA1/2* mutation status. 2 blood samples: One blood sample to test for *BRCA* mutations using the current commercial Myriad *BRCA*nalysis test, and the second blood sample for a bridging study to validate the companion diagnostic test for olaparib
- AE and concomitant medications (including any blood transfusions) at every visit
- Patient Reported Outcomes and Quality of life questionnaire: EORTC QLQ-C30 at baseline (prior to randomisation once eligibility is confirmed), and then every 6 weeks until disease progression. CTSQ-16 every 6 weeks and at end of study treatment.

- An optional pharmacogenetic sample will be obtained from consenting patients and stored for future exploratory pharmacogenetic analysis (Section 6.7.1)
- Optional tumour biopsy at disease progression (Section 6.6.4)
- Mandatory blood sample for biomarker analysis at Day 1 and disease progression (Section 6.6.1)

Once patients have discontinued study treatment, other treatment options will be at the discretion of the investigator. Within this study chemotherapy patients will not be offered olaparib at any time.

### 6.2.3 Follow-up procedures

#### 6.2.3.1 Treatment discontinuation visit due to objective radiological disease progression

Patients should be discontinued from study treatment if they have objective radiological disease progression according to RECIST (see Appendix G).

Following radiological disease progression patients will be followed for PFS2 and OS.

#### 6.2.3.2 Treatment discontinuation visit due to any other discontinuation criteria

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 5.8). The assessments to be carried out at the visit are detailed in the study schedule (Table 1).

Patients who have discontinued from treatment but do not have radiological disease progression will continue to be followed for PFS by RECIST assessments every 6 weeks from date of randomisation during the first 24 weeks and then every 12 weeks thereafter. Relevant PRO assessments should also continue until disease progression as per the study plan.

#### 6.2.3.3 Patients who have objective radiological disease progression but continue on study treatment

Patients should be discontinued from study treatment if they have objective radiological disease progression according to RECIST (see Appendix G), however, patients may be allowed to continue study treatment if the investigator believes, and AZ Study Physician concurs, that the patient could continue to receive benefit, the patient is not experiencing serious toxicity, and there is no available better alternative treatment that could benefit the patient. These patients will continue study procedures as per Table 1 and will be followed for PFS2 and OS. Safety assessment can occur with the same frequency as the visits unless more frequent testing is clinically indicated.

#### 6.2.3.4 Follow-up 30 day after last dose of study treatment (follow-up visit)

A follow-up visit should be conducted 30 days after the last dose of study treatment. Any serious and/or non-serious AEs ongoing at the time of the Discontinuation Visit or which have

occurred during the defined 30-day follow-up period must be followed-up (in accordance with Section 6.4.3). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30 day follow up visit are detailed in the study schedule (Table 1).

### 6.2.4 Survival

Assessments for survival should be made every 8 weeks ±7days following objective radiological disease progression. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. Survival data will be collected up to the time of the final overall survival (OS) analysis. In addition, patients should be contacted in the week following the data cut-off for the primary PFS and overall survival analyses to provide complete survival data.

Patients will be followed up as per Table 1 to the point of the final analysis. At this point investigators will be notified that no further data collection for the study is required. Monitoring and recording of SAEs will continue as per Section 6.4.4.

The status of patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 5.9).

### 6.2.5 Second Progression

Following first objective progression as per RECIST, copies of the patient's radiological scans are no longer required to be sent for blinded independent central review, provided the central read confirms progression. If first objective progression is not confirmed by the central review then a further scan should be scheduled at the next RECIST visit and submitted for central review. Following first objective progression patients will be assessed every 8 weeks for a second progression (using the patient's status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of objective radiological, symptomatic disease progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of disease progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

### 6.2.6 Patient management post primary PFS analysis

The data cut off date for the statistical analysis for the primary objective of the study will be established when approximately 230 confirmed progression events (~75% maturity for PFS analysis) are expected to have occurred.

Patients on study treatment at the time of the data cut-off will continue to receive study treatment until they meet any discontinuation criteria as per Section 5.8.

Patients on study treatment will be followed for core safety assessments (haematology, clinical chemistry, AEs/SAEs, concomitant medications and study treatment dosing details).

Once the primary PFS analysis has been performed the collection of RECIST data for independent central review will cease. Patients who have not had an objective disease progression at the time of the data cut off for the primary PFS analysis should continue to have RECIST assessments until first objective disease progression is determined by the investigator. RECIST assessments should be performed every 12 weeks from the last assessment prior to the data cut off date. Following first progression patients should be assessed for second progression based on radiological or symptomatic progression or death. Patients will also be followed for information on vital status to obtain the data needed for the OS analysis.

### 6.2.7 Patient management post final OS analysis

The data cut off date for the final statistical analysis of the study will be established when ~190 confirmed OS (~60% maturity for OS analysis) are expected to have occurred.

At this time point, the clinical study database will close to new data. Patients who are receiving treatment can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit; patients may continue to receive study treatment. All patients will receive follow up care in accordance with standard local clinical practice.

AstraZeneca will continue to supply olaparib after completion of this study until either olaparib is licenced in that country, or it is determined that the benefit to risk profile does not support continued development of olaparib, or the national health authority has deemed the drug not approvable. In all these scenarios, AstraZeneca will work with investigators on the proper transition of patients to alternative therapies if possible.

SAEs will continue to be reported to AstraZeneca Patient Safety Department, for any patients who continue on olaparib until 30 days after study treatment is discontinued, in accordance with Section 6.4.4. Additionally as stated any SAE or non-serious adverse event, that is ongoing at the end of the study, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

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). If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca Patient Safety.

For Pharmacovigilance purposes, however, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported as a SAE (**and will generally meet at least one of the serious criteria, see section 6.4.2**) to AstraZeneca Patient Safety **regardless of investigator's assessment of causality or knowledge of the treatment arm**. A Questionnaire will be sent to any investigator reporting MDS/AML requesting detailed information on the case.

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.

Drug accountability should continue to be performed until the patient stops study treatment completely.

## 6.3 Efficacy

### 6.3.1 CT and MRI scans Tumour assessments (RECIST 1.1)

Following the baseline assessment, subsequent tumour assessments according to RECIST should be performed at the end of every 6 weeks (±1week) for the first 24 weeks and then every 12 week (±1week) thereafter up to objective disease progression by RECIST. Patients who are determined to have progressed according to RECIST 1.1 criteria by the Investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled RECIST visit.

All patients should be followed until objective progression, regardless of treatment decisions (study treatment and subsequent therapies).

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

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

Anonymised copies of the scans are to be sent to an AstraZeneca appointed CRO for blinded independent central review.

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

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit ± 1 week window interval and the patient has not

progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST as per the study schedule (see Table 1 and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

### 6.3.2 Tumour Evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment by determining progression free survival (PFS) times (the RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in Appendix G.).

Categorisation of objective tumour response assessment will be based on the RECIST criteria of response: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD) and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of a best response of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before randomisation.

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

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

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

### 6.3.3 Central reading of scans

An independent review of all scans used in the assessment of tumours according to RECIST will be conducted for data collected up to the data cut off for the primary analysis of PFS. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (CRO) for central analysis. The management of patients will be based upon the results of the RECIST assessment conducted by the investigator.

The primary analysis for this study will be based on the blinded independent central review (BICR) of the radiological scans.

## 6.4 Safety

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

### 6.4.1 Definition of adverse events

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

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

### 6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

### 6.4.3 Recording of adverse events

**Time period for collection of adverse events**

Adverse Events will be collected from time of signature of informed consent throughout the treatment period up to and including the 30-day follow-up period. However, in Screening PART 1 of the study only SAEs related to study procedures will be collected.

All ongoing and any new AEs/SAEs identified during the 30 calendar days follow up period after the last dose of study medication must be followed to resolution.

**Follow-up of unresolved adverse events**

Any SAEs or non-serious adverse event 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.

**Variables**

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Outcome.

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

- D ate AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

**Severity of AE**

For each episode on an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. 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. 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.

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 NCI website.

**Causality collection**

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, 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 investigational product?'

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

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

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

**Adverse Events based on examinations and tests**

The reporting of laboratory/vital signs/ECG abnormality as AE should be avoided unless 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 (eg. 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.

**NB.** Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law' for further instructions.

**Disease progression**

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. The development of loco regional recurrence or distant 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.

**New cancers**

The development of a new primary cancer (including skin cancer) should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 6.4.2). New primary cancers 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.

**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.

**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 6.4.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

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

### 6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, 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 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events 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 immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

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

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

### 6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Schedule (see Table 1).

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

The following laboratory variables will be measured:

#### 6.4.5.1 Full haematology assessments for safety

- haemoglobin
- red blood cells [RBC]
- platelets
- mean cell volume [MCV]
- mean cell haemoglobin concentration [MCHC]
- mean cell haemoglobin [MCH]
- white blood cells [WBC]
- absolute differential white cell count
  - (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials

#### 6.4.5.2 Coagulation

- Activated partial thromboblastin time (APTT) will be performed at baseline and if clinically indicated.
- International normalised ratio (INR) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR

and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

#### 6.4.5.3 Biochemistry assessments for safety

- sodium
- potassium
- calcium
- creatinine
- total bilirubin
- gamma glutamyltransferase [GGT]
- alkaline phosphatase [ALP]
- aspartate transaminase [AST]
- alanine transaminase [ALT]
- urea or blood urea nitrogen [BUN]
- total protein
- albumin

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

For blood volume see Section 7.1.

#### 6.4.5.4 Urinalysis

Urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

#### 6.4.5.5 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 5.5.7.1.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then

attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database.

### 6.4.6 Physical examination

For timing of individual measurement refer to study schedule (Table 1).

A physical examination will be performed and include a clinical examination of the breasts and local lymph nodes, and an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

### 6.4.7 ECG

#### 6.4.7.1 Resting 12-lead ECG

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

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

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

### 6.4.8 Vital signs

Supine 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 on a bed.

Body temperature will be measured in degrees Celsius using an automated thermometer.

Height will be assessed at screening only.

Weight will be assessed at screening and as clinically indicated at any other time.

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

For timings of assessments refer to the Study Schedule (seeTable 1).

### 6.4.9 Other safety assessments

#### 6.4.9.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential as per the study schedule. Tests will be performed by the hospital's

local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

## 6.5 Patient reported outcomes (PRO)

The assessment of patient-reported outcomes (PROs) in clinical research provides important insight into how therapies impact the daily lives of patients. Patient reports regarding health-related quality of life have proven more comprehensive than provider-collected data in breast cancer patients (Oberguggenberger et al 2011). Because olaparib is a new drug about which little is known regarding toxicity and impact on quality of life, we will use questionnaires to assess overall quality of life, treatment satisfaction and tolerability symptoms in each of the two study arms

### 6.5.1 EORTC QLQ-C30

In this study patient-reported disease related symptoms and health-related quality of life (HRQoL) will be evaluated using the validated EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 questionnaire was developed to assess HRQoL and is the most commonly used cancer-specific tool in oncology. It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation and has been used in gastric cancer trials.

The EORTC QLQ-C30 comprises 30 questions designed for all cancer types. Questions can be grouped into the following scales:

- 5 multi-item functional scales (physical, role, emotional, cognitive and social)
- 3 multi-item symptom scales (fatigue, pain, nausea vomiting)
- A 2-item global QoL scale
- 5 single items assessing the following common cancer symptoms:
  - dyspnoea,
  - loss of appetite,
  - insomnia,
  - constipation,
  - diarrhoea
- 1 item on the financial impact of the disease.

All the EORTC scales range from 0 to 100 (through transformation of scores). A high scale score represents a higher response level. Thus a high score for a functional scale represents a

high / healthy level of functioning, while a high score for a symptom scale / item represents a high level of symptomatology / problems.

### 6.5.2 CTSQ-16

The Cancer Therapy Satisfaction Questionnaire (CTSQ-16) has been psychometrically validated in breast cancer, colorectal cancer, lung cancer and melanoma patients who had received treatment in the last 6 months or were currently receiving more than one cycle of chemotherapy, biological or hormonal therapy. Its primary objective is to assess satisfaction with and preference for chemotherapy treatment, and for biological therapy in either pill or IV form (Trask et al 2008).

### 6.5.3 Administration of PRO questionnaires

Paper-based EORTC QLQ-C30 will be administered at baseline (prior to randomisation once eligibility is confirmed), and then every 6 weeks until disease progression.

Paper-based CTSQ will be administered every six weeks and at discontinuation of study treatment.

Each centre must allocate the responsibility for the administration of the questionnaires to a specific individual (e.g., a research nurse, study coordinator) and if possible assign a back-up person to cover if that individual is absent. The AZ Study Delivery Team (or delegate) will provide relevant training in administration of the questionnaires. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the PRO questionnaires are as follows:

- The EORTC QLQ-C30 should be completed before the CTSQ.
- They must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions. They must be completed in private by the patient
- The patient should be given sufficient time to complete at their own speed
- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire.
- On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness
- Only one answer should be recorded for each question

## 6.6 Biomarkers

Tumour and blood samples will be collected for mandated and optional biomarker work as detailed in the laboratory manual

For blood volume see Section 7.1.

### 6.6.1 Biomarker samples

The archival diagnostic tumour sample, the baseline blood samples for *BRCA* mutation status and the baseline and disease progression blood samples for biomarker analysis are all mandated samples.

**Table 5 Samples for Biomarker Research**

| Sample Type | Visits | Optional or Mandatory |
|---|---|---|
| Whole blood sample for prospective germline *BRCA* testing at central laboratory for patients with unknown *BRCA* status for confirmation of *BRCA* status for those with previous results | Screening for patients with unknown *gBRCA* status<br>Day 1 for patients with known local *gBRCA* test | Mandatory |
| Whole blood sample for assessment of current and future *BRCA* mutation assay(s) | Screening for patients with unknown *gBRCA* status<br>Day 1 for patients with known local *gBRCA* test | Mandatory |
| Archival tumour sample | Screening | Mandatory, if available, for all randomised patients |
| On-study screening and disease progression tumour biopsy | Screening and disease progression | Optional |
| Blood samples for biomarker analysis (including buffy coat sample only on day 1) | Day 1 and disease progression | Mandatory |
| Blood for optional exploratory pharmacogenetics | Day 1 | Optional |

The samples and data from this research will be coded and not labelled with any personal details. Each sample will be identified with the study and patient enrolment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled. However, only the investigator will be able to link the biomarker sample to the individual patient. The coded samples may be made available to groups or organisations working with AstraZeneca on this research or as part of the development of the drug and companion diagnostic. However, the samples and any results will remain the responsibility of AstraZeneca at all times. AstraZeneca will not give samples,

sample derivatives or data derived from the samples to any other parties except as required by law.

Biomarker data may be generated in real time during the study or retrospectively and will have unknown clinical significance. AstraZeneca will not provide biomarker results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party unless required to do so by law. The patient's samples will not be used for any other purpose other than those described in the protocol.

The exception to the above is the *gBRCA* status result from the Myriad assessment for patients with previously unknown local *BRCA* status. This result will be provided to the investigator and will be collected as part of the patient's demography and medical history details.

### 6.6.2 Collection of blood sample for Myriad germline *BRCA1* and *BRCA2* testing

All patients must have a known deleterious or suspected deleterious *gBRCA* mutation to be randomised; this may have been determined prior to study entry or may be assessed as part of the enrolment procedure for the study (via Myriad).

#### 6.6.2.1 Guidance for *BRCA* testing of patients with known *BRCA* status.

For patients that can be randomised to the study on the basis of a pre-existing known *gBRCA* mutation test result, a blood sample for a confirmatory *BRCA* mutation test by Myriad must be taken once the patient has consented to the study. Should the result from the Myriad test indicate the patient does not have a deleterious or suspected deleterious *BRCA* mutation, the patient can continue in the study and can continue to receive their allocated study treatment if deemed appropriate by the investigator.

Residual blood (or its derivatives) may be used to evaluate future BRCA companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence (including BRCA mutation status and its role in response).

#### 6.6.2.2 Guidance for *BRCA* testing of patients with unknown *BRCA* status.

Patients that do not know their *BRCA* status, but meet all other eligibility criteria must have a Myriad test prior to randomisation in to the study. A blood sample for the Myriad *BRCA* test can be taken once all local ethical procedures for such testing have been completed. If the result shows that the patient has a deleterious/suspected deleterious *gBRCA* mutation, the patient can then be randomised to the study. In order to limit the time that the patient is not receiving study treatment after their last dose of chemotherapy, it may be necessary for the patient to have a Myriad *BRCA* test whilst still on chemotherapy.

Residual blood (or its derivatives) may be used to evaluate future BRCA companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response,

understand the mode of action of study treatment, and improve the understanding of disease recurrence (including BRCA mutation status and its role in response).

#### 6.6.2.3 Collection of a blood sample for assessment of current and future BRCA mutation assay(s)

All patients will be required to provide a mandatory 9 ml blood sample that will be stored for subsequent assessment of current and future BRCA mutation assay(s).

Samples may be required to support subsequent analysis as part of a bridging study between the Myriad BRCA test to be used in this study and the "to be marketed" diagnostic test which is currently under development. Samples are required to be collected from all patients including those shown not to have a deleterious or suspected deleterious BRCA1 or BRCA2 mutation.

Samples may also be used to investigate future BRCA mutation assays as well as mutations in other genes known/predicted to have a role in breast cancer.

### 6.6.3 Exploratory Biomarker Research on Archival Tumour Samples (Mandatory, if available)

These samples will be collected from the site pathologist during the screening period. An adequately sized (minimum of 2 mm x 2 mm) historical tumour tissue paraffin block from a core biopsy or resection from the primary tumour or metastatic site should be provided. This sample will have been collected anytime since the time of original diagnosis but prior to study entry. Alternatively, sections mounted on glass slides prepared from the block can be provided.

Collection of an archival tumour sample is mandated if available for all randomised patients for the assessment of tissue *BRCA* mutation status, however further exploratory work is planned on surplus tissue. This material may be used for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, improve the understanding of disease progression (including tumour *BRCA* mutation status and its role in response).

Please refer to Investigator Laboratory Manual for further details of archival tissue collection, shipping and storage.

### 6.6.4 Exploratory Biomarker Research on Tumour Biopsy Samples (Optional)

Biopsies may be particularly valuable where there is a marked phenotypic change in a particular lesion and investigators are encouraged to contact AstraZeneca in these cases.

When a patient presents with a biopsiable tumour, an on-study tumour biopsy sample should be obtained, (only in patients that have signed the additional optional consent). A sample should be taken prior to dosing with study drug and a second tumour biopsy sample taken at disease progression.

Patients will not be excluded from the study if these samples are not collected.

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

Please refer to Investigator Laboratory Manual for further details of on-study tumour tissue collection, shipping and storage.

#### 6.6.5 Exploratory Blood samples for biomarker analysis (Mandatory)

All consenting patients will be required to provide a blood sample at day 1 and disease progression for exploratory biomarker research.

Patients will be required to provide:

- 1x 6ml blood sample for preparation of serum at day 1 and disease progression.
- 2x 10ml blood sample for preparation of plasma at day 1 and disease progression.
  - A buffy coat collection in addition to the plasma layer collection is required from the blood sample for preparation of plasma only on day 1.

Please refer to Laboratory Manual for further details of on-study biomarker blood sample collection, shipping and storage.

## 6.7 Pharmacogenetics

#### 6.7.1 Collection of pharmacogenetic samples

An optional pharmacogenetic sample (9 mL) will be obtained from consenting patients and stored for future exploratory pharmacogenetic analysis. The sample will be taken after randomisation on day 1of the first randomised treatment preferably or at subsequent visits. Patients do not have to consent to this sample in order to participate in the study.

Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

## 6.8 Health economics

For the purposes of economic evaluation it is necessary to capture hospital resource use related to the treatment and the underlying disease. Within the clinical trial the following will be captured:

1. Number of hospitalisations and attendances

2. Primary symptom/reason associated with hospitalisation or attendance

3. Length of stay, including time in intensive care.

Additional information, including concomitant medication and procedures undertaken will also be collected.

## 6.9 Pharmacokinetics

PK sampling to be performed in a subset of patients. Each patient will be asked to contribute 5 blood samples, one from each of the pre defined time windows below on Day 1 Cycle 2.

- Pre-dose
- Between 0 and 0.5 hour post-dose
- Between 0.5 and 1.5 hour post-dose
- Between 3 and 6 hours post-dose
- Between 6 and 12 hours post-dose

### 6.9.1 Pharmacokinetic samples (Subset of patients)

Approximately 50 patients randomised to olaparib, at pre-agreed sites will have PK assessment samples taken.

### 6.9.2 Collection of samples

PK samples are to be taken as blood sample (4 mL) for determination of olaparib concentrations in plasma. It is essential that PK blood sampling is conducted within the sampling windows indicated above.

To ensure that the assessments are carried out according to this order, and that PK sampling is as close as possible to the time window, it will be necessary to arrange the assessment procedures so that the PK assessments fall on/around the correct timing. The actual time of dosing and collection of all PK samples must be recorded as described below:

On Day 1 Cycle 2 the times of ALL five samples, the morning dose (pre-dose) and the evening dose on the day of sampling and the evening dose the day before should be recorded

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1

### 6.9.3 Determination of drug concentration

Samples for determination of olaparib concentrations in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Full instructions for collection, labeling, storage and shipment of samples are provided in the Laboratory Manual. Results will only be reported for samples shipped within a timeframe for which the stability of olaparib in the samples has been validated and shown to be acceptable.

# *7.* BIOLOGICAL SAMPLING PROCEDURES

## 7.1 Volume of blood

The volume of blood that will be drawn from each patient will vary, dependent upon the length of time that the patient remains in the trial and if the patient is in the subset having PK samples taken. The total volume of blood to be drawn from each patient in the study (including for PK samples), assuming they complete screening, 4 cycles of treatment, a treatment discontinuation visit and the 30-day follow-up visit, is 189 mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change. Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.

The total volume of blood that will be drawn from each patient in this study is as follows:

**Table 6 Volume of blood to be drawn from each patient**

| Assessment | | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|---|
| Safety | Clinical chemistry | 5 | 9 | 45 |
| | Haematology | 5 | 9 | 45 |
| Whole blood sample for Myriad BRCA test (retrospective/prospective) | | 9 | 1 | 9 |
| Whole blood sample for assessment of current and future BRCA mutation assay(s) | | 9 | 1 | 9 |
| Pharmacogenetics (optional) | | 9 | 1 | 9 |
| Serum Pregnancy test | | Site dependent | Site may use urine instead | |
| Serum sample for exploratory biomarkers, day 1 (mandatory) | | 6 | 1 | 6 |

**Table 6 Volume of blood to be drawn from each patient**

| Assessment | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|
| Plasma / buffy coat sample for exploratory biomarkers, day 1 (mandatory) | 10 | 2 | 20 |
| Serum sample for exploratory biomarkers, disease progression (mandatory) | 6 | 1 | 6 |
| Plasma sample for exploratory biomarkers, disease progression (mandatory) | 10 | 2 | 20 |
| Pharmacokinetic (Blood samples processed to plasma & frozen) | 4 | 5 | 20 |
| Total | | | 189 |

## 7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research will be retained at AstraZeneca or a CRO, on behalf of AstraZeneca for a maximum of 15 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report.

### 7.2.1 Pharmacogenetic samples

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

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used

to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

#### 7.2.2 Pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses will be reported separately from the CSR. Anonymised samples will be retained for no more than 5 years after the CSR is finalised.

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

## 7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

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

## 7.4 Chain of custody of biological samples

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

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site, according to local regulations or at the end of the retention period, whichever is the sooner.

## 7.5 Withdrawal of informed consent for donated biological samples

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

*BRCA* sample: As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

Archival tumour sample: Although mandatory, the patient may continue in the study if the patient is already randomised.

Tumour biopsy samples: As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

Blood samples for biomarker analysis: Although mandatory, the patient may continue in the study if the patient is already randomised.

Blood sample for pharmacogenetic analysis: As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

# 8. ETHICAL AND REGULATORY REQUIREMENTS

## 8.1 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/Good Clinical Practice, applicable

regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

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

The exception to the above is the result of the Myriad *gBRCA* test. This will be made available to the Investigator and patient.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

## 8.3 Ethics and regulatory review

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

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

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

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

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

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

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

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

## 8.4 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.

## 8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, National Co-ordinating Investigator, and the Principal Investigator and AstraZeneca.

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

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

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

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

## 8.6 Audits and inspections

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

# 9. STUDY MANAGEMENT BY ASTRAZENECA

## 9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

## 9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the

investigational staff and also train them in any study specific procedures and the WBDC system 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).

## 9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

### 9.3.1 **Source data**

Refer to the Clinical Study Agreement for location of source data.

## 9.4 Study agreements

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

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

#### 9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

## 9.5 Study timetable and end of study

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

The study is expected to start in [redacted] and to end by [redacted]

The study may be terminated at individual centres if the study procedures are not being performed according to 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.

# 10. DATA MANAGEMENT BY ASTRAZENECA

Data management will be performed by AstraZeneca Data Management Centre staff.

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

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, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Data from external providers (e.g. central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database. In the case of biomarker (tumour tissue or blood for exploratory analyses) data, the results of any analyses will not be recorded in the database, but information relating to the processing of the sample, including the original date of biopsy (historical tumour tissue

sample and the actual date the sample(s) were collected) will be recorded in the eCRF and database.

Exploratory genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this exploratory genetic research may be reported in the CSR.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Site staff will enter PRO booklet data into Medidata Rave.

# 11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

## 11.1 Calculation or derivation of efficacy variable(s)

At each visit patients will be programmatically assigned a RECIST visit response of CR, PR, SD, PD, NE depending on the status of their disease compared to baseline and previous assessments, based on the BICR review. This will be repeated using the Investigator assessed RECIST data.

### 11.1.1 **Primary endpoint**

PFS is defined as the time from randomisation until the date of objective radiological disease progression according to RECIST 1.1 or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to disease progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline (13 weeks allowing for visit window).

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

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

(c) The date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or for either reviewer where both select PD as time point response and there is no adjudication for BICR data.

(d) For investigational site assessments, date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that triggered the progression.

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

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

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

The primary analysis will be based on the blinded independent central review (BICR) of the radiological scans. A charter for the BICR will be developed in advance of the start of the study. A sensitivity analysis based on the programmatically derived PFS based on Investigator-recorded assessments will be carried out.

As a supportive summary to PFS, time to start of first subsequent cancer therapy or death will be assessed (see Section 12.2.3.1). Time to first subsequent cancer therapy or death is defined as the time from the date of randomisation to the earlier of first subsequent cancer therapy start date, or death date. Any patient not known to have had a further subsequent cancer therapy or death will be censored at the last known time to have not received subsequent cancer therapy.

### 11.1.2 Secondary endpoints

#### 11.1.2.1 Overall Survival

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

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

#### 11.1.2.2 Time from randomisation to second progression (PFS2)

Time from randomisation to second progression is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death. The date of second progression will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. Second progression status will be reviewed every 8 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a

second disease progression, i.e. censored at the last progression assessment date if the patient has not had a second progression or death).

As a supportive summary to PFS2, time to start of second subsequent cancer therapy or death (TSST) will be assessed. Time to second subsequent cancer therapy or death is defined as the time from the date of randomisation to the earlier of the date of second subsequent cancer therapy start date, or death date. Any patient not known to have had a further second subsequent cancer therapy or death will be censored at the last known time to have not received second subsequent therapy.

#### 11.1.2.3 Best overall RECIST response (BoR)

Best overall RECIST response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Appendix G. It is the best response a patient has had following randomisation but prior to starting any subsequent cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorisation of best overall response will be determined programmatically based on the RECIST 1.1 criteria (Appendix G) for the BICR data, using the following response categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Best overall response will be determined programmatically from the time point response using BICR data. In addition, this will also be reported using investigator-recorded assessment.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 6 weeks +/- 1 week, i.e. at least 35 days (to allow for the assessment window), after randomisation. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For patients whose disease progression event is death, BoR will be calculated based on data up until the last evaluable RECIST assessment prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurred ≤13 weeks (i.e. 12 weeks ±1 week) after randomisation then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurred > 13 weeks (i.e. 12 weeks ±1 week) after randomisation then BoR will be assigned to the non-evaluable (NE) category.

Progression events that have been censored due to them being more than two missed visits after the last evaluable assessment will not contribute to the BoR derivation.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time up to and including the defined analysis cut-off point. For each treatment group, the objective response rate (ORR) is the number patients with a CR and PR divided by the number of patients in the treatment group in the evaluable for response (EFR) analysis set.

Only patients with measurable disease at enrolment can achieve an objective response of CR or PR.

## 11.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, physical examination, laboratory data including clinical chemistry and haematology, vital signs including blood pressure(BP), pulse and ECG. These will be collected for all patients. Appropriate summaries of these data will be presented.

### 11.2.1 Other significant adverse events (OAE)

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 DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are 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.

## 11.3 Calculation or derivation of patient reported outcome variables

All items/questionnaires will be scored according to published scoring guidelines or the developer's guidelines, if published guidelines are not available.

**EORTC-QLQC30**

The EORTC QLQ-C30 will be scored according to the EORTC scoring manual (Fayers et al 1999). Each scale will be transformed to a 100-point scale as per the manual.

Mean change from baseline in health related quality of life (HRQoL) will be assessed using the EORTC QLQ-C30 global QoL scale which includes two items from the QLQ-C30: "How would you rate your overall health during the past week? (Item 29) and "How would you rate your overall quality of life during the past week? (Item 30).

HRQoL Visit responses

A change of at least 10 points in the global QoL score will be considered as a clinically relevant or a minimally important difference (Osoba D et al 1998).

A visit response of "deterioration" will be defined as a decrease of 10 points or more or where "Subject too heavily affected by symptoms of disease under investigation" is answered as the reason for not completing HRQoL at visit.

**Table 7 Visit response in Health Related QoL**

| Score | Change from baseline | Visit response |
|---|---|---|
| EORTC QLQ-C30 Global QoL score | ≥ +10 | Improved |
| | ≤ -10 or "Subject too heavily affected by symptoms of disease under investigation" is answered as the reason for not completing HRQoL at visit | Deterioration |
| | Otherwise | No change |
| EORTC QLQ-C30 functional scales: physical, role, emotional, cognitive and social | ≥ +10 | Improved |
| | ≤ -10 or "Subject too heavily affected by symptoms of disease under investigation" is answered as the reason for not completing HRQoL at visit | Deterioration |
| | Otherwise | No change |

A patient's best overall QoL response will be derived as the best QoL response the patient achieved, based on evaluable QoL data collected from randomisation up to the earliest of starting any subsequent cancer therapy or death. The criteria in Table 8 will be used to assign a best QoL response for HRQoL based on the 2-item global QoL score.

**Table 8 Best response in QLQ-C30 scores: FAS population**

| Overall Score Response | Criteria |
|---|---|
| Improved | Two visit responses of "improved" a minimum of 21 days apart without an intervening visit response of "deterioration" |
| No Change | Does not qualify for overall score response of "improved". Two visit responses of either "no change" or "improved" and "no change" a minimum of 21 days apart without an intervening visit response of "deterioration" |
| Deterioration | Does not qualify for overall score response of "improved". A visit response of "deterioration" without response of "improved" or "no change" within 21 days. |
| Other | Does not qualify for one of the above. |

Change must be sustained for at least 21 days (i.e. there must be no response of "improved" or "no change" within 21 days of the visit response of "deterioration").

For each subscale, if less than 50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of

items on the subscales (Fayers et al 1999). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimised.

## 11.4 Calculation or derivation of pharmacokinetic variables

PK analysis of the plasma concentration data for olaparib will be performed at AstraZeneca R&D or by a CRO identified by AstraZeneca R&D. The actual sampling times will be used in the PK calculations. For each patient providing a complete set of PK samples, non-linear mixed effects modelling (NONMEM) will be used to estimate steady state Cmax, AUC and Cmin.

## 11.5 Calculation or derivation of pharmacodynamic variable(s) not applicable

## 11.6 Calculation or derivation of pharmacogenetic variables

To be defined in an exploratory analysis plan.

## 11.7 Calculation or derivation of health economic variables

Frequency of resource use including type, length of stay and procedures undertaken, and the primary symptom/reason for the hospitalisation or hospital attendance will be estimated.

# 12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

## 12.1 Description of analysis sets

A comprehensive statistical analysis plan (SAP) will be prepared and finalised before first patient in.

Table 9 gives a summary of outcome variables and analysis populations.

### 12.1.1 Full analysis set

**Intention to treat (ITT)**: The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and health-related QoL data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis.

### 12.1.2 Safety analysis set

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

### 12.1.3 Evaluable for response (EFR) analysis set

This is a subset of the ITT population, who have measurable disease at baseline as per the RECIST 1.1 criteria. Measurable disease will be defined using the BICR data for analyses of BICR data and using the investigator assessment data for analyses of investigator assessment.

### 12.1.4 PK Analysis set

PK data will be analysed according to treatment received. This population will comprise all patients who receive study treatment as per protocol (PP) and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

**Table 9 Summary of Outcome Variables and Analysis Populations**

| Outcome Variable | Populations |
|---|---|
| **Efficacy Data** | |
| - PFS | FAS (ITT) |
| - OS, PFS2, objective response rate, symptom/QoL endpoints | FAS (ITT) |
| Demography | FAS (ITT) |
| Pharmacokinetic data | PK |
| **Safety Data** | |
| - Exposure | Safety |
| - Adverse Events | Safety |
| - Lab measurements | Safety |
| - Vital Signs | Safety |

## 12.2 Methods of statistical analyses

The treatment comparison is olaparib 300 mg bid vs physician's choice of chemotherapy.

Results of all statistical analysis will be presented using a 95% confidence interval and 2-sided p-value.

The following table details which endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint

**Table 10 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses**

| Endpoints Analysed | Notes |
|---|---|
| PFS (Time from randomisation to first progression or death) | Primary analysis stratified log-rank test using BICR data |
| | Sensitivity/supportive analyses[a]: |
| | 1) Evaluation time bias analysis; stratified log-rank test using BICR data |
| | 2) Attrition bias analysis (using alternative censoring rules); stratified log-rank test using BICR data |
| | 3) Ascertainment bias analysis; stratified log-rank test using Investigator data |
| | 4) Deviation bias (if meaningful to do); stratified log-rank test using BICR data |
| | 5) Stratified log rank test of time from randomisation to first subsequent therapy or death<br>6) stratified log rank test using BICR data in randomised patients confirmed as *BRCA* mutation positive by central Myraid test (if applicable) |
| Overall Survival (Time from randomisation to death due to any cause) | Primary analysis: stratified log-rank test<br>Supportive analysis: KM plot of time to censoring for OS |
| PFS2 (Time from randomisation to second progression or death) | Primary analysis: Stratified log rank test based on investigator assessment of second progression<br>Supportive analysis: Stratified log rank test of time from randomisation to second subsequent therapy or death |
| Objective Response Rate (Number of patients who have a CR or PR determined using RECIST 1.1 criteria divided by the number of patients with measurable disease.) | Primary: ORR per treatment arm (descriptive only) based on BICR data<br>Supportive: ORR per treatment arm (descriptive only) based on investigator assessment |

**Table 10 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses**

| Endpoints Analysed | Notes |
|---|---|
| Adjusted mean change from baseline in global QoL score from the EORTC QLQ-C30 questionnaire | Primary analysis: mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit |

[a] See Section 12.2.2.1 for further details

### 12.2.1 Multiplicity strategy for primary and key secondary endpoints

In order to describe the nature of the effects of olaparib compared to chemotherapy, PFS, PFS2, and OS will be tested at a two-sided significance level of 5%.

In addition to these planned analyses, which will be performed and reported in the CSR, in order to strongly control the type I error at 2.5% (one-sided) for key label claims, a multiple testing procedure (MTP) will be employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS).

A hierarchical testing strategy will be employed where PFS will be tested first using the full test mass (full test mass = alpha 2.5% one-sided) and key secondary endpoints of PFS2 and OS will then be tested using the MTP with a recycling strategy (i.e., the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 2). The MTP is detailed below.

**Figure 2 Multiple Testing Procedure**


PFS2 will only be tested if statistical significance is shown for PFS. OS will only be tested if statistical significance is shown for PFS2. This testing will occur at the time of the primary PFS analysis (approximately 230 PFS events), and again when there are approximately 60% deaths (approximately 190 OS events). The Lan and DeMets approach that approximates the O'Brien & Fleming spending function will be employed to preserve the overall 1-sided type-I error rate of 2.5% (Lan and DeMets 1983).

If the first analysis for PFS2 occurs at exactly 180 PFS2 events (58% overall data maturity predicted at the time of the primary PFS analysis), statistical significance for PFS2 will be declared if the null hypothesis for PFS is rejected and the observed one-sided p-value for

PFS2 is p<0.007, which equates to a HR of ≤0.68. The significance level at the final analysis will be determined based on the exact number of events at the time of the first and final analyses. If the first analysis for PFS2 occurs at exactly 180 PFS2 events and the final analysis occurs at exactly 255 PFS2 events, then the significance level to be applied at the final analysis will be 2.3%. Statistical significance for PFS2 will be declared if the observed p-value for PFS2 is p<0.023, which equates to a HR of ≤0.77.

If the first analysis for OS occurs at exactly 114 OS events (37% overall data maturity predicted at the time of the primary PFS analysis), statistical significance for OS will be declared if the null hypotheses for PFS and PFS2 are rejected and the observed one-sided p-value for OS is p<0.004, which equates to a HR of ≤0.59. If the first analysis for OS occurs at exactly 114 OS events and the final analysis occurs at exactly 190 OS events, then the significance level to be applied at the final analysis will be 2.4%. Statistical significance for OS will be declared if the observed p-value for OS is p<0.024, which equates to a HR of ≤0.74.

### 12.2.2 **Analysis of primary endpoint**

PFS will be analysed when approximately 230 progression events have occurred, based on the BICR data. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

PFS will be analysed using a log rank test stratified by the stratification factors. The hazard ratio (HR) and confidence interval will be estimated from the U and V statistics obtained directly from the LIFETEST model with inclusion of STRATA terms for the stratification variables (and using the Breslow approach for handling ties).

The HR and its confidence interval will be estimated from the log-rank as follows (Berry et al 1999 and Sellke et al 1983)

HR = exp(U/V)

95% CI for HR = (exp{U/V – 1.96/ √V}, exp{U/V + 1.96/ √V})

Where $U = \sum_i (d_{1i} - e_{1i})$ is the log-rank test statistic (with d1i and e1i the observed and expected events in group 1) and √V the standard deviation of the log-rank test statistic as produced in the LIFETEST output.

The HR (olaparib vs chemotherapy) together with its corresponding 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour olaparib).

Stratification variables will be defined according to data from the interactive voice/web response system (IVRS/IWRS). If there are any patients who were mis-stratified, a sensitivity analysis will be carried out using the (correct) baseline data collected in the eCRF.

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST or death) will be provided along with median PFS for each treatment arm.

The assumption of proportionality will be assessed. Note that in the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by producing plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation.

The primary analysis will be based on the programmatically derived PFS based on BICR assessments, and using all scans regardless of whether they were scheduled or not.

The estimated PFS rates at 6 months and 12 months will be summarised (using the KM curve) and presented by treatment group.

The number of patients prematurely censored will be summarised by treatment arm together with baseline prognostic factors of the prematurely censored patients. A patient is defined as prematurely censored if they had not progressed and the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

As patients will be randomised, imbalances in demographic factors between the treatment groups are not anticipated. However if any imbalances should occur, the HR and associated confidence interval calculated from a Cox Proportional Hazards model containing treatment, stratification variables and these additional demographic variables, may be reported.

Subgroup analyses will be conducted comparing PFS between treatments. The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and PFS will not be formally analysed. In this case, only descriptive summaries will be provided

The following subgroups of the full analysis set will be analysed for PFS

Stratification factors

- Received prior chemotherapy regimens for metastatic breast cancer (yes/no)
- ER and/or PgR positive vs ER and PgR negative
- Prior platinum for breast cancer (yes/no)

Additional subgroups of interest include:

- Progressive disease at time of randomisation (yes/no)

- Measurable versus non measurable disease
- *BRCA* mutation type, e.g. *BRCA1, BRCA2* or *BRCA1/2* (both)
- Age at randomisation
- Region
- Race

Other baseline variables may also be assessed if there is clinical justification.

For each subgroup, the HRs (olaparib: physician's choice of chemotherapy) and associated CIs will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term, factor and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison along with their confidence intervals will be obtained for each level of the subgroup from this single model. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall population (using the primary analysis).

No adjustment to the significance level for testing of subgroups will be made since all these subgroup analyses will be considered exploratory and may only be supportive of the primary analysis of PFS.

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates (stratification factors), and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach Gail and Simon 1985.

A further analysis of PFS (using Investigator assessed RECIST) may be performed at the time of the OS analyses, if requested by Health authorities.

#### 12.2.2.1 Sensitivity Analyses for Primary Endpoint

As a sensitivity analysis to the primary endpoint of PFS, the primary analysis will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used and the HR and associated 95% CI from a Cox Proportional Hazards model will be reported.

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (i.e., differential assessment times between treatment groups).

Summary statistics for the number of weeks between the time of progression and the last evaluable RECIST assessment prior to progression will be presented for each treatment group.

(a) Evaluation-Time bias

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analysed using a stratified log rank test, as described for the primary analysis of PFS. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010). This approach will use the BICR RECIST assessments.

(b) Attrition bias

Attrition bias will be assessed by repeating the primary PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

Additionally a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary PFS analysis is reversed will be presented.

(c) Ascertainment bias

A stratified log-rank test will be repeated using the programmatically derived RECIST using Investigator assessed PFS. The HR and 95% Confidence Interval will be presented.

If there is an important discrepancy between the primary analysis using BICR assessments and this sensitivity analysis using Investigator assessments, then the proportion of patients with site but no central confirmation of progression will be summarised. The approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value, but only if an important discrepancy exists.

Disagreements between investigator and central reviews of RECIST progression will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of investigator review progressions declared before the BICR as a proportion of all investigator review progressions and the late discrepancy rate which is the frequency of investigator review progressions declared after the BICR as a proportion of all discrepancies.

(d) Deviation bias (if meaningful to do)

As a sensitivity analysis to the primary endpoint of PFS, an analysis excluding patients with deviations that may affect the efficacy of the trial therapy will be performed if > 10% of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy

A stratified log-rank test will be repeated using the BICR RECIST data, using the same ties and stratification factors as described for the primary analysis of PFS. The HR and 95% CI will be presented.

As a supportive analysis, time to first subsequent therapy or death (TFST) will be analysed using the same methodology and model. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan Meier plot of time to start of subsequent therapy or death will be presented by treatment arm. The time between progression and starting subsequent therapy will also be assessed. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

A summary table of first subsequent therapies by treatment arm will be provided.

### 12.2.3 Analysis of secondary endpoints

#### 12.2.3.1 Analysis of PFS2 endpoint

An initial PFS2 analysis will be performed at the same time as the primary analysis of PFS and will use the same methodology and model. A further analysis of PFS2 will be performed when the OS data are approximately 60% mature. A Kaplan-Meier plot of PFS2 will be provided along with median PFS2 for each treatment. The number and percentage of patients experiencing a PFS2 event and the type of progression (objective radiological progression, symptomatic progression or death) will be summarised by treatment arm.
As a supportive analysis, time to start of second subsequent therapy or death (TSST) will be analysed using the same methodology and model. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan Meier plot of time to start of second subsequent therapy or death will be presented by treatment arm. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

A summary table of second subsequent therapies by treatment arm will be provided.

#### 12.2.3.2 Analysis of OS endpoint

OS data will be analysed at the time of the primary analysis of PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [> 20 deaths], if not descriptive summaries will be provided). A further analysis of OS will be performed when the OS data are approximately 60% mature.
The sensitivity analysis outlined for 12.2.2.1 will not be repeated for OS with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary OS is reversed.

#### 12.2.3.3 Summary of Best overall RECIST Response (BoR) and ORR

For each treatment arm, best overall response (BoR) will be summarised by n (%) for each category (CR, PR, SD, PD, NE). No formal statistical analyses are planned.

The objective response rate (ORR) will be summarised (i.e., number of patients (%)) by treatment group.

ORR and BOR will be presented based on the BICR data and also the investigator recorded data.

#### 12.2.3.4 Analysis of PRO endpoints

**HRQoL – Global score**

The primary assessment of HRQoL will focus on comparing mean changes from baseline in the global QoL Score (from the EORTC QLQ-C30 questionnaire) between the treatment arms. The analysis population for mean changes in HRQoL data will the FAS (ITT) set and will include all randomised patients with an evaluable baseline assessment and at least one evaluable post baseline assessment.

Change from baseline will be derived using a mixed model for repeated measures analysis of all of the post-baseline scores for each visit. Restricted maximum likelihood (REML) estimation will be used.

The model will include treatment, visit and treatment by visit interaction as explanatory variables and the baseline QoL score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model. The treatment by visit interaction will remain in the model regardless of significance.

The adjusted mean change from baseline estimates and corresponding 95% confidence intervals will be presented by visit for each treatment group and corresponding plots over time will be presented.

Data will be descriptive and plots will be used to visualise the adjusted mean global QoL score across time for each treatment arm.

An overall adjusted mean estimate will also be derived that will estimate the average treatment effect over visits giving each visit equal weight. For this overall treatment comparison, adjusted mean estimates per treatment group and corresponding 95% confidence intervals will be presented along with an estimate of the treatment difference, 95% confidence interval and p-value.

In addition, summary tables of the overall responses in global QoL score for each visit (improvement, deterioration and no change) will be presented by treatment arm as well as the best overall response. Only patients who have a baseline global QoL scores ≥10 will be included in the summaries of overall visit response and best response.

**HRQoL – additional item scores**

To support the primary assessment of HRQoL other items of interest will be summarised.

Unadjusted mean changes from baseline and overall visit responses (including best overall response) will be summarised for the following multi-item functional sub-scales from the EORTC QLQ-C30:

- Physical
- Role
- Emotional
- Cognitive
- Social

These additional sub-scales are considered exploratory to support the primary HRQoL endpoint (global score) and assess if any observed differences are driven by particular domains of functioning, symptoms or group of symptoms.

The remaining symptom scale scores of the QLQ-C30 (fatigue, pain vomiting and nausea) will be summarised descriptively based on tables and plots of unadjusted mean change from baseline. Overall visit responses and best visit response will not be reported for these domains..

HRQoL questionnaire compliance overall and over time will be summarised by randomised treatment.

**CTSQ**

Data from the CTSQ-16 scores of treatment satisfaction (as measured by the Satisfaction with Therapy scale and the other sub-scales and items of the CTSQ-16) will be summarised and listed by treatment arm.

**Compliance**

Overall compliance will be defined as the number of patients who provided both a baseline and at least one post baseline assessment for which there were sufficient data recorded for the visit to be evaluable for the global QoL score, divided by the number of patients randomised. Compliance over time is calculated separately for each visit, including baseline, as the number of patients providing an evaluable assessment for the global QoL score at that visit divided by the number of patients expected to have provided an assessment.

#### 12.2.3.5 Analysis of Healthcare Resource Use

An exploratory health economic analysis of resource use will be estimated, including descriptive statistics relating frequency of hospitalisations and hospital admission, type of attendance, length of stay and procedures undertaken, and the primary symptom/reason for the attendance.

#### 12.2.3.6 Pharmacokinetic analysis

The plasma concentration-time data will be analysed by non-linear mixed effects modelling in order to evaluate the pharmacokinetic characteristics of olaparib, quantify variability in the pharmacokinetics, identify demographic or pathophysiological covariates, which may explain the observed variability and explore exposure-response relationships.

The olaparib plasma concentration data obtained from the samples collected in this study will be included in the listings of the CSR but these data will be pooled with data from other studies in order to perform a population PK analysis. The results of this analysis will be reported in a separate population PK report.

### 12.2.4 Impact of Switching to PARP inhibitors (or other potentially active investigational agents) on Overall Survival Analyses

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of patients receive the therapies of interest. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), Inverse Probability of Censoring Weighting (IPCW) (Robins 1993) and other methods in development will be explored. The decision to adjust and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions. Baseline and time-dependent characteristics will be explored, and summaries of baseline characteristics will be summarised for patients receiving physician's choice of chemotherapy, splitting between those that have and haven't received a PARP inhibitor at the time of the analyses. Further detail will be provided in the SAP and Payer Analysis Plan. These analyses are intended to support reimbursement appraisals.

### 12.2.5 Exploratory translational science endpoints

Full statistical methods for exploratory endpoints will be defined in a separate translation science analysis plan.

**Biomarkers**

Biomarker data will be summarised descriptively using tables and plots. If the data is available at the time of developing the CSR then the biomarker data will be included in the CSR. Otherwise the biomarker data will be reported in a separate addendum to the CSR (if applicable). Further details on the data summaries and plots for the biomarker data for the CSRwill be provided in the SAP.

*BRCA* status will be summarised for all patients based on the central myriad test result. This will highlight any patients with a negative *BRCA* result from the central test.

### 12.2.6 Interim analysis

No interim analyses for PFS are planned for this trial. The primary analysis will occur when approximately 230 PFS events, based on BICR, have occurred. PFS2 and OS will be analysed at the time of the primary analysis for PFS. An additional PFS2 and OS analysis may be conducted with further follow up (~60% OS events) if PFS is statistically significant based on the primary analysis.

## 12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.
The primary endpoint of the study is PFS. In total 230 PFS events in the study would have 90% power to show statistically significant PFS at the one-sided 2.5% level if the assumed truetreatment effect were HR 0.635; this translates to an approximate 2 month clinically relevant improvement in median PFS over an assumed 4 month median PFS on chemotherapy assuming PFS is exponentially distributed.
Approximately 310 patients will be recruited (2:1 ratio) so that data maturity for the PFS analysis is approximately 75%.
It is estimated that the study recruitment period will be approximately 22 months and that 230 progression events will have occurred approximately 27 months after the first patient is randomised in the study. This will be the primary analysis of PFS. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

## 12.4 Independent Data monitoring committee

This study will use an external Independent Data Monitoring Committee (IDMC) to perform interim reviews of accumulating study safety data. This committee will be composed of therapeutic area experts and a statistician, who are not employed by AZ, and do not have any major conflict of interest. Following the review, the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will only include the recommendation and any potential protocol amendments. It will not contain any unblinded information. A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

In addition to the periodic review of safety data by an IDMC, the safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the study protocol and letters to investigators.

# 13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

## 13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4.**

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician/other physician at the AstraZeneca Research and Development

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## 13.2 Overdose

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

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 Investigators 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 SAE, standard reporting timelines apply (see Section 6.4.4). For other overdoses, reporting should be done within 30 days.

## 13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

### 13.3.1 Maternal exposure

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

The outcomes of any conception occurring from the date of the first dose of study medication until 3 months after the last dose of study medication must be followed up and documented.

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

If any pregnancy occurs in the course of the study, then Investigators 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 within 1 or 5 days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and Pregnancy Outcome Report on paper is used to report the outcome of the pregnancy.

### 13.3.2 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 partners is not considered to be an adverse event. 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.

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**Clinical Study Protocol Appendix B**

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|---|---|
| Drug Substance | Olaparib |
| Study Code | D0819C00003 |
| Edition Number | [redacted] |
| [redacted] | [redacted] |

# Appendix B
# Additional Safety Information

# FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

## Life threatening

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

## Hospitalisation

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

## Important medical event or medical intervention

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

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

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

# A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered 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 subject 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?

- Dechallenge 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.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

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

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

**Clinical Study Protocol Appendix C**

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| Drug Substance | Olaparib |
| Study Code | D0819C00003 |
| Edition Number | [redacted] |
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# Appendix C
# International Airline Transportation Association (IATA) 6.2 Guidance Document

# LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories
**(http://www.iata.org/whatwedo/cargo/dgr/Documents/DGR52_InfectiousSubstances(DGR362).pdf)**.
For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (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 **(http://www.iata.org/whatwedo/cargo/dgr/Documents/DGR52_PI650_EN.pdf)**

- **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.

**Clinical Study Protocol Appendix D**

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| Drug Substance | Olaparib |
| Study Code | D0819C00003 |
| Edition Number | [redacted] |
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# Appendix D
# Pharmacogenetics Research

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| CSR | Clinical Study Report |
| DNA | Deoxyribonucleic acid |
| LIMS | Laboratory information management system |
| PGx | Pharmacogenetics |

# 1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the olaparib clinical development programme to explore how genetic variations may affect the clinical parameters associated with olaparib and/or agents used in combination or as comparators. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Examples of genes that may be looked at are those encoding metabolising enzymes and transporter proteins. Future research may suggest other genes or gene categories as candidates for influencing not only response to olaparib but also susceptibility to cancer. Thus, this genetic research may involve study of additional un-named genes, but only as related to disease susceptibility, drug reaction and clinical response.

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to olaparib and/or agents used in combination or as comparators, and breast cancer under study within the current Clinical Study Protocol. No other research will be performed on the samples.

# 2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to olaparib and/or agents used in combination and/or as comparators and/or susceptibility to or prognosis of cancer.

# 3. GENETIC RESEARCH PLAN AND PROCEDURES

## 3.1 Selection of genetic research population

### 3.1.1 Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

### 3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

### 3.1.3 Exclusion criteria

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

### 3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

## 3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects on day 1 after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn on day 1, it may be taken on any day until the last study visit.

Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

## 3.3 Coding and storage of DNA samples

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

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.).

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results

with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

# 4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

## 4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

## 4.2 Subject data protection

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

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

# 5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

# 7. LIST OF REFERENCES

None

**Clinical Study Protocol Appendix E**

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| Drug Substance | Olaparib |
| Study Code | D0819C00003 |
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# Appendix E
# Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

# TABLE OF CONTENTS PAGE

# 1. INTRODUCTION

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 Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

# 2. DEFINITIONS

**Potential Hy's Law (PHL)**

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

**Hy's Law (HL)**

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

# 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 ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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

- Determine whether the patient meets PHL criteria (see Section 2 of 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:

- 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:

- Notify the AstraZeneca representative who will then inform the central Study Team

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

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

# 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 Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

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

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

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

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

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

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

# 6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT (NOT APPLICABLE)

# 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 chronic or progressing malignant disease?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 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 total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

# 8. 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

**Clinical Study Protocol Appendix F**

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| Drug Substance | AZD2281/Olaparib |
| Study Code | D0819C00003 |
| Edition Number | [redacted] |
| [redacted] | [redacted] |

# Appendix F
# Acceptable Birth Control Methods

# 1. ACCEPTABLE BIRTH CONTROL METHODS

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

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], 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).

<*include if recruiting male patients*> Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination [as listed below], throughout the period of taking study treatment and for 3 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below). Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drug(s).

## Acceptable Non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose. <<for 3 months after last dose *for male patients*>>. Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

## Acceptable hormonal methods:

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

**Clinical Study Protocol Appendix G**

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| Drug Substance | Olaparib |
| Study Code | D0819C00003 |
| Edition Number | [redacted] |
| [redacted] | [redacted] |

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

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# LIST OF TABLES

# 1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D0819C00003 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

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

Patients with at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT/MRI and is suitable for repeated assessment may be entered on this study.

**Measurable:**

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

**Non-measurable:**

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination
- Brain metastasis

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

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

**Special Cases:**

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

**Target lesions:**

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

**Non-Target lesions:**

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

# 3. METHODS OF ASSESSMENT

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

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

**Table 1: Summary of Methods of Assessment**

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

## 3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D0819C00003 study it is recommended that CT examinations of the chest, abdomen, and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

## 3.2 Clinical examination

In the D0819C00003 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

## 3.3 X-ray

### 3.3.1 Chest X-ray

In the D0819C00003 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

### 3.3.2 Plain X-ray

In the D0819C00003 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

## 3.4 Ultrasound

In the D0819C00003 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

## 3.5 Endoscopy and laparoscopy

In the D0819C00003 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

## 3.6 Tumour markers

In the D0819C00003 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

## 3.7 Cytology and histology

In the D0819C00003 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

## 3.8 Isotopic bone scan

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

In the D0819C00003 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

## 3.9 FDG-PET scan

In the D0819C00003 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

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

# 4. TUMOUR RESPONSE EVALUATION

## 4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment, and as close as possible to the start of study treatment and prior to randomisation. Follow-up assessments will be performed every 6 ±1 weeks for the first 24 weeks after randomisation and then every 12 ±1 weeks thereafter until objective

disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should also be adequately imaged at follow-up. Prior to primary analysis for PFS patients who are determined to have progressed according to RECIST 1.1 criteria by the Investigator will have progression confirmed by independent cental review. If progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled visit

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

## 4.2 Target lesions (TL)

### 4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

**Special cases:**

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

### 4.2.2 Evaluation of target lesions

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

**Table 2: Evaluation of target lesions**

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

## 4.3 Non-Target lesions (NTL)

### 4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

**Table 3: Evaluation of Non-Target Lesions**

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

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

## 4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

## 4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

## 4.6 Evaluation of Overall Visit Response

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

**Table 4: Overall Visit Response**

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

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

# 5. CENTRAL REVIEW

The Contract Research Organisation (CRO) appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

# 6. REFERENCES

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

**Clinical Study Protocol Appendix H**

| | |
|---|---|
| Drug Substance | Olaparib |
| Study Code | D0819C00003 |
| Edition Number | [redacted] |
| [redacted] | [redacted] |

# Appendix H
# ECOG Performance Status

# 1. ECOG PERFORMANCE STATUS

## 1.1 Example of Performance Status (ECOG SCALE)

| DESCRIPTION | ECOG GRADE |
|---|---|
| Fully active, able to carry on all pre-disease performance without restriction. | 0 |
| Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e. light housework, office work. | 1 |
| Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 2 |
| Capable of only limited self care, confined to bed or chair more than 50% of waking hours. | 3 |
| Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 4 |

**Clinical Study Protocol Appendix I**

| | |
|---|---|
| Drug Substance | Olaparib |
| Study Code | D0819C00003 |
| Edition Number | [redacted] |
| [redacted] | [redacted] |

# Appendix I
# CYP3A Guidance regarding potential interactions with concomitant medications

## TABLE OF CONTENTS PAGE



## LIST OF TABLES

# GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

NB. While this is not an exhaustive list, it covers the known potent inhibitors and inducers, which have most often previously been reported to be associated with clinically significant drug interactions. Please contact the Medical Monitor or AstraZeneca physician if further clarification is required.

## 1. POTENT INHIBITORS OF CYP3A:

In vitro data has shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4. Clinical studies conducted with a tablet formulation to evaluate the impact of known CYP3A inhibitors and inducers have shown that co-administration of a potent CYP3A inhibitor, itraconazole, increased olaparib Cmax 1.42-fold (90% CI: 1.33-1.52) and increased mean AUC 2.70-fold (90% CI: 2.44-2.97) and that co-administration of a potent CYP inducer, rifampicin, decreased Cmax by 71% (treatment ratio: 0.29; 90% CI: 0.24-0.33) and mean AUC by 87% (treatment ratio: 0.13; 90% CI: 0.11-0.16). It is therefore recommended that, to ensure patient safety, **the following inhibitors of CYP3A must not be used during this study.**

**Table 1 Competitive inhibitors of CYP3A**

| Drug | Minimum washout period prior to starting olaparib |
|---|---|
| Ketoconazole | 1 Week |
| Itraconazole | |
| Indinavir | |
| Saquinavir | |
| Telithromycin | |
| Nelfinavir | |

**Table 2 Time dependent inhibitors of CYP3A**

| Drug | Minimum washout period prior to starting olaparib |
|---|---|
| Clarithromycin | 1 Week |
| Ritonavir | |

## 2. INDUCERS OF CYP3A:

In addition, to avoid potential reductions in exposure due to drug interactions, **the following CYP3A inducers should be avoided:**

**Table 3 Inducers of CYP3A**

| Drug | Minimum washout period prior to starting olaparib |
|---|---|
| Carbamazepine | 3 Weeks |
| Modafinil | |
| Nevirapine | |
| Phenytoin | |
| Rifabutin | |
| Rifampicin | |
| Rifapentin | |
| St John's Wort (Hypericum perforatum) | |
| Phenobarbitone | 5 Weeks |

After randomisation if the use of any potent inducers or inhibitors of CYP3A are considered necessary for the patient's safety and welfare, the investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

## 3. NATURAL / HERBAL PRODUCTS:

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

## 4. EFFECT OF OLAPARIB ON OTHER DRUGS

Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 and UGT1A1 substrates in the liver or GI tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP3A4 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and Pgp is unknown. It cannot be excluded that olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.

In vitro, olaparib has been shown to be an inhibitor of Pgp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and is a weak inhibitor of BRCP. It cannot be excluded that olaparib may increase the exposure to substrates of Pgp (eg, statins, digoxin, dabigatran, colchicine), OATP1B1 (eg, bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (eg, metformin), OCT2 (eg, serum creatinine), OAT3, MATE1 and MATE2K. In particular, caution should be exercised if olaparib is administered in combination with any statin.

**Interaction of olaparib and specific co-medications**

Preliminary data suggest that there is no clinically meaningful drug-drug interaction between anti-hormonal agents, tamoxifen (20 mg), anastrozole (1 mg) or letrozole (2.5 mg) when given in combination with olaparib (300 mg tablet), at steady state.

AstraZeneca

| **Clinical Study Protocol Appendix J** | |
|---|---|
| Drug Substance | Olaparib |
| Study Code | D0819C00003 |
| Edition Number | [redacted] |
| [redacted] | [redacted] |

# Appendix J
# Patient Reported Outcomes EORTC QLQ-C30, CTSQ-16.

# EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

---

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

## During the past week:

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

## For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Cancer Therapy Satisfaction Questionnaire
## US English

**The following pages ask some questions about your cancer therapy (IV/pills). Within this questionnaire, "Cancer therapy (IV/pills)" refers to your current or most recent cancer therapy or cancer pills (including: hormonal therapy, IV therapy, and cancer pills). Please read each question and answer as honestly as you can without the help of anyone. There are no right or wrong answers; the answers should be based on your own personal experiences.**

### Your Thoughts about Cancer Therapy (IV/pills)

The following statements ask you to share your **thoughts about cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best represents your opinion (check only one box per question).

| | **In general, in the last four weeks, how *often did you feel*:** | **Always** | **Most of the time** | **Some-times** | **Rarely** | **Never** |
|---|---|---|---|---|---|---|
| 1. | That cancer therapy (IV/pills) would help you to return back to a normal life? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. | That cancer therapy (IV/pills) would get rid of the cancer? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. | That cancer therapy (IV/pills) would help prevent the cancer from coming back? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. | That cancer therapy (IV/pills) would stop the cancer from spreading? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. | That your cancer therapy (IV/pills) limited your daily activities? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. | Upset about the side effects? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. | That cancer therapy (IV/pills) was worth taking even with the side effects? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. | That cancer therapy (IV/pills) would help you live longer? | ☐ | ☐ | ☐ | ☐ | ☐ |

9. In general, **in the last four weeks**, how often did you think about stopping your cancer therapy (IV/pills)?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Always | Most of the time | Sometimes | Rarely | Never |

## Satisfaction with Cancer Therapy (IV/pills)

The following statements are about your satisfaction with your **most recent cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best describes your level of satisfaction (check only one box per question).

10. **Overall**, how worthwhile was your cancer therapy (IV/pills)?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Very worthwhile | Quite worthwhile | Moderately worthwhile | A little worthwhile | Not worthwhile at all |

11. **Overall,** was taking cancer therapy (IV/pills) as difficult as you expected?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Much more difficult than I thought it would be | Somewhat more difficult than I thought it would be | As difficult as I thought it would be | Somewhat easier than I thought it would be | Much easier than I thought it would be |

12. **Overall,** how well did the **benefits** of cancer therapy (IV/pills) meet your expectations?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Much better than my expectations | Somewhat better than my expectations | Met my expectations | Somewhat worse than my expectations | Much worse than my expectations |

13. **Overall,** were the **side effects** of cancer therapy (IV/pills) as you expected?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Much better than I expected | Somewhat better than I expected | Exactly as I expected | Somewhat worse than I expected | Much worse than I expected |

14. How satisfied were you with the **form** of your cancer therapy (IV/pills)?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Very satisfied | Satisfied | Neither satisfied nor dissatisfied | Dissatisfied | Very dissatisfied |

15. **Overall,** how satisfied were you with your most recent cancer therapy (IV/pills)?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Very satisfied | Satisfied | Neither satisfied nor dissatisfied | Dissatisfied | Very dissatisfied |

16. Taking everything into consideration, if given the choice again, would you decide to take this cancer therapy treatment?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Yes, definitely | Probably Yes | I don't know | Probably not | Definitely not |

**Thank you.**