AstraZeneca

Revised Clinical Study Protocol

Drug Substance	AZD2281
Study Code	D0818C00001
GOG Code	GOG-3004

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

This study is conducted by AstraZeneca in partnership with the Gynecologic Oncology Group (GOG) who are an expert in the disease area and will review and contribute to study specific documents such as the protocol, consent, statistical analysis plan and the clinical study report. GOG network sites in the US, Canada, Japan and Korea will be invited to participate in the study, GOG will also be involved in the review of site contracts and administer payments for US and Canada sites.

AstraZeneca Research and Development site representative

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

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

PROTOCOL SYNOPSIS

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy.

International Co-ordinating Investigators:

Study centre(s) and number of patients planned

The study will be conducted in approximately 18 countries world-wide. Approximately 200 centres will be initiated to randomise approximately 344 patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q3 2013	III
Estimated date of last patient completed	Q1 2023	III

Objectives

Primary:

To determine the efficacy by progression free survival (PFS) using investigator assessment according to modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.

Secondary:

1. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of overall survival (OS), time to earliest progression by RECIST or Cancer Antigen-125 (CA-125), or death, and time from randomisation to second progression (PFS2)

2. To compare the effects of olaparib maintenance monotherapy compared to placebo on Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy

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 potential future *BRCA* mutation assays (gene sequencing and large rearrangement analysis)

4. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST) and time from randomisation to study treatment discontinuation or death (TDT).

Safety:

1. To assess the safety and tolerability of olaparib maintenance monotherapy in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy

Exploratory:

1.

2. To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L)

3. To explore the impact of treatment and disease on resource use

4. To explore the effects of olaparib maintenance monotherapy as assessed by the individual domains of the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)

5. To explore the efficacy of olaparib by assessment of overall survival (OS) adjusting for the impact of spontaneous switching [outside of study design] to Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or other potentially active investigational agents

6.

7. Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumor samples that were mandatory for entry onto the study or on optional tumor biopsy samples collected during the course of the study

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.

Study design

This is a phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in high risk advanced ovarian cancer patients (including patients with primary peritoneal and / or fallopian tube cancer) with BRCA mutations [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) who have responded following first line platinum based chemotherapy.

Patients will be randomised in a 2:1 ratio to the treatments as specified below:

- olaparib tablets *p.o.* 300mg twice daily.
- placebo tablets *p.o.* twice daily.

Randomisation will be stratified by:

- response to first line platinum chemotherapy (clinical complete response or partial response)

Patients will be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

Patients in both treatment arms will have tumour assessments according to RECIST at baseline and every 12 weeks (±1 week) up to 3 years (156 weeks) and then every 24 weeks (±1 week) relative to date of randomisation, until objective radiological disease progression according to RECIST. All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. After the primary Progression Free Survival (PFS) analysis, central review of scans will no longer be required.

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

All patients will continue to be assessed for radiological tumour assessments according to the study schedule (Table 1, Table 2, Table 3 and Table 4), until objective radiological disease progression, irrespective of their continuation on study treatment.

If a patient progresses and remains on treatment they will continue to be assessed and will be followed for second progression and then survival according to the study schedule (Table 3). Once a patient has progressed and discontinued treatment the patient will be followed as per local clinical practice, but assessment should be made every 12 weeks for second progression and then survival until the final analysis (Table 4).

Target patient population

Eligible patients will be those patients with newly diagnosed, histologically confirmed, high risk advanced (International Federation of Gynecology and Obstetrics (FIGO) stage III-IV)

BRCA mutated high grade serous or high grade endometriod (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who are in clinical complete response or partial response following completion of first line platinum-based chemotherapy. Patients who re-present following prior diagnosis at an earlier stage of disease are not eligible. Stage III patients should have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.

Patients must have completed a minimum of six treatment and a maximum of nine treatment cycles of first line platinum-based therapy (e.g., carboplatin or cisplatin) before randomisation to the study and should have a clinical complete response or a partial response. However, if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of four cycles of the platinum regimen.

Patients must not have received bevacizumab (either in combination or as maintenance therapy following combination therapy) or any investigational agent during their first line course of treatment.

Patients known to have germline BRCA mutation/s (gBRCAm i.e., blood) prior to randomisation can enter the study based on this result. The result must be made available to AstraZeneca. In addition the patients must consent to provide 2 blood samples. One sample will be used for a confirmatory Myriad gBRCA test post randomisation using the current commercial Myriad BRAC*Analysis*® (gene sequencing and large rearrangement analysis), which will be paid for by AstraZeneca.

Patients with unknown BRCA status must consent to provide 2 blood samples for germline BRCA testing, which will be paid for by AstraZeneca, and follow all local ethical procedures for genetic testing. One sample will be used to test for BRCA mutations using the current commercial Myriad BRAC*Analysis*® test prior to study entry. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious BRCA mutation, the patient can be randomised into the study (providing they have fulfilled all other screening requirements).

These samples will be required for the study even if the patients are found not to have a BRCA mutation.

Patients that have a BRCA mutation identified via assessment of tumour may also be enrolled on the trial provided that all such testing has been undertaken in appropriately accredited laboratories (i.e., testing done for research use only will not be acceptable). These patients still

need a Myriad test, regardless of the result, they are eligible for randomisation as long as they fulfil all other screening criteria.

Investigational product, dosage and mode of administration

Olaparib is available as a green film-coated tablet containing 150 mg or 100 mg of olaparib. Patients will be administered study treatment orally at a dose of 300 mg twice daily (twice daily). The planned dose of 300 mg twice daily will be made up of two x 150 mg tablets twice daily with 100 mg tablets used to manage dose reductions.

Comparator, dosage and mode of administration

Placebo will be available as green film-coated tablets matching the olaparib tablets. These should be taken as per instructions for olaparib tablets.

Duration of treatment

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Patients should continue with study treatment to RECIST progression as described above despite rises in CA-125. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. Within this study patients are not permitted to switch over to the opposite arm from which they were randomised.

Outcome variable(s):

- **Primary outcome variable**
  - Progression Free Survival (PFS) by review of investigator-reported RECIST data
- **Secondary outcome variables**
  - Overall Survival

- Time to earliest Progression by RECIST or CA-125 or death
- Time from randomisation to second progression (PFS2)
- Time from randomisation to first subsequent therapy or death (TFST)
- Time from randomisation to second subsequent therapy or death (TSST).
- Time from randomisation to study treatment discontinuation or death (TDT)
- The Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy - Ovarian Cancer (FACT-O) will be used to determine:
  - Change from baseline in TOI score
  - Proportion improved
-

- **Safety outcome variables**
  - Adverse event (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology.
- **Exploratory outcome variables**
  -
  - EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index.
  - Patient-reported outcomes based on the Functional Assessment of Cancer Therapy - Ovarian (FACT-O).
  - Resource use as captured including inpatient admissions, intensive care unit (ICU) and length of stay in hospital
  - Overall survival adjusted for impact of subsequent PARP inhibitor trial or treatment
  - Potential retrospective biomarker & pharmacogenetic research (optional).
  - The individual domains of the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy –Ovarian Cancer (FACT-O) will be used to determine:

– Change from baseline in TOI domain score

– Proportion improved

Statistical methods

In total 206 PFS events in the study would have 90% power to show statistically significant PFS at the 2-sided 5% level if the assumed true treatment effect were hazard ratio (HR) 0.62; this translates to a 8 month benefit in median PFS over 13 months on placebo (estimated from data reported by Alsop et al 2012) if PFS is exponentially distributed. Approximately 344 patients will be recruited (2:1 ratio) so that data maturity for the PFS analysis is approximately 60%. Assuming 18 months non-linear recruitment, 206 investigator-assessed PFS events are expected to occur approximately 36 months after first subject in is enrolled in the study (FSI). This will be the primary analysis of PFS.

The global recruitment to the study will close when approximately 344 patients are randomised. The primary statistical analysis of the efficacy of olaparib will include all patients who are randomised as part of the global enrolment.

The primary analysis will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised as part of the global enrolment but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and health-related quality of life (HRQoL) data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis.

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 placebo). The safety data will be summarised descriptively and will not be formally analysed.

PFS will be analysed using a log rank test stratified by response to first line platinum chemotherapy (clinical complete response or partial response). The HR together with its 95% confidence interval and p-value will be presented (a HR less than 1 will favour olaparib). This analysis will be performed when approximately 196 events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first. The primary analysis will be based on investigator-recorded assessment of disease progression by RECIST; however, sensitivity analyses will be performed including using the blinded independent central review (BICR) of disease progression.

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). Included will be a subgroup analysis by Myriad gBRCA mutation status (gBRCAm status confirmed by Myriad test vs gBRCA wildtype (wt) or missing by Myriad gBRCA test). 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). 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.

Analyses of time to first subsequent therapy (TFST) and time to second subsequent therapy (TSST) will be conducted, using the same methodology as specified for the primary analyses of PFS.

Supportive analyses of time to earliest progression by RECIST or CA-125 or death and TDT will be provided, using the same methodology as specified for the primary analyses of PFS, however no multiple adjustment will be applied as these are viewed as supportive endpoints.

In order to describe the nature of the benefits of olaparib maintenance treatment, PFS, PFS2, TFST, TSST, change from baseline in TOI score and OS will be tested at a 2-sided significance level of 5%. However, in order to strongly control the type I error, a multiple testing procedure will also be employed where PFS is tested first using the full test mass, PFS2 will be tested if the null hypothesis for PFS is rejected, and OS will only be tested if statistical significance is shown for PFS and PFS2.

An interim analysis for OS and PFS2 will be performed at the time of the PFS analysis (approximately 100 OS events).

A further analysis of OS and PFS2 will be performed when the OS data are approximately 60% mature (approximately 206 events); this is anticipated to occur approximately 80 months after FSI.

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment (or other potentially active investigational agents) may be performed if a sufficient proportion of patients switch. 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. Details will be pre-specified in the statistical analysis plan (SAP) and Payer analysis plan.

Analysis of Patient Reported Outcomes (PRO) endpoints:

The analysis population for HRQoL data will be the FAS (ITT) set. Change from baseline in TOI score will be regarded as the primary analysis of the FACT-O questionnaire and will be analysed using a mixed model repeated measures (MMRM) analysis of the change from baseline TOI score.

Analysis of Exploratory endpoints:

EQ-5D-5L

Descriptive statistics, graphs and listings will be reported for health state utility values and visual analogue scale by visits as well as change in these scores from baseline. To support future economic evaluations of olaparib, additional appropriate analyses may be undertaken, for example, mean health state utility pre and post treatment, and pre and post progression.

FACT-O

Descriptive statistics, graphs and listings will be reported to explore the impact of olaparib on symptoms and HRQoL. The relationship between patient-reported outcomes and progression and AEs will be assessed using descriptive summaries.

Further details of the exploratory analysis based on the FACT-O will be outlined in the SAP.

Resource Use

Appropriate analyses of resource use, including hospitalisations and reasons thereof, will be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of olaparib.

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.

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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 phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboblastin time
AST	Aspartate aminotransferase
Baseline	Refers to the most recent assessment of any variable prior to dosing with study treatment
BD	Twice daily
BICR	Blinded Independent Central Review
BoR	Best Overall RECIST Response
BP	Blood pressure
BRCA	Breast Cancer susceptibility gene
BRAC*Analysis*®	Gene sequencing and large rearrangement analysis for Hereditary Breast and Ovarian Cancer, registered trademark of Myriad Genetics, Inc
BRCA mutation or BRCAm	Breast Cancer susceptibility gene mutation (see gBRCA mutation or gBRCAm)
BUN	Blood urea nitrogen
CA-125	Cancer Antigen - 125
cfDNA	Circulating free DNA
CHO	Chinese hamster ovary
CI	Confidence Interval

Abbreviation or special term	Explanation
CCR	Clinical Complete Response. 'Response' is used throughout the protocol and refers to patients being, in the opinion of the investigator, in clinical complete response or partial response on the post-treatment scan. Clinical complete response is defined as no evidence of RECIST measurable or non-measurable disease on the post-treatment scan and a normal CA-125. Partial response is defined as ≥30% reduction in tumor volume demonstrated from the start to finish of chemotherapy OR no evidence of RECIST measurable disease on the post-treatment scan with a CA-125 which has not decreased to within the normal range.
CR	Complete response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
CTC / CTCAE	Common Terminology Criteria for Adverse Event
CYP450	Cytochrome P450 (enzyme)
DAE	Discontinuation of Investigational Product due to Adverse Event
DCIS	Ductal Carcinoma in Situ
DCO	Data Cut Off
DNA	Deoxyribonucleic acid
DSB	Double strand break
DUS	Disease under Study
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E-code	Enrolment code (allocated by IVRS/IWRS)
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patients disease is progressing
EMA	European Medicines Agency
EQ-5D-5L / EQ-5D	EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index
EWB	Emotional well being
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-O	Functional Assessment of Cancer Therapy – Ovarian: A multidimensional questionnaire for patients with ovarian cancer

Abbreviation or special term	Explanation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FIGO	International Federation of Gynecology and Obstetrics
FSH	Follicle stimulating hormone
FSI	First Subject In
FWB	Functional well being
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 (Richards et al 2008).
GBRCA wt	gBRCA wildtype
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
GOG	Gynecologic Oncology Group
Grand	AZ Global Randomisation system
Hb	Haemoglobin
HCT	Haematocrit
HDPE	High-density polyethylene
HGSOC	High-grade serous ovarian cancer
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HR	Homologous recombination repair
HRCT	High Resolution Computed Tomography
HRD	Homologous recombination repair deficiencies
HRT	Hormone replacement therapy
HRQoL	Health-related Quality of Life
IATA	International Air Transport Association
IB	Investigator’s brochure

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
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.
ICR	Independent Central Review
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intentions to Treat
IPCW	Inverse Probability of Censoring Weighting
IVR System	Interactive Voice Response System
IWR System	Interactive Web Response System
KM	Kaplan Meier
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
LPLV	Last Patient Last Visit
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milli-gram
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic resonance imaging
MTP	Multiple Testing Procedure
NCI	National Cancer Institute
NE	Not evaluable
NED	No Evidence of Disease
NTL	Non-target lesions

Abbreviation or special term	Explanation
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
ORR	Objective response rates
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation
PD	Progressive disease
PFS / PFS1	Progression Free Survival
PFS2	Time from randomisation to second progression
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetics
p.o.	Per os (by mouth, orally)
PR	Partial response. 'Response' is used throughout the protocol and refers to patients being, in the opinion of the investigator, in clinical complete response or partial response on the post-treatment scan. Clinical complete response is defined as no evidence of RECIST measurable disease on the post-treatment scan and a normal CA-125. Partial response is defined as ≥30% reduction in tumor volume demonstrated from the start to finish of chemotherapy OR no evidence of RECIST measurable disease on the post-treatment scan with a CA-125 which has not decreased to within the normal range.
PRO	Patient Reported Outcomes
PWB	Physical well being
QoL	Quality of Life
R&D	Research and Development
RBC	Red blood cell
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use modified RECIST version 1.1
RI	Reticulocyte index
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
SGPT	Serum Glutamic Pyruvate Transaminase

Abbreviation or special term	Explanation
SSB	Single strand break
SUSARs	Suspected Unexpected Serious Adverse Reactions
SWB	Social well being
Study treatment	Olaparib or matching placebo
tBRCA mutation or tBRCAm	The term "tBRCA mutation" is used to refer to a somatic tumour 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 (Richards et al 2008).
TDT	Time from randomisation to study treatment discontinuation or death
TFST	Time from randomisation to first subsequent therapy or death
TL	Target lesions
TOI	Trial Outcome Index
TSST	Time from randomisation to second subsequent therapy or death
UCL	Upper Confidence Limit
ULN	Upper limit of normal
WBC	White blood cells
WBDC	Web Based Data Capture
wt	Wildtype (patients without evidence of BRCA1 or BRCA2 deleterious or suspected deleterious mutations)

1. INTRODUCTION

1.1 Background

1.1.1 Ovarian cancer and its treatment

Ovarian cancer is the fifth most common cause of death from cancer in women (Colombo et al 2010; NCCN Clinical Practice Guidelines in Oncology). In the United States there are about 21,550 new cases and 14,600 deaths estimated annually. In the European Community, approximately 28,000 new cases of ovarian cancer and approximately 17,000 deaths are reported annually, ranking ovarian cancer as the leading cause of death from gynaecological cancer. The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life. More than 70% of the patients are diagnosed with advanced disease and less than 40% of women with ovarian cancer are cured (Fleming et al 2009; Jemal et al 2010).

The standard therapy for advanced ovarian cancer consists of radical debulking surgery followed by post-operative platinum-based first-line chemotherapy. Since 1996, platinum and paclitaxel combination therapy has become the standard-of-care first-line chemotherapy regimen (McGuire et al 1996). Worldwide, the use of carboplatin has replaced that of cisplatin because of carboplatin's superior tolerability profile together with equal effectiveness. However, the success of this approach is limited and approximately 70% of patients fail to achieve complete responses, or eventually relapse, after a varying disease-free interval.

1.1.2 BRCA mutation positive ovarian cancer

An important risk factor for ovarian cancer is genetic predisposition with BRCA1 or BRCA2 mutations (ie, gBRCAm) which account for the majority of hereditary ovarian cancer. If a lifetime risk for ovarian cancers among women in the general population is estimated to be 1.4 percent (14 out of 1,000), a woman with BRCA1 or BRCA2 deleterious mutation has a lifetime risk of 15 to 40 percent (150–400 out of 1,000). BRCA mutated ovarian cancer patients can also develop ovarian cancer earlier in their life than those without the mutation. Deficiency in BRCA ultimately leads to the accumulation of genetic alterations as a result of the failure of cells to arrest and repair DNA damage or to undergo apoptosis, resulting in tumorigenesis. If all ovarian cancer patients underwent gBRCA testing, current estimates indicate that 13% to 14% of the overall ovarian cancer population would have gBRCA1/2 mutations, and the proportion of patients with gBRCA mutations may be as high as 22% in patients with high-grade serous ovarian cancer (HGSOC). In addition, a population of ovarian cancer patients whose tumours harbour BRCA1 and BRCA2 mutations that are not detected in the germline (~7%) also exist and are defined as somatic BRCA mutations (tBRCAm).

Patients with BRCA-mutated ovarian cancer currently have identical treatment options as sporadic ovarian cancer patients. They seem to have a better prognosis compared with the overall relapsed ovarian cancer patient population but the pattern of disease is similar, with patients eventually dying from their disease. Ovarian cancer patients with BRCA mutation

represent a small, well defined and medically recognised subpopulation for whom, despite the potential for personalised healthcare, no targeted treatment currently exists.

1.1.3 PARP inhibition as a target for BRCA mutation positive ovarian 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 the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumours with HR 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 HR repair. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

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

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

1.2 Research hypothesis

Olaparib administered as monotherapy in the maintenance setting improves progression free survival compared to placebo in patients with newly diagnosed BRCA mutated high risk advanced ovarian cancer who are in clinical complete response or partial response following first line platinum-based chemotherapy.

1.3 Rationale for conducting this study

Based on the results of a pivotal phase II trial (D0810C00019), investigating olaparib maintenance therapy in relapsed ovarian cancer patients AstraZeneca is planning to conduct the current phase III trial to investigate the benefit of olaparib as maintenance monotherapy in the first line setting in patients with newly diagnosed high risk advanced BRCA mutation positive ovarian cancer. The phase II study was conducted with the capsule formulation of olaparib. The phase III trial will be conducted with the more patient friendly tablet formulation.

Study D0810C00019 is a randomised, double-blind, placebo-controlled study to evaluate maintenance treatment with olaparib (capsule formulation) in patients with platinum-sensitive relapsed HGSOC who had received ≥2 previous platinum regimens and were in partial or complete response following their last platinum-containing regimen. The primary endpoint was investigator-assessed PFS. In total, 265 patients were randomised to olaparib 400 mg twice daily (136) or placebo (129). The primary analysis was carried out following 153 PFS events and demonstrated that maintenance treatment with olaparib led to a significant PFS improvement vs placebo [HR 0.35 (95% confidence interval (CI) 0.25 -0.49); p<0.00001] (Ledermann et al 2012). A subgroup analysis (pre-specified in the SAP) suggested that olaparib may lead to a greater clinical benefit in patients with a known germline BRCAm. gBRCAm status was determined retrospectively for all consenting patients (n=166) using blood samples taken before randomisation. tBRCAm status was determined from archival

tumor samples of 196 patients. Since gBRCA wild-type patients may develop somatic tumor BRCA mutations, efficacy analyses were performed by known gBRCA mutation status and known total BRCA mutation status. gBRCAm patients had the greatest PFS benefit with olaparib maintenance vs placebo (HR, 0.17; 95% CI 0.09-0.31; median: 11.2 vs 4.1 months; $P<0.001$). The PFS benefit was consistent when tBRCAm patients were included (HR, 0.18; 95% CI 0.11-0.31; median: 11.2 vs 4.3 months; $P<0.0001$). In an interim analysis of OS (58% maturity), OS HRs from the gBRCAm and gBRCAwt subgroups were similar (0.85 and 0.84, respectively), however 30% gBRCAm placebo patients received a subsequent PARP inhibitor, confounding the OS data in this subgroup. The analysis of all BRCAm patients was less confounded and resulted in an OS HR of 0.74 (95% CI 0.46-1.19; median: 34.9 vs 31.9 m). Olaparib tolerability was similar in BRCAm patients and the overall population.

The phase II study D0810C00019 demonstrated the efficacy of olaparib maintenance when using the capsule formulation (8 capsules twice daily). A more patient friendly tablet formulation (2 tablets twice daily) has been developed and this phase III study will investigate the efficacy of the tablet formulation when given as a maintenance therapy to newly diagnosed high risk advanced BRCA mutated ovarian cancer patients. The tablet dose of olaparib that will be investigated in this study is 300 mg twice daily. This tablet dose has been chosen based on data from an ongoing 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 twice daily is considered to have similar efficacy in terms of tumour shrinkage in BRCA mutated ovarian cancer patients to the 400 mg twice daily capsule together with an acceptable tolerability profile.

The tolerability profile of the 300 mg twice daily tablet dose in study D0810C00024 was considered similar to the 400 mg twice daily capsule formulation. The most common adverse events were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue and anaemia. Further information is provided in the IB.

A preliminary analysis of the effect of food (a light snack) on the pharmacokinetics of olaparib tablets was also investigated in study D0810C00024 and preliminary analysis of this data suggest that the intake of a light snack does not impact the pharmacokinetics (PK) of olaparib. Patients will be allowed to take olaparib tablets with a light snack during the phase III study.

The findings from study D0810C00019 are supported by clinical data from over 350 additional patients with BRCAm ovarian cancer in six other olaparib trials demonstrating consistent response rates.

1.3.1 Rationale for Study Design

The magnitude of PFS benefit demonstrated in patients with gBRCA mutation positive ovarian cancer in Study D0810C00019 (median PFS delay of approximately 7 months following completion of chemotherapy; (HR, 0.18; 95% CI 0.11-0.31; median: 11.2 vs 4.3 months; $P<0.0001$) is considered to be clinically meaningful and robust, with the upper CI of 0.31 being the most conservative estimate of the PFS benefit that can be expected in this

patient population. This translates to a 69% reduction in the risk of disease progression or death.

The proposed Phase III study will investigate the efficacy of olaparib administered as maintenance therapy in the first line setting for the treatment of newly diagnosed high risk advanced BRCA mutation positive ovarian cancer. PFS is considered the most appropriate primary endpoint for the Phase III study in this patient population because it is a meaningful and widely accepted measure of clinical benefit that can be measured robustly. The primary assessment of PFS will be based on investigator review of objective radiological findings as per the RECIST 1.1 guidelines.

An increased interval between lines of chemotherapy enables patients to delay further hospitalisation, the cumulative toxicities associated with chemotherapy, the associated risks of infection, and/or postpone major surgery. Furthermore, PFS is a clinically significant and clinically meaningful endpoint in its own right, as subsequent disease progression is associated with delayed development or worsening of cancer-related symptoms.

A number of secondary endpoints will provide further support for the clinical benefit of olaparib in this patient population, and will include OS, time from randomisation to progression by RECIST v1.1 or CA-125, time from randomisation to second progression (PFS2; see details in the study plan), time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST), time from randomisation to study treatment discontinuation or death (TDT), and patient reported outcome (PRO) measures.

All patients will be followed for OS in this study, however it is expected that the OS results will be confounded by an imbalance in subsequent anti-cancer treatment and particularly subsequent PARP inhibitor use between the arms, given the anticipated availability of trials of other PARP inhibitors for BRCAm ovarian cancer patients. Hence, PFS is considered the most robust measure to confirm the clinical benefit in this patient population.

1.4 Benefit/risk and ethical assessment

Olaparib in this current study is considered to have a positive benefit-risk profile for the treatment of first line BRCA mutated platinum responsive advanced (FIGO Stage III-IV) ovarian cancer patients who are considered at high risk of disease progression.

Ovarian cancer is the leading cause of death from gynaecological tumors in the Western world. Olaparib has demonstrated a large clinically meaningful prolongation of PFS as a maintenance therapy in BRCA mutated platinum responsive patients in the relapsed ovarian setting (D0810C00019) and has a tolerability profile that is considered suitable for use in the maintenance setting. In the phase II maintenance study in the relapsed ovarian cancer setting (D0810C00019) a number of patients have remained on therapy for periods >3 years (21 patients remained on olaparib maintenance therapy for >3 years and 32 patients for >2 years). Refer to the current IB for a complete description of the safety and tolerability profile.

Platinum-containing therapy is considered the treatment of choice for patients with newly diagnosed advanced ovarian cancer, including those patients with BRCA1/2 mutated high risk ovarian cancer, however the duration of response and the prolongation of the progression free interval are usually brief and these chemotherapy regimens cannot be continued until progression as they are associated with neurological, renal and haematological toxicity and cannot generally be tolerated for more than about 6 cycles. Since chemotherapy is not a viable treatment option in the maintenance setting, there is a need for a well tolerated maintenance treatment (following completion of chemotherapy) that can be taken until disease progression to extend the progression free interval in this patient population. Recently, the European Medicines Agency (EMA) approved bevacizumab, in combination with carboplatin and paclitaxel, for the first-line treatment or first recurrence of platinum sensitive advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer; the approval was based on improved PFS in trials of bevacizumab in combination with chemotherapy followed by bevacizumab maintenance monotherapy.

Patients with BRCA mutation ovarian cancer, however, represent a targeted and clinically identifiable subpopulation for whom, despite the potential for personalised healthcare, no targeted treatment is currently available.

The current study design will allow patients to complete their platinum-containing regimen as per normal clinical practice prior to enrolment. The use of olaparib as a maintenance therapy after completion of chemotherapy may provide further benefit to patients in terms of prolongation of the progression free interval, increasing the interval between lines of chemotherapy, delaying further hospitalisation and the cumulative toxicities associated with chemotherapy. Additionally, PARP inhibition with olaparib is expected to have less effect on normal cells that are wild type or heterozygous for both BRCA1 and BRCA2 (Farmer et al 2005). In patients with gBRCA mutations, their normal tissues will carry only one mutated copy of the relevant BRCA gene, but their tumours are expected to have lost both functional copies. This is important for the selective therapeutic window of olaparib (i.e., effect on the tumour versus the effect on normal tissue) and leads to an acceptable tolerability profile for

long term clinical use in a clearly identifiable and targeted patient population most likely to derive benefit.

Since ovarian cancer patients who respond to platinum based chemotherapy do not routinely receive additional treatment at this point in their therapy, the use of a placebo comparator to olaparib following completion of the platinum-containing regimen in those patients who, in the investigator's opinion, have achieved a clinical complete response or partial response is acceptable in order to objectively test the hypothesis of improved efficacy with the addition of olaparib maintenance treatment after a platinum regimen. The study will be conducted as a double-blind placebo-controlled study in which patients are randomised 2:1 to receive olaparib or matching olaparib placebo (tablet formulation), with a primary efficacy endpoint of PFS.

The tablet formulation is considered to be a more patient friendly formulation for long term use requiring patients to take up to 2 tablets twice daily as compared to the capsule formulation requiring 8 capsules twice daily.

In view of the potential for olaparib maintenance monotherapy to have a clinically meaningful PFS advantage in BRCA1/2 mutated patients with ovarian cancer, the current study is designed to allow patients to continue on olaparib therapy for up to two years or until progression of disease, whichever is earlier. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. Patients may stop treatment at any time if they choose to do so or if the investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing, interrupting or discontinuing olaparib are provided.

In the current study, prior to entry some patients will already know their germline BRCA mutation status. In addition, in some rare circumstances the patient may know their tumour BRCA mutation status. For those who do not know their BRCA mutation status but wish to participate in the study, patients will have to consent to undergo gBRCA testing. Any counselling procedures required before such testing will be carried out in accordance with local hospital practice. Patients who then chose to undergo testing and in whom a gBRCA mutation is identified will be eligible to continue study screening procedures.

During screening, patients will be required to consent to provide a sample of archival tumour tissue (to be submitted only if they are subsequently randomised), as well as a blood sample to either ascertain or reconfirm their BRCA mutation status.

A further (optional) blood sample will also be collected for future biomarker research. This research may further identify correlates for the response and possible resistance mechanisms that may exist for olaparib, a targeted therapy that is being

developed for ovarian cancer patients with BRCA 1/2 mutations. Such an understanding of response and resistance to olaparib may assist in ultimately ensuring that AstraZeneca will be able to prospectively identify patients most likely to benefit from treatment with olaparib.

2. STUDY OBJECTIVES

2.1 Primary objective

To determine the efficacy by progression free survival (using investigator assessment of scans according to modified RECIST 1.1) of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.

2.2 Secondary objectives

1. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of overall survival (OS), time to earliest progression by RECIST or CA-125, or death, and time from randomisation to second progression (PFS2)

2. To compare the effects of olaparib maintenance monotherapy compared to placebo on Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy

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 potential future BRCA mutation assays (gene sequencing and large rearrangement analysis)

4. To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy by assessment of time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST) and time from randomisation to study treatment discontinuation or death (TDT).

2.3 Safety objective

1. To assess the safety and tolerability of olaparib maintenance monotherapy in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy

2.4 Exploratory objectives

1.

2. To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L)

3. To explore the impact of treatment and disease on resource use

4. To explore the effects of olaparib maintenance monotherapy compared to placebo on Health-related Quality of Life (HRQoL) as assessed by the individual domains of the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)

5. To explore the efficacy of olaparib by assessment of overall survival (OS) adjusting for the impact of spontaneous switching [outside of study design] to PARP inhibitors or other potentially active investigational agents

6.

7. Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumor samples that were mandatory for entry onto the study or on optional tumor biopsy samples collected during the course of the study

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, 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 is a phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in high risk advanced ovarian cancer patients (including patients with primary peritoneal and / or fallopian tube cancer) with BRCA mutations [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) who have responded following first line platinum based chemotherapy.

Approximately 344 patients will be randomised using an Interactive Voice Response System / Interactive Web Response System (IVR/IWR system) in a 2:1 ratio to the treatments as specified below:

- Olaparib tablets *p.o.* 300 mg twice daily
- Placebo tablets *p.o.* twice daily

Eligible patients will be those patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III-IV) BRCA mutated high grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who are in clinical complete response or partial response following completion of first line platinum-based chemotherapy. Patients who re-present following prior diagnosis at an earlier stage of disease are not eligible. Stage III patients should have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.

Patients must have completed a minimum of six and maximum of nine treatment cycles of first line platinum-based therapy (e.g., carboplatin or cisplatin) before randomisation to the study and should be in the opinion of the investigator in clinical complete response or partial response. However, if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of four cycles of the platinum regimen.

Patients must not have received bevacizumab (either in combination or as maintenance therapy following combination therapy) or any investigational agent during their first line course of treatment.

Patients known to have germline BRCA mutation/s (gBRCAm i.e., blood) prior to randomisation can enter the study based on this result. The result must be made available to

AstraZeneca. In addition the patients must consent to provide 2 blood samples. One sample will be used for a confirmatory Myriad gBRCA test post randomisation using the current commercial Myriad BRAC*Analysis*® (gene sequencing and large rearrangement analysis), which will be paid for by AstraZeneca.

Patients with unknown BRCA status must consent to provide 2 blood samples for germline BRCA testing and follow all local ethical procedures for genetic testing. One sample will be used to test for BRCA mutations using the current commercial Myriad BRAC*Analysis*® test prior to study entry. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious BRCA mutation, the patient can be randomised into the study (providing they have fulfilled all other screening requirements).

These samples will be required for the study even if the patients are found not to have a BRCA mutation.

Patients will be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

Randomisation will be stratified by:

- response to first line platinum chemotherapy (in the opinion of the investigator, clinical complete response or partial response).

Following randomisation patients in both treatment arms will attend clinic visits weekly for the first 4 weeks of treatment (Days 8, 15, 22 and 29). Patients will then attend clinic visits every 4 weeks whilst on study treatment.

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Patients should continue with study treatment to RECIST progression as described above despite rises in CA-125. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

Once a patient has discontinued study treatment, or has progressed, clinic visits will be reduced to every 12 weeks. Following discontinuation of study treatment, further treatment

will be at the discretion of the investigator. Any further systemic anti-cancer treatment will be collected until death, loss to follow-up or withdrawal of consent. In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis. Assessments will be performed as described in Table 3, and Table 4.

Patients in both treatment arms will have tumour assessments according to RECIST at baseline and every 12 weeks (±1week) up to 156 weeks and then every 24 weeks (±1 week) relative to date of randomisation until objective radiological disease progression according to RECIST. 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. 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).

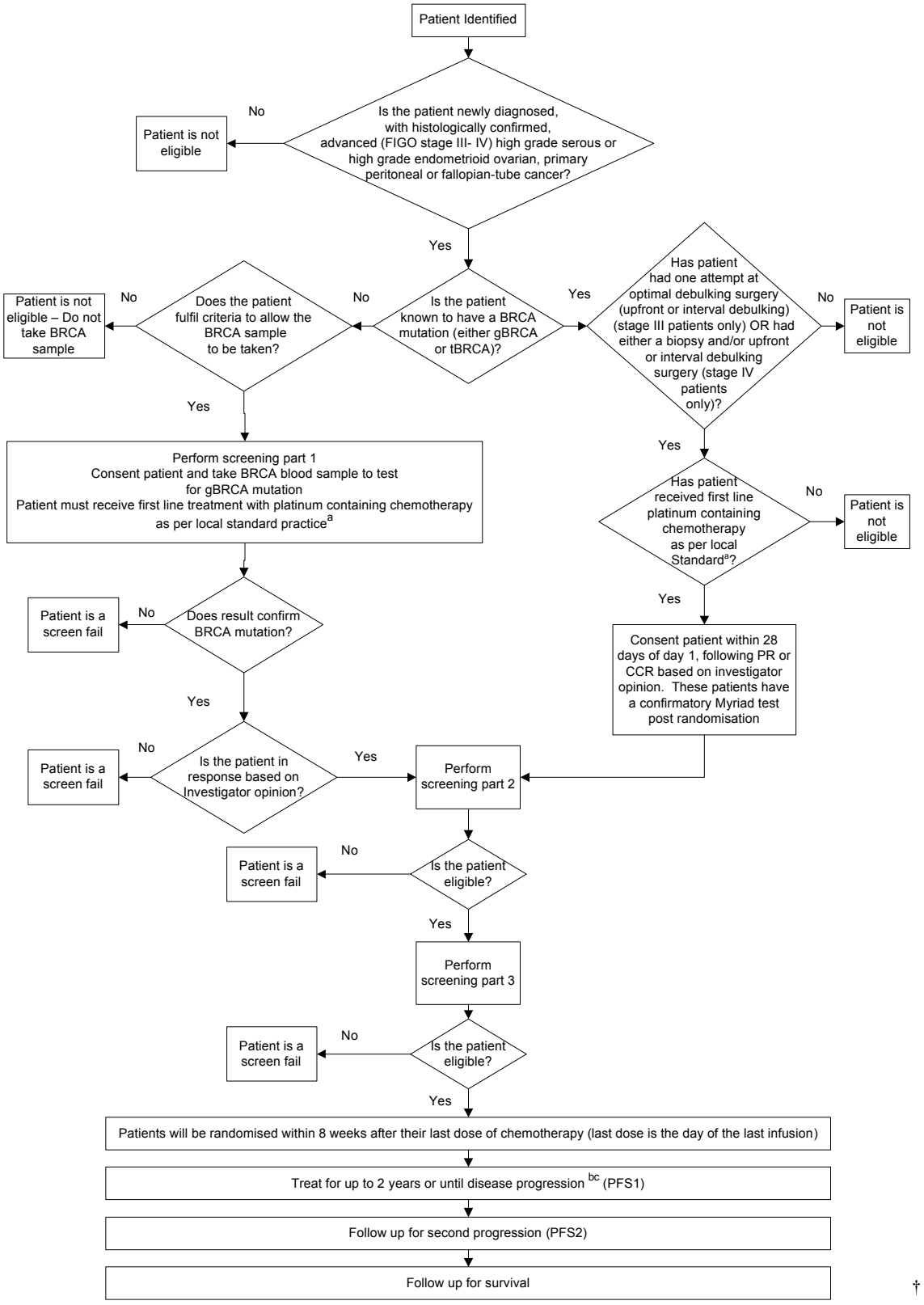
RECIST will be modified to assess patients with clinical CR at entry who will be assessed as having no evidence of disease (NED) unless they have progressed based on the appearance of new lesions.

Any patient who discontinues study treatment for reasons other than objective radiological progression should continue, to undergo scheduled objective tumour assessments according to the study plan (see Table 3 and Table 4) in order to assess objective radiological progression of disease. Failure to do so may result in bias to the study results.

Once a patient has progressed the patient will be followed for second progression (PFS2) every 12 weeks and then survival until the final analysis. Patients will be contacted in the week following last patient last visit for each analysis of survival.

The primary analysis of the study will be occur when approximately 196 events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first (there will be no interim analysis of progression free survival). The primary analysis will be based on investigator assessment of scans; however, a sensitivity analysis will be performed using the BICR data. All efficacy variables including overall survival will be analysed at the time of the primary analysis (providing sufficient events are available to make the analyses meaningful).

Figure 1 Overall Study Design Flow Chart



[a] First line chemotherapy must comprise of a minimum of 6 and a maximum of 9 cycles of platinum based chemotherapy) and not containing bevacizumab. However if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients may be eligible if they have received a minimum of four cycles of platinum regimen

[b] Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Patients should continue with study treatment to RECIST progression as described above despite rises in CA-125. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

[c] All ongoing adverse events/serious adverse events (AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution. See Section 6.4.3 for post 30 day safety follow up adverse event reporting.

Figure 2 Screening Plan

Screening Part 1 (From diagnosis to –28d) applicable to:

- only those patients who **do not** know their gBRCA or tBRCA mutation status prior to entry in to the study

These patients will undergo screening assessments as described for part 1 in Table 1. Screening part 1 is conducted to determine if the patient is considered **eligible to undergo the BRCA status blood test**. The BRCA test may be performed from diagnosis to –28 days at the discretion of the investigator. To perform the BRCA testing from diagnosis to the end of cycle 3, investigator judgement of patient's potential eligibility to enter the study should be assessed as per Table 1 and by reviewing the inclusion/exclusion criteria. For post cycle 3 of first line chemotherapy gBRCA status testing the patient must meet the inclusion criteria in Section 4.1 and none of the exclusion criteria in Section 4.2, and be showing a response to their current platinum chemotherapy prior to having the blood sample taken for the Myriad gBRCA status test. Once part 1 has been successfully completed these patients will continue to part 2 and have all procedures performed as described for part 2 in Table 1.

Screening Part 2 (-28d to –1) applicable to:

- those patients who already know their BRCA mutation status **and** have a deleterious or suspected deleterious mutation. These patients will undergo screening assessments as described for part 2 in Table 2 and have confirmatory Myriad test post randomisation.
- those patients who have a confirmed mutation after completing screening part 1. These patients will undergo screening assessments as described for part 2 in Table 1.

Screening Part 3 (-7d to –1) applicable to:

- those patients who are still deemed eligible to continue with screening after completing part 1 and / or part 2.

Once screening has been completed and eligibility confirmed these patients will continue to visit 2 and have procedures performed as described in Table 3.

Figure 3 Study Flow Chart Up to 108 Weeks on Treatment

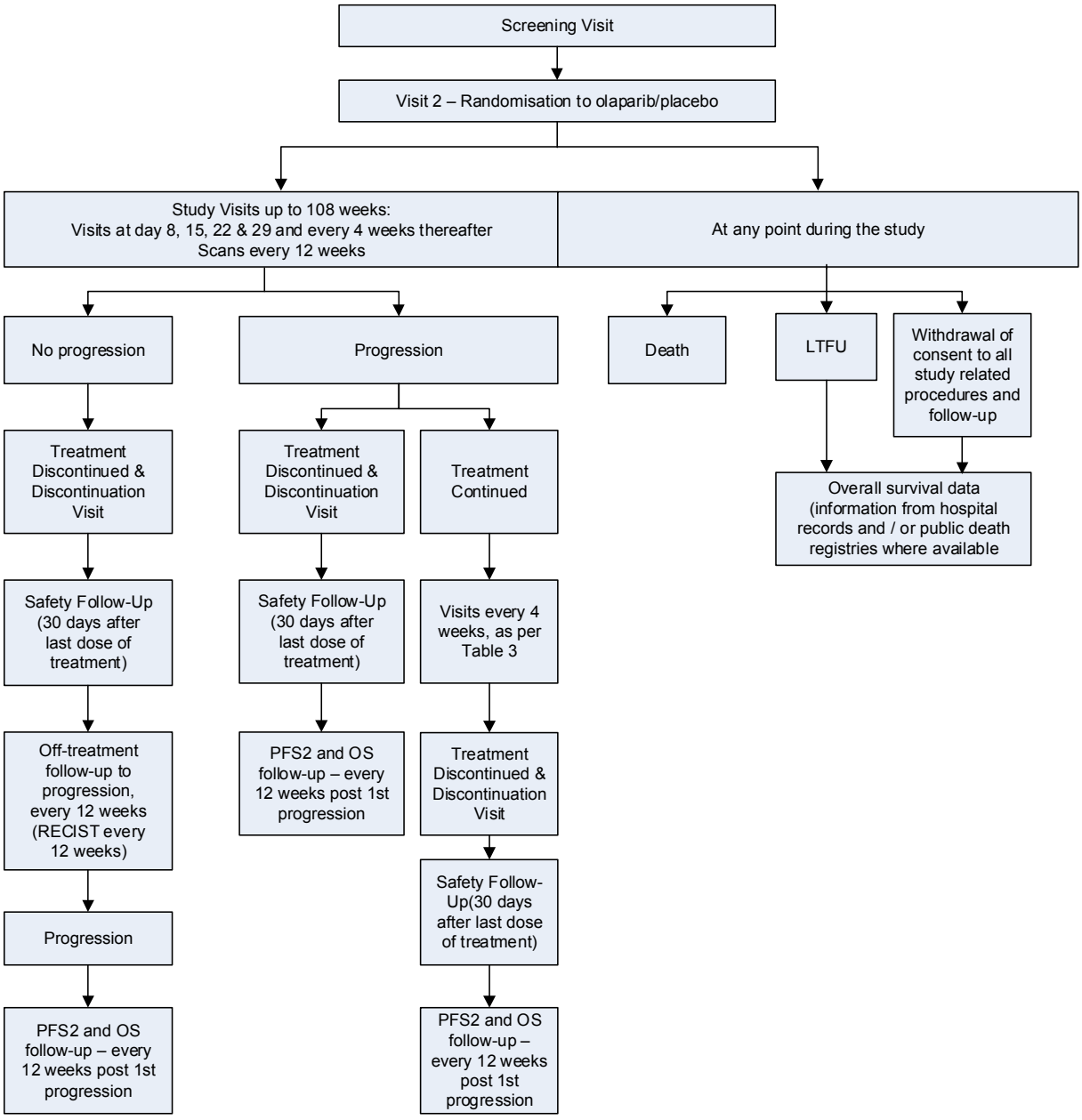
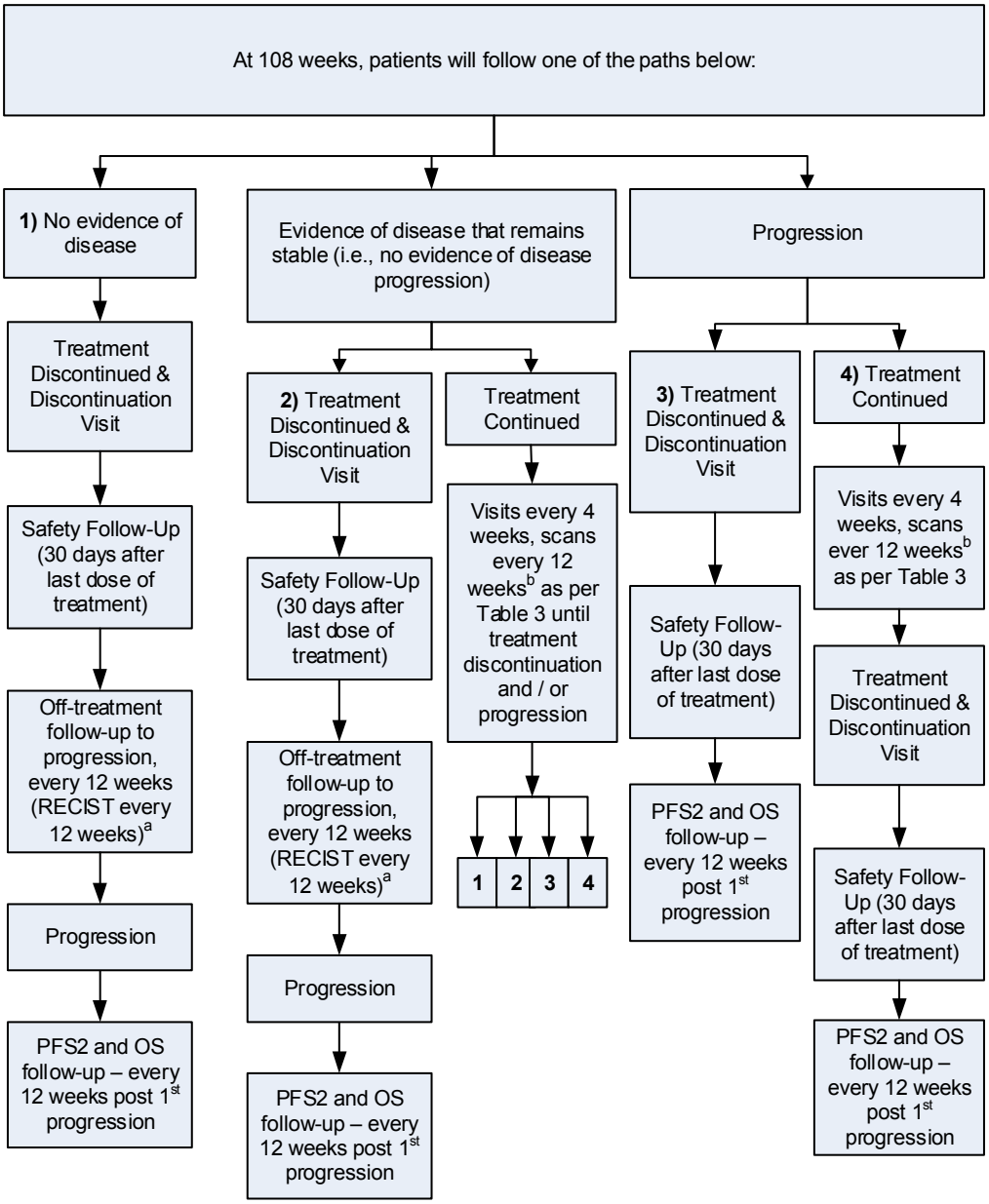


Figure 4 Study Flow Chart At 108 Weeks on Treatment



[a] Patients off treatment: Off-treatment follow-up visits and scans will continue to be conducted every 12 weeks (±1 week) up to 156 weeks (3 years), then every 24 weeks (±1 week) relative to date of randomization.

[b] Patients continuing treatment: Treatment visits will continue every 4 weeks (±3 days) up to 156 weeks (3 years), then every 12 weeks (±1 week) relative to date of randomization. Scans will continue every 12 weeks (±1 week) up to 156 weeks (3 years), then every 24 weeks (±1 week) relative to date of randomization.

d

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e

3.2 Rationale for study design, doses and control groups

The proposed Phase III study is designed to investigate the efficacy and clinical benefit of olaparib as maintenance therapy for the treatment of newly diagnosed high risk advanced BRCA mutation positive ovarian cancer based upon the benefit demonstrated in the phase II study D0810C00019 (Section 1.3). The primary assessment of PFS will be based on investigator assessment of objective radiological findings as per the RECIST guidelines. A number of secondary endpoints will provide further support for the clinical benefit of olaparib in this patient population, and will include OS, time from randomisation to progression by RECIST 1.1 or CA-125, time from randomisation to second progression (PFS2; see details in the study plan) and patient reported outcome measures.

The study design will allow patients to complete their platinum-containing regimen as per normal clinical practice prior to enrolment. The use of olaparib as a maintenance therapy after completion of chemotherapy may provide further benefit to patients in terms of prolongation of the progression free interval, increasing the interval between lines of chemotherapy, delaying further hospitalisation and the cumulative toxicities associated with chemotherapy. Additionally, PARP inhibition with olaparib is expected to have no effect on normal cells that are wild type or heterozygous for both BRCA1 and BRCA2 (Farmer et al 2005). In patients with gBRCA mutations, their normal tissues will carry only one mutated copy of the relevant BRCA gene, but their tumours are expected to have lost both functional copies. This is important for the selective therapeutic window of olaparib (i.e., effect on the tumour versus the effect on normal tissue) and leads to an acceptable tolerability profile for long term clinical use in a clearly identifiable and targeted patient population most likely to derive benefit.

Since ovarian cancer patients who respond to platinum based chemotherapy do not routinely receive additional treatment at this point in their therapy, the use of a placebo comparator to olaparib following completion of the platinum-containing regimen in those patients who have achieved in the opinion of the investigator a clinical complete response or partial response is considered acceptable in order to objectively test the hypothesis of improved efficacy with the addition of olaparib maintenance treatment after a platinum regimen. Given the promising phase II data from Study D0810C00019 (Section 1.3), the phase III study will be conducted with a 2:1 randomisation for olaparib:placebo to minimise the number of patients receiving placebo.

A more patient friendly tablet formulation (2 tablets twice daily) has been developed and this phase III study will investigate the efficacy of the tablet formulation when given as a maintenance therapy to BRCA mutated ovarian cancer patients following first line platinum based chemotherapy. The tablet dose of olaparib that will be investigated in this study is 300mg twice daily. This tablet dose has been chosen based on data from an ongoing 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 300mg twice daily is considered to have similar efficacy in terms of tumour shrinkage in BRCA mutated ovarian cancer patients to the 400mg twice daily capsule together with an acceptable tolerability profile. The tolerability profile of the 300mg twice daily tablet dose in

study D0810C00024 was considered similar to the 400mg twice daily capsule formulation. The most common adverse events were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue and anaemia. Further information is provided in the IB.

4. PATIENT SELECTION CRITERIA

The patient population should be selected without bias.

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

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

4.1 Inclusion criteria

Patients that already know they have a mutation in BRCA1 or BRCA2 gene that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) must fulfil all of the criteria below. Patients that do not know their mutation status, and 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. Patients that do not know their BRCA mutation status and who are being tested post cycle 3 of their first line chemotherapy must fulfil all of the criteria marked with an asterisk (*) below prior to BRCA mutation testing being carried out. To perform the BRCA testing from diagnosis to the end of cycle 3, investigator judgement of patient's potential eligibility to the study should be assessed as per Table 1 and by reviewing the inclusion/exclusion criteria. All inclusion criteria will then be assessed following confirmation that they harbour an appropriate BRCA mutation.

Any patient that fulfils the eligibility criteria for the BRCA test, are required to have their eligibility assessed again prior to randomisation.

All patients must provide informed consent prior to any study specific procedures.

1. *Patients must be ≥18 years of age.

2. *Female patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III – IV) BRCA mutated high grade serous or high grade endometriod (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who have completed first line platinum based chemotherapy (intravenous or intraperitoneal). Guidance on grading of serous ovarian carcinomas is covered by Appendix J.

3. * Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.

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)

5. Patients who have completed first line platinum (e.g. carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation:

   – Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post-treatment scan or a rising CA-125 level, following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first line platinum-containing therapy are not eligble for the study.

   – 'Response' is used throughout the protocol and refers to patients being, in the opinion of the investigator, in clinical complete response or partial response on the post-treatment scan. Clinical complete response is defined as no evidence of RECIST measurable or non-measurable disease on the post-treatment scan and a normal CA-125. Partial response is defined as ≥30% reduction in tumor volume demonstrated from the start to finish of chemotherapy OR no evidence of RECIST measurable disease on the post-treatment scan with a CA-125 which has not decreased to within the normal range.

   – Platinum based chemotherapy course must have consisted of a minimum of 6 treatment cycles and a maximum of 9, however if platinum based therapy must be discontinued early as a result of toxicities specifically related to the platinum regimen, patients must have received a minimum of 4 cycles of the platinum regimen.

   – *Patients must **not** have received bevacizumab during their first line course of treatment, either in combination or as maintenance therapy following combination therapy.

   – Patients must not have received an investigational agent during their first line course of chemotherapy

   – Patients must be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

6. Pre-treatment CA-125 measurements must meet criterion specified below:

- If the first value is less than or equal to the upper limit of normal (ULN) the patient is eligible to be randomised and a second sample is not required

- If the first value is greater than ULN a second assessment must be performed at least 7 days after the first. If the second assessment is ≥ 15% more than the first the patient is not eligible

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

   - Haemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days

   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

   - Platelet count ≥ 100 x 10^9/L

   - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)

   - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN

   - Serum creatinine ≤ 1.5 x institutional ULN

8. *Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix G).

9. *Patients must have a life expectancy ≥ 16 weeks.

10. *Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test prior to Myriad BRCA test during screening part 1, within 28 days of study treatment and confirmed prior to treatment on day 1.

    Postmenopausal is defined as:

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

    - Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post menopausal range for women under 50

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

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

- surgical sterilisation (bilateral oophorectomy or hysterectomy)

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

12. *Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary cancer **must** be available for central testing. If there is not written confirmation of the availability of an archived tumour sample prior to enrolment the patient is **not** eligible for the study.

For inclusion in i) the optional exploratory genetic research and ii) the optional biomarker research, patients must fulfil the following criteria:

- Provision of informed consent for genetic research

- Provision of informed consent for biomarker research

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

4.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled (any asterisked* are also applicable as an exclusion criteria for patients that are being screened post cycle 3 of their first line chemotherapy to determine their BRCA mutation status via Myriad. To perform the BRCA testing from diagnosis to the end of cycle 3, investigator judgement of patient's potential eligibility to the study should be assessed as per Table 1 and by reviewing the below exclusion criteria):

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

2. BRCA 1 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, favor polymorphism" or "benign polymorphism" etc)

3. *Patients with early stage disease (FIGO Stage I, IIA, IIB or IIC)

4. Stable disease or progressive disease on the post-treatment scan or clinical evidence of progression at the end of the patient's first line chemotherapy treatment

5. *Patients where more than one debulking surgery has been peformed before randomisation to the study. (Patients who, at the time of diagnosis, are deemed to be unresectable and undergo only a biopsy or oorphorectomy but then go on to receive chemotherapy and interval debulking surgery are eligible).

6. *Patients who have previously been diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer.

7. *Patients who have previously received chemotherapy for any abdominal or pelvic tumour, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritoneal cancer. (Patients who have received prior adjuvant chemotherapy for localised breast cancer may be eligible, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease).

8. *Patients with synchronous primary endometrial cancer unless both of the following criteria are met:

   (i) stage <2

   (ii) less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 endometrioid adenocarcinoma OR ≥ 60 years old at the time of diagnosis of endometrial cancer with Stage IA grade 1 or 2 endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium are not eligible.

9. Patients who have had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study.

10. *Previous randomisation in the present study.

11. *Participation in another clinical study with an investigational product during their chemotherapy course immediately prior to randomisation.

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

13. *Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with a history of localised breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease

14. *Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome

15. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used).

16. *Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir.

17. *Persistent toxicities (≥Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.

18. *Patients with myelodysplastic syndrome/acute myeloid leukaemia.

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

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

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

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

23. *Breast feeding women.

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

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

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

27. *Previous allogeneic bone marrow transplant

28. *Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.7)

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions apply while the patient is receiving olaparib and for the specified times before and after:

5.1.1 Olaparib and CYP3A4

Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 5.6.2) from the time they enter the screening period until 30 days after the last dose of study medication.

5.1.2 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.

For details refer to Appendix E Acceptable Birth Control Methods.

5.2 Patient enrolment and randomisation and initiation of investigational product

The Principal Investigator will:

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

2. Assign potential patients a unique enrolment number, beginning with 'E#'. (This number will be obtained through Interactive Voice/Web Response System [IVRS/IWRS]).

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

4. Obtain the randomisation code (patient number) through IVRS/IWRS

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 his/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 study treatment.

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:

- response to first line platinum chemotherapy (clinical complete response or partial response)

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

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

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

- olaparib tablets *p.o.* 300 mg twice daily
- placebo tablets *p.o.* twice daily

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

The IVRS/IWRS Centralised Randomisation Centre will inform the Investigator of the Kit ID number to be allocated to the patient at the randomisation visit. The Investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new Kit ID number.

The Kit ID number dispensed at each visit will correspond to the treatment to which the patient was originally randomised

5.3 Procedures for handling patients incorrectly enrolled or randomised or initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomised or receive study medication. 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 treatment stopped and be withdrawn from the study.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Olaparib and placebo treatment will be blinded.

The study medication will be labelled using a unique Kit ID number, which is linked to the randomisation scheme. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the study medication.

5.4.2 Methods for unblinding the study

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

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff. Where a treatment code break is sought for an individual patient in situations other than medical emergencies, it is strongly recommended to discuss with the relevant AstraZeneca staff in collaboration with the Principal Investigator before the patient is unblinded.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

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

Investigational product	Dosage form and strength	Manufacturer
Olaparib	Tablet – 150 mg and 100 mg	
Placebo to match olaparib	Tablet to match each strength of olaparib	

[a] Descriptive information for olaparib can be found in the Investigator's Brochure

5.5.2 Doses and treatment regimens

5.5.2.1 Olaparib and matching placebo (study treatment)

For all centres, olaparib and matching placebo (study treatment) 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. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Patients will be administered their randomised study treatment tablets orally at a dose of 300mg twice daily.

Study treatment is available as a green film-coated tablet containing 150mg or 100mg of olaparib or matching placebo Tablets are to be taken orally, twice daily (bd). Doses of study treatment should be taken at the same times each day approximately 12 hours apart. All doses should be taken with approximately 240 mL of water. The study treatment tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Study treatment tablets can be taken with a light meal/snack (e.g., two pieces of toast or a couple of biscuits).

If vomiting occurs shortly after the study treatment tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Patients should

continue with study treatment to RECIST progression as described above despite rises in CA-125. Patients who continue to have evidence of disease that remains stable (i.e., no evidence of disease progression) at two years or those who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. Within this study patients are not permitted to switch over to the opposite arm from which they were randomised.

5.5.3 Labelling

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

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

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

5.5.4 Storage

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

5.5.5 Management of toxicity of study treatment

Any toxicity observed during the study treatment phase could be managed by interruption of the dose of study treatment if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the AstraZeneca study team must be informed. Study treatment must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (current version) grade 1 or less.

Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment. Treatment

must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of study treatment.

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

Management of anaemia:

Adverse events of anaemia CTCAE grade 1 or 2 (Haemoglobin (Hb) ≥ 8 g/dl) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia. Common treatable causes of anaemia (e.g. iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases management of anaemia may require blood transfusions. However, if patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and patient should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to ≥ 9 g/dl. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions to 250 mg bd as a first step and to 200 mg bd as a second step.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.

Management of neutropenia and leukopenia:

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 CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if 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 of the last dose of study treatment.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTCAE grade ≤1 (ANC ≥ 1.5 x 10^9/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require study treatment dose reductions to 250 mg bd as a first step and to 200 mg bd as a second step.

Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a max of 4 weeks. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

Management of prolonged haematological toxicities while on study treatment:

If 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 (calculate reticulocyte index (RI), RI = reticulocyte count x haematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) (Bessman JD 1990) 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. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

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.

Interruptions for intercurrent non-toxicity related events

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

If a patient discontinues treatment for intercurrent condition and progresses while off treatment, they can restart study treatment if the investigator feels the patient is receiving clinical benefit. Please note that evidence of objective radiological disease progression is required.

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 therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Table 5 Dose reductions for study treatment

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

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 as per Table 1, Table 2, Table 3 and Table 4.

5.6.1 Medications that may NOT be administered

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

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.

5.6.2 CYP3A4

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 is an investigational drug for which no data on in vivo interactions are currently available. Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (e.g. irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine). In vitro data have also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 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, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 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 CYP3A4 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.

5.6.3 Anticoagulant Therapy

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

5.6.4 Anti-emetics/Anti-diarrhoeals

From screening part 2 onwards, 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 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

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

5.6.7 Subsequent therapies for cancer

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

5.7 Treatment compliance

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

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

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

5.7.1 Accountability

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

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

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 investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patients decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML).
- Objective radiological disease progression according to RECIST criteria (unless in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8)
- If at two years of study treatment the patient has no evidence of disease. Presence of structural disease should be assessed according to RECIST guidelines at week 108.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue investigational product 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 (e.g., for patient reported outcomes) and all study drugs should be returned by the patient.

By discontinuing from treatment, the patient is not withdrawing from the study. Patients should be followed for progression (if discontinuation in the absence of progression), PFS2 and OS following treatment discontinuation as per the protocol schedule. If a patient is withdrawn from study, see Section 5.9.

Any patient discontinuing investigational product should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the principal Investigator/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. If patients discontinue study treatment, the AstraZeneca monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see 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 medication to collect and / or complete AE information. Procedures for handling of any untoward events occurring subsequent to the 30-day follow-up AE reporting period are described in Section 6.4.3 under Post follow-up adverse event reporting.

Any patient who has not yet shown objective radiological disease progression at withdrawal from IP should continue to be followed as per RECIST as detailed in Section 6.2.3.1.

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

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product 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 (e.g., for patient reported outcomes*)* and all study drugs should be returned by the patient.

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

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.
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca.
- Incorrectly enrolled patients i.e., the patient does not meet the required inclusion/exclusion criteria for the study.
- Patient lost to follow-up.
- Death

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

- to further participation in the study including any further follow up (e.g., survival calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples (see Section 7.5)

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave 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 (CSA).

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

6.2 Data collection at enrolment and follow-up

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 Table 1, Table 2, Table 3 and Table 4.

6.2.1 Enrolment/Screening procedures

The following assessments and procedures should be performed during screening prior to –28 days and / or within 28 days prior to first dose of study treatment as per Table 1 and Table 2. For details of the schedule and nature of the assessments, see below:

- Date of birth, race and ethnicity
- Current and concomitant medications including previous cancer therapies
- Medical and surgical history including previous cancer and radiotherapy, history of blood transfusions in previous 120 days and response to current therapies
- Physical examination, ECOG performance status, vital signs (blood pressure and pulse; body temperature), body weight, height and ECG (within 7 days prior to the start of the study treatment).

- Haematology/Clinical chemistry/Urinalysis
- Menopausal status; serum or urine pregnancy test for women of childbearing potential. The pregnancy test should be within 28 days prior to the start of study treatment and confirmed on day 1 prior to dosing.
- Blood sample for disease specific marker (CA-125) (see Section 6.4.5.4)
- BRCA1/2 mutation status:

All patients must have a known deleterious or suspected deleterious BRCA 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). Patients must consent to provision of duplicate blood samples, to be taken at the same time. One sample will be used to assess the presence of a germline BRCA mutation by the Myriad test.

For patients with an unknown BRCA status one sample will be used to assess the presence of a germline BRCA mutation by the Myriad test prior to first dose of study treatment. It is recommended that the Myriad gBRCA test is undertaken during the patients last chemotherapy regimen to allow sufficient time for:

(i) all associated local procedures for genetic testing

(ii) the return of the Myriad BRCA result

(iii) the patient to be randomised to study treatment within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion)

Provision of an archival tumour sample is also mandated for subsequent analysis for randomised patients only. See Section 6.8.1.1 for gBRCA Myriad testing criteria.

- Tumour assessment (scans of chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease. [CT/MRI]).
  - Baseline assessments should be performed no more than 28 days before randomisation, and ideally should be performed as close as possible to the start of study treatment. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and consistent with the acquisition guidelines for CT or MRI provided by the central imaging CRO. To note the scan taken after completion of platinum containing regimen, can serve as the baseline scan as long as it was performed no more than 28 days prior to start of treatment (see Section 6.3.1).

- In screening part 1 only SAEs related to study procedures (e.g. blood sampling for BRCA & pregnancy test [if applicable]) must be reported (AEs do not require reporting). From screening part 2 onwards - all AEs/SAEs must be reported.

- Confirmed availability and collection of an archival paraffin embedded tumour tissue sample (see Section 6.7.2)

- Tumour biopsy (optional) (see Section 6.7.3)

- Baseline scores (prior to dosing on Day 1) for patient reported outcomes and quality of life will be obtained (EQ-5D-5L and FACT-O) (see Section 6.5 and Appendix H)

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 study assessments

Study treatment is self administered by the patient twice daily as instructed. The visit schedule is based on 28-day periods. Patients will attend the clinic on days 1 (1st day of treatment), 8, 15, 22, 29, and every 4 weeks from visit 7 until 108 weeks (if not progressed and still on treatment). Patients who remain on treatment post progression or after week 108 continue to attend clinic visits every 4 weeks for up to 156 weeks (3 years), after which they will attend clinic for every 12 weeks (relative to date of randomisation), unless more visits are clinically indicated. Treatment beyond 108 weeks can only be continued at the discretion of the investigator and only after fulfilling specific conditions (see Table 3). The following assessments will be performed at time points specified in the study schedule (see Table 3):

- Physical examination (data is not required to be captured on an eCRF, however any significant changes from baseline must be reported as an AE).

- ECOG performance status: required at day 1 of 1st day of study treatment, if it has not been assessed within 7 days of randomisation, then every 4 weeks up to 108 weeks (if not progressed and still on treatment); see Table 3 for details.

- Vital signs: day 1 and day 29. Body weight is only required at day 1 of 1st day of study treatment, if it has not been assessed within 7 days of randomization and then any other time as clinically indicated. From visit 7, temperature and weight are only required if clinically indicated, blood pressure and pulse are to be taken in line with RECIST assessments.

- ECG: Day 57 (i.e., week 9), at safety follow up and at any other time if clinically indicated.

- Haematology and clinical chemistry: Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose

of chemotherapy and within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly

- 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.

- gBRCA1/2 mutation status: Confirmation of BRCA mutation status result using Myriad test (for those patients that knew their gBRCA status prior to study entry)

- tBRCA1/2 mutation status: Determination of germline BRCA mutation status using the Myriad test for those patients that knew their tumour BRCA status prior to study entry. Confirmation of tumour BRCA mutation status for all patient result using a central laboratory

- Disease specific Tumour marker (CA-125)

- Tumour assessments scans of the chest*, abdomen and pelvis with other regions as clinically indicated for assessment of disease (CT/MRI) (see Section 6.3).

  – *Chest, abdomen and pelvis CT/MRI scans should be performed at base-line.

  – *In those patients with disease present in the chest or upper abdomen lymphadenopathy chest, abdomen and pelvis should be performed at follow-up.

  – *In those patient with no disease present in the chest and no upper abdomen lymphadenopathy then follow-up is by abdomen and pelvis only.

- AE and concomitant medications (including any blood transfusions) at every visit.

- Patient Reported Outcomes and Quality of Life questionnaire: EQ-5D- 5L and FACT-O: at baseline, Day 29, every 12 weeks (+/- 7 days) for 156 weeks, then every 24 weeks (+/- 7 days) or until the data cut off for the primary analysis. In addition, Quality of Life questionnaire will be collected at the discontinuation of study treatment visit and 30 days post last dose. Patients who had RECIST 1.1 disease progression will complete the questionnaires during the 12 weekly survival follow-ups either in person or over the phone.

- Resource use will be captured including inpatient admissions, ICU and length of stay in hospital

- An optional pharmacogenetic sample will be obtained from consenting patients and stored for future exploratory pharmacogenetic analysis (Section 6.8.4)

- Optional tumour biopsy at objective progression (Section 6.7.3)

- Optional blood sample for biomarker analysis (e.g. cfDNA) at randomisation (Section 6.8.3)

Patients will continue with study treatment for up to two years or until objective radiological disease progression by RECIST, whichever is earlier. Patients who continue to have evidence of stable disease at two years or who have progressed may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued. A decision about continuing treatment with the investigational product beyond two years should be made after assessing the patient's disease status according to RECIST guidelines at week 108, and/or by assessing the patient's clinical condition. Continuation of treatment beyond week 108, based solely on clinical progression, is permissible only after case-by-case discussion with the AZ study physician. Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator. Within this study patients are not permitted to switch over to the opposite arm from which they were randomised.

6.2.3 Follow-up procedures

6.2.3.1 Treatment Discontinuation Visit

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 3).

6.2.3.2 Treatment discontinuation due to objective radiological disease progression or any other discontinuation criteria

Patients should be discontinued from study treatment if they have radiological objective disease progression according to RECIST (see Appendix F), unless in the investigator's opinion they are benefiting from treatment, or if they meet any other discontinuation criteria as outlined in Section 5.8. The assessments to be carried out are detailed in the study schedule (Table 3) and include:

- An optional tumour biopsy sample
- An optional blood sample for biomarker analysis (e.g. cfDNA)
- EQ-5D-5L and FACT-O questionnaires

Following the discontinuation visit and safety follow up visit patients who have discontinued due to radiological disease progression will be followed for PFS2 and OS as per Table 4 and patients who have discontinued but do not have radiological disease progression will continue to be followed for PFS1 as per Table 4.

6.2.4 Follow-up 30 day after last dose of study medication (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 3).

6.2.5 Survival

Assessments for survival should be made every 12 weeks following radiological objective disease progression according to RECIST. 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 final survival analyses to provide complete survival data.

Patients will be followed up as per Table 3 or Table 4 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. Since some cases MDS/AML or new primary malignancies developed after discontinuing treatment with olaparib, investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any cases as SAE (or AE for non-melanoma skin cancers, if at least one of the criteria for SAE is not met, see Section 6.4.2) even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm.

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

6.2.6 Second Progression

Following objective progression, copies of the patient's radiological scans are no longer required to be sent for blinded independent central review. Patients will be assessed every 12 weeks for a second progression (using the patients 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, CA-125, symptomatic progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

6.2.7 Patient management post primary analysis

The data cut off date for the statistical analysis for the primary objective of the study will be established when approximately 196 confirmed progression events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first.

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 and disease progression (haematology, clinical chemistry, AEs/SAEs and concomitant medications (including any subsequent cancer therapy), study treatment dosing details, objective radiological disease progression according to RECIST, as per Table 3). These patients should be followed according to routine clinical practice but visits should take place at least every 12 weeks see Table 3.

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

6.2.8 Patient management post final analysis

The data cut off date for the final statistical analysis of the study will be established when ~206 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 and post the data cut off all patients will be unblinded. Patients who are receiving active 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.

Patients that are on placebo will not be offered olaparib as a study treatment.

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. 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.

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 (modified RECIST 1.1)

Following the baseline assessment, subsequent tumour assessments according to RECIST should be performed at the end of every 12 weeks (±1week) up to 156 weeks then every 24 weeks (±1 week) relative to date of randomisation, according to the planned study schedule (see Table 3 and Table 4) up to objective progression by RECIST.

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

The imaging modalities used for RECIST assessment will be CT or MRI scans of the chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease, see Section 6.2.2. Any other sites at which new disease is suspected should also be appropriately imaged.

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. Ongoing collection of site review tumour assessment is required and must be recorded in the eCRF.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of 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 3 and Table 4), 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

Modified RECIST 1.1 criteria will be used to assess patient response to treatment by determining progression free survival (PFS) times. (The modified 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, no evidence of disease) are presented in Appendix F).

Although CA-125 is measured in this study it will not be directly used for assessing objective response or progression and patients should be continued on treatment until objective radiological disease progression as defined by RECIST.

The methods of assessment of tumour burden used at baseline - CT or MRI scans of chest, abdomen and pelvis, with other regions as clinically indicated for the assessment of disease must be used at each subsequent follow-up assessment, see Section 6.2.2.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 12 weeks (±1 week) up to 156 weeks then every 24 weeks ((±1 week) relative to date of randomisation, according to the planned study schedule Table 3 and Table 4 until objective radiological disease progression as defined by RECIST.

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

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), no evidence of disease (NED) and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (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.

Patients with no disease at baseline will be assessed according to RECIST criteria for new lesions with responses of No Evidence of Disease (NED) or progression of disease.

If the Investigator is in doubt as to whether 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 progression, then the date of the initial scan should be declared as the date of progression.

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

Following progression, patients should continue to be followed up for survival every 12 weeks as outlined in the study plan (Table 4 or Table 5). It is important to follow the assessment

schedule as closely as possible. Please refer to the study plan (Table 4 or Table 5) and CT/MRI scans in Section 6.3.1.

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. 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. Results of this independent review will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted by the investigator.

A sensitivity analysis for this study will be based on the independent central review (ICR) of the radiological scans.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study are 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 (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events, including Serious Adverse Events, will be collected from time of signature of informed consent*, throughout the treatment period and up to and including the 30-day follow-up period. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

*Exception: In screening part 1 only SAEs related to study procedures must be reported (AEs do not require reporting). From screening part 2 onwards - all AEs/SAEs must be reported.

Follow-up of unresolved adverse events

Any SAE 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.

Post Follow-up adverse events

For Pharmacovigilance purposes and characterisation of events of special interest, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported as SAE (or AE for non-melanoma skin cancers, if at least one of the criteria for SAE is not met, 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 or new primary malignancy as an aid to provide detailed information on the case.

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

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

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

Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in CTCAE grade
- 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:

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

Severity of AE

For each episode 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 an SAE (this would be recorded as an SAE as per the guidance found in this section (Section 6.4.3)).

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation Program 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 results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory

values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

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 D '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. It may be an increase in the severity of the disease under study and/or increases in the signs and symptoms of the cancer. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

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 ovarian 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 in screening part 1 related to study procedures should be reported as a SAE.

All deaths that occur from screening part 2 onwards, including 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

In Screening part 1, only SAEs related to study procedures must be reported. From Screening part 2 onwards, 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 reportable 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.

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

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

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, Table 2 and Table 3).

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 if clinically indicated
- international normalised ratio {INR} will be performed 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
- magnesium
- creatinine
- total bilirubin
- gamma glutamyltransferase [GGT]
- alkaline phosphatase [ALP]
- aspartate transaminase [AST]
- alanine transaminase [ALT]
- urea or blood urea nitrogen [BUN]
- total protein
- albumin
- lactic dehydrogenase [LDH])

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

6.4.5.4 Disease specific tumour marker samples (CA-125)

As part of the routine safety blood samples, all patients will supply blood sample for CA-125 (2 mL) for assessment at the beginning of each 28 day period prior to the patient receiving study treatment.

It is important to follow the assessment schedule as closely as possible. If CA-125 assessment is performed outside of scheduled visit ± 1 week window interval, every attempt should be made to assess the CA-125 at the scheduled time points. Patients will be evaluated until objective disease progression, based on progressive serial elevation of serum CA-125 according to the modified Gynecologic Cancer InterGroup criteria GCIG criteria (note GCIG criteria is not validated for this trial population). See Section 11.1.2.2.

Further assessment of CA 125 post serological progression will be at the discretion of the investigator according to local clinical practice.

For blood volume see Section 7.1.

6.4.5.5 Urinalysis

Urinalysis by dipstick should be performed as stated in Table 1, Table 2 and Table 3. Microscopic analysis should be performed by the hospital's local laboratory if required.

6.4.5.6 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 5.5.5.

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 (see Table 1, Table 2 and Table 3).

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

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

ECGs are required prior to obtaining the Myriad blood samples during screening for patients with unknown BRCA status, within 7 days prior to starting study treatment, at week 9 after starting study treatment when clinically indicated and at the follow up visit after patient has discontinued study medication.

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

Height will be assessed at screening only.

Weight will be assessed according to the Study Schedule (see Table 1, Table 2 and Table 3) and as clinically indicated at any other time.

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

6.4.8.1 Pulse and blood pressure

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. For timings of assessments refer to the Study Schedule (see Table 1, Table 2 and Table 3).

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

6.4.8.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Schedule (see Table 1, Table 2 and Table 3).

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

6.4.9 Other safety assessments

6.4.10 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential, prior to obtaining the Myriad blood samples during screening for patients with unknown BRCA status, within 28 days prior to the start of study treatment and

on Day 1 of the study prior to commencing treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

6.5 Patient reported outcomes (PRO): FACT-O and EQ-5D-5L

6.5.1 Administration of PRO questionnaires

Paper questionnaires will be given to the patient at baseline, at Day 29 and then every 12 weeks (+/- 7 days) for 156 weeks, then every 24 weeks (+/- 7 days) or until the data cut off for the primary analysis. In addition, Quality of Life questionnaire will be collected at the discontinuation of study treatment visit and 30 days post last dose. Patients who had RECIST 1.1 disease progression will complete the questionnaires during the 12 weekly survival follow-ups either in person or over the phone (see Table 3 and Table 4). Following collection of the paper questionnaire (in person or over the phone), the site staff can either enter the information directly into the WBDC (RAVE) electronic database system or arrange to have the paper questionnaires transcribed into the WBDC (RAVE) database.

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:

- It 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
- It must be completed in private by the patient, where a visit to the clinic is not planned, i.e. for patients followed up for survival with no scheduled clinic visits, the site staff will administer questionnaires via telephone.
- 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. However, if the patient is unable to read the questionnaire (e.g., is blind or illiterate) the questionnaire may be read out by trained clinic staff and responses recorded
- On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness

Only 1 answer should be recorded for each question

6.5.2 FACT-O

Patient-reported health-related quality of life (HRQoL) will be assessed using the FACT-O questionnaire (Basen-Engquist K et al 2001). The FACT-O is composed of the following sub-scales: physical, social/family, emotional, and functional well-being as well as the additional concerns scales consisting of specific ovarian cancer symptoms.

6.5.3 PRO method or questionnaire for other purposes

The end point for health-related quality of life analysis will be the Trial Outcome Index (TOI), an established single targeted index derived from the FACT-O questionnaire and it is considered to target the most relevant symptoms together with function and physical well-being and can be directly related to signs and symptoms and AEs. The TOI is composed of the following scales of the FACT-O: physical and functional well-being and additional concerns.

6.5.4 EQ-5D-5L

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

6.6 Pharmacokinetics – Not Applicable

6.7 Biomarkers

Tumour and blood samples will be collected for mandated and optional biomarker work as detailed in Table 6.

6.7.1 Biomarker samples

The archival tumour sample, and the baseline blood samples for BRCA mutation status are all mandated samples.

Table 6 Samples for Biomarker Research

Sample Type	Visits	Optional or Mandatory
Whole blood (for prospective germline BRCA testing at central laboratory or retrospective confirmation of BRCA mutation at central laboratory)	Screening sample	Mandatory

Table 6 Samples for Biomarker Research

Sample Type	Visits	Optional or Mandatory
Whole blood sample (to be used for the retrospective determination of gBRCA mutation status by Myriad).	Screening sample	Mandatory
Archival tumour sample	Screening	Mandatory for all randomised patients
On-study baseline tumour biopsy	Baseline	Optional
On-study progression tumour biopsy	At progression as defined in Section 6.3.1	Optional
Blood sample for biomarker analysis (e.g. cfDNA)	At randomisation and progression	Optional
Blood for optional exploratory pharmacogenetics	Baseline	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.

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.

6.7.2 Exploratory Biomarker Research on Archival Tumour Samples (Mandatory)

These samples will be collected from the site pathologist once patient has been randomised. An adequately sized (minimum of 2 mm x 2 mm) historical tumour tissue paraffin block from resection or a core biopsy from the primary tumour or metastases 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 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.

6.7.3 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 but must be taken after the baseline RECIST scan has been performed and a second tumour biopsy sample taken at documented RECIST progression. The provision of tumour tissue is encouraged only if clinically appropriate and not considered detrimental to patient care.

The biopsied tumour must not be used as part of the RECIST assessments.

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.

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

6.8 Pharmacogenetics

6.8.1 Collection of blood sample for Myriad germline BRCA1 and BRCA2 testing

All patients must have a known deleterious or suspected deleterious BRCA 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).

6.8.1.1 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 BRCA 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 indicates 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.

For blood volume see Section 7.1.

6.8.1.2 Guidance for BRCA testing of patients with unknown BRCA status

Patients that do not know their BRCA status, must have a Myriad test prior to randomisation to the study. 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 performed after initial diagnosis. Patients will need to have met the local ethical requirements for such genetic tests (e.g., genetic counseling) prior to the test procedure.

The following clinicopathological features are known to be associated with an increased probability of BRCA mutations:

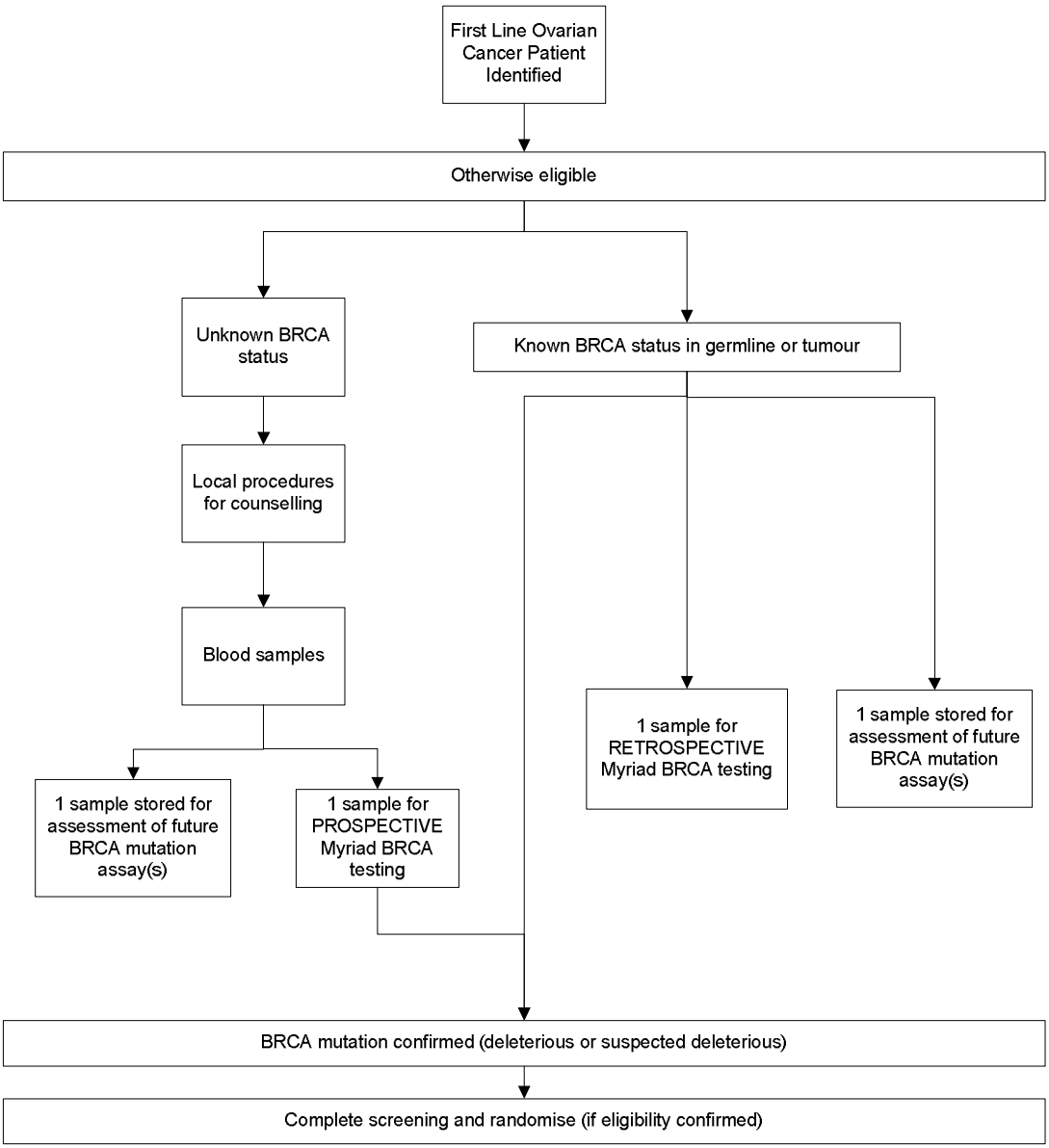
1. Family history of breast or ovarian cancer, ethnicity and age (Pal et al 2005; Risch et al 2006)

2. High grade serous ovarian cancer (Alsop et al 2012)

The BRCA test may be performed from diagnosis to – 28 days at the discretion of the investigator. To perform the BRCA testing from diagnosis to the end of cycle 3, investigator judgement of patient's potential eligibility to the study should be assessed as per Table 1 and by reviewing the inclusion/exclusion criteria. For post cycle 3 of first line chemotherapy gBRCA status testing the patient must meet the inclusion criteria in Sections 4.1 and 4.2, and be showing a response to their current platinum chemotherapy prior to having the blood sample taken for the Myriad gBRCA status test. This response is in the opinion of the investigator but there should be documented evidence eg CA-125 results, radiological assessments.

The blood and tumour sample collection algorithm for patients with known or unknown BRCA mutation status is documented in the flow diagram below:

Figure 5 Flow diagram for patients with known or unknown BRCA mutation status



6.8.3 Exploratory blood sample for biomarker analysis (e.g. cfDNA) (Optional)

A 12 mL blood sample will be collected from all patients at randomisation and at progression for exploratory biomarker work.

6.8.4 Collection of pharmacogenetic samples (optional)

An optional pharmacogenetic sample 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 Visit 2, 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.

6.9 Health economics

6.9.1 Resource Use

Resource use will be captured including inpatient admissions, ICU and length of stay in hospital.

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 on treatment. However the volume of blood to be drawn from each patient during screening and up to Day 29 should not exceed 110 mL.

The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 months of treatment, a treatment discontinuation visit and the 30-day follow-up visit, should not exceed 195 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 estimated total volume of blood that will be drawn from each patient in this study is as follows:

Table 7 Estimated maximum volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples - screening	No. of samples -month 1 (including day 29)	Months 2-6	Treatment discontinuation visit and 30 day follow-up visit	Objective radiological disease progression	Total volume (mL)
Safety	Clinical chemistry (locally assessed)	5	1	5	1(x4)	1(x2)		60
	Haematology (locally assessed)	5	1	5	1(x4)	1(x2)		60
Whole blood sample: Prospective Myriad BRCA test for patients with unknown BRCA status or for confirmation of BRCA status for those with previous results)		9	1					9
Blood sample for biomarker analysis (e.g. cfDNA)		12		1			1	24
Blood cytogenetic analysis		Site dependent	Depends on the blood smear result					

Table 7 Estimated maximum volume of blood to be drawn from each patient

Assessment	**Sample volume (mL)**	**No. of samples - screening**	**No. of samples -month 1 (including day 29)**	**Months 2-6**	**Treatment discontinuation visit and 30 day follow-up visit**	**Objective radiological disease progression**	**Total volume (mL)**
Serum pregnancy test	Site dependent	Site may use urine instead	Site may use urine instead				
Blood sample for CA-125 (locally assessed)	2	3	1(x2)	1x4	1(x1) (only treatment discontinuation visit)		20
Total volume (ml)		34	75	48	22	12	191

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 can be retained at R&D site or 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 additional exploratory analysis will not be reported in the Clinical Study Report but separately in a Scientific Report.

7.2.1 Pharmacogenetic (optional exploratory) 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 relevant sample tracking system 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.

7.3 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 'International Air Transport Association (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 sample: As collection of the biological samples is an optional part of the study, the patient may continue in the study.

Blood samples for biomarker analysis (e.g. cfDNA): As collection of the biological samples is an optional part of the study, 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 archival tumour samples may be returned to site), 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 International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), 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 (EC) should approve the final study protocol, including the final version of the Informed Consent Form(s) including biomarker and/or pharmacogenetic sample consents 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 IRB/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 IRB/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 IRB/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 Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

Each Principal Investigator is responsible for providing the IRB/Ethics Committees 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, including any information on the mandatory and optional sampling; e.g. BRCA testing and tumour biopsies.
- 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, 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 CSA 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(s) utilised.

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

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

9.3 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 (e.g., clinic charts).

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

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

9.3.1 Source data

Refer to the CSA 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 CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the 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 Quarter 3 2013 and to end by Quarter 1 2023.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.

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 research will not 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.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

A comprehensive SAP will be prepared before the first patient is entered.

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, NED, 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 Progression Free Survival (PFS)

PFS is defined as the time from randomisation until the date of objective radiological disease progression according to RECIST or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised study treatment or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last 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. (25 weeks allowing for visit window).

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

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

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

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

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

Objective progression is defined as at least a 20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) or an overall non-target lesion assessment of progression or a new lesion. For patients with no evidence of disease at baseline, following a clinical complete response to chemotherapy, progression is defined by the detection of new lesions on follow-up radiological assessments.

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

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) 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 to earliest progression by RECIST 1.1 or CA-125 or death

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

- Patients with elevated CA-125 pre-treatment (i.e. greater than the upper limit of normal (ULN)):-

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

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

- Patients with CA-125 in the normal range pre-treatment must show evidence of CA-125 greater than, or equal to, 2 times the ULN on 2 occasions at least 1 week apart CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted.

Time to progression by RECIST or CA-125 progression or death is defined as the time from randomisation to the earlier date of RECIST or CA-125 progression or death by any cause. Patients without a CA-125 progression or a RECIST progression who are still alive at the time of analysis will be censored at their last evaluable RECIST assessment or their last available CA-125 measurement, whichever is the most recent at the time of the analysis. If a patient progresses or dies after two or more missed RECIST and CA-125 assessments, then the patient will be censored at the time of their last evaluable assessment. If only one assessment is missing during this period, no censoring is required.

11.1.2.3 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, CA-125 or symptomatic progression or death. Second progression status will be reviewed every 12 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 latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death).

11.1.2.4 Time to first subsequent therapy or death (TFST)

Time to start of first subsequent therapy or death (TFST) will be assessed (see Section 12.2.3.3). TFST is defined as the time from the date of randomisation to the earlier of the date of therapy start date following study treatment discontinuation, or death. Subsequent therapies will be reviewed to assess which represent clinically important treatments intended to control ovarian cancer. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received subsequent therapy, i.e. the last follow-up visit where this was confirmed.

11.1.2.5 Time to second subsequent therapy or death (TSST)

Time to start of second subsequent therapy or death (TSST) will be assessed (see Section 12.2.3.3). TSST is defined as the time from the date of randomisation to the earlier of the date of second subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a second further intervention of this type will be censored at the last known time to have not received second subsequent therapy, i.e. the last follow-up visit where this was confirmed.

11.1.2.6 Time to study treatment discontinuation or death (TDT)

Time to study treatment discontinuation or death (TDT) will be assessed (see Section 12.2.3.3). TDT is defined as the time from the date of randomisation to the earlier of the date of study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the date of Data Cut Off (DCO) 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.

11.1.2.7 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 F. It is the best response a patient has had during their time in the study 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 based on the RECIST criteria (Appendix F) using the following response categories: complete response (CR), partial response (PR), stable disease (SD), No Evidence of Disease (NED; applies only to those patients entering the study with no disease at baseline), progressive disease (PD) and not evaluable (NE).

Best overall response will be determined programmatically based on the RECIST criteria using investigator data.

For patients whose 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 ≤25 weeks (i.e. 24 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 > 25 weeks (i.e. 24 weeks ±1week) after randomisation then BoR will be assigned to the non-evaluable (NE) category.

Progression events that have been censored due to them being >25 weeks 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 the earliest of the defined analysis cut-off point or the start of subsequent therapy. For each treatment group, the objective response rate (ORR) is the number of CR and PR divided by the number of patients in the group in the FAS with measurable disease at baseline. Only patients with PR and measurable disease at enrolment can achieve an objective response of CR or PR, other permissible categories of BoR are NE, PD.

11.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs and ECG. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 12.2.

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 Discontinuation of Investigational Product due to Adverse Events (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.

11.4 Calculation or derivation of pharmacokinetic variables – Not Applicable

11.5 Calculation or derivation of pharmacodynamic variables – Not Applicable

11.6 Calculation or derivation of pharmacogenetic variables

To be defined in the exploratory analysis plan.

11.7 Calculation or derivation of resource use

Frequency and estimates of resource use, including length of stay and number of hospital admissions, will be derived from the resource use information.

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 subject in (FSI).

Table 10 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 patients who are randomised as part of the global enrolment. The global recruitment to the study will close when approximately 344 patients are randomised.

The primary analysis will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised as part of the global enrolment 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 investigational product, olaparib or placebo and as part of the global enrolment will be included in the primary safety analysis set. Throughout the safety results sections, erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the treatment group of the treatment they actually received.

Table 10 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- PFS	ITT
- OS, PFS2, TFST, TSST, TDT, symptom/QoL endpoints	ITT
Demography	ITT
Safety Data	
- Adverse Events	Safety
- Lab measurements	Safety
- Vital Signs	Safety

12.2 Methods of statistical analyses

The treatment comparison is olaparib 300 mg bd vs placebo.

All efficacy analyses will be performed on the ITT population. In addition, as a sensitivity to the main analyses of PFS, PFS2, OS, TDT, TFST and TSST, analyses of these endpoints will be performed in those patients whose gBRCAm status is confirmed by the central Myriad test.

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 11 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 investigator data
	Sensitivity Analyses[a]
	1) Evaluation time bias analysis; stratified log-rank test using investigator data
	2) Attrition bias analysis (using alternative censoring rules); stratified log-rank test using investigator data
	3) Ascertainment bias analysis; stratified log-rank test using BICR data
	4) Deviation bias (if meaningful to do); stratified log-rank test using investigator data
	5) Analysis in randomised patients confirmed as gBRCA mutation positive by central Myriad test; stratified log rank test using investigator data

Table 11 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
Overall Survival (Time from randomisation to death due to any cause)	Stratified log-rank test Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test
PFS2 (Time from randomisation to second progression or death)	Stratified log rank test based on investigator assessment of second progression Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test
TFST (Time to first subsequent therapy or death)	Stratified log rank test using investigator data Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test
TSST (Time to second subsequent therapy or death)	Stratified log rank test using investigator data Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test
Change from baseline in TOI score	Mixed model for repeated measures (MMRM) analysis of the change from baseline in TOI score
Time to earliest progression by RECIST 1.1, CA-125 or death	Stratified log rank test using investigator data
TDT (Time to study treatment discontinuation or death)	Stratified log rank test using investigator data Sensitivity analysis: Stratified log rank test using investigator data in randomised patients confirmed as gBRCA mutation positive by central Myriad test

[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 benefits of olaparib maintenance treatment, PFS, PFS2, TFST, TSST, change from baseline in TOI score and OS will be tested at a 2-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% 1-sided for key label claims, a multiple testing

procedure (MTP) will also be employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS). There is no requirement to adjust for multiplicity due to PFS interim analyses, since there are no planned interim PFS analyses with the opportunity to make an early claim of efficacy.

A hierarchical testing strategy will be employed where PFS is tested first using the full test mass (full test mass = alpha) and key secondary endpoints of PFS2 and OS will then be tested using a 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 6). The MTP is detailed below.

Figure 6 Multiple Testing Procedure

PFS2 will only be tested (with the test mass split between interim and final PFS2 analyses) if statistical significance is shown for PFS. OS will only be tested if the null hypothesis (of no difference) is rejected for PFS2.

Both PFS2 and OS will be tested at the time of the primary analyses of PFS and again when there are approximately 60% deaths. A proportion of alpha will be spent at this first analyses time point for both endpoints to control for multiple testing however different spending functions will be applied for each.

An interim analysis for PFS2 will be performed at the time of the PFS analysis (approximately 180 PFS2 events expected at this time). Statistical significance will be declared at the interim analysis for PFS2 if the 1-sided $p<0.0125$. Assuming 180 PFS2 events, a HR ≤ 0.70 would equate to a 1-sided p-value <0.0125.

If the null hypothesis for PFS2 is not rejected at this first analyses time point then PFS2 will be tested again when the final analysis of OS occurs (approximately 300 PFS2 events expected when approximately 206 death events have occurred). The type I error will be controlled at 2.5% 1-sided by assigning approximately 1.8% significance level (1-sided) to the final analysis of PFS2 (final significance level to be determined accounting for correlation between the interim and final PFS2 analyses) (Stone 2010). Assuming 300 PFS2 events, a HR ≤ 0.77 would equate to a 1-sided p-value <0.018. If PFS2 is significant at either the interim or final analyses, the full test mass (alpha) will be carried forward to OS.

An interim analysis for OS will be performed at the time of the PFS analysis (approximately 100 OS events). Statistical significance will be declared at the interim analysis for OS if the null hypothesis for PFS2 is rejected at the PFS analysis and the observed p-value for OS is $p<0.0001$. This allows the significance level at the final analysis for OS to be controlled at the 2.5% level (1-sided) (Haybittle J L 1971)).

12.2.2 Analysis of primary endpoint

PFS will be analysed when approximately 196 events have occurred or after the last patient randomised has had the opportunity to have been on the study for at least 36 months, whichever comes first. 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 response to first line platinum chemotherapy (clinical complete response partial response) for generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval will be estimated from a Cox Proportional Hazards model (with ties = Efron and the stratification variable as a covariate) and the CI will be calculated using a profile likelihood approach.

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.

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

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

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

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

The proportion of patients alive and progression free 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.

Subgroup analyses will be conducted comparing PFS between treatments in the following subgroups of the full analysis set:

- Response to previous platinum chemotherapy (clinical complete response or partial response)
-
- ECOG performance status at baseline (0 or 1)
- Baseline CA-125 value (≤ ULN vs > ULN)
-
- Age at randomisation (<65 vs. ≥ 65)
- Stage of disease at initial diagnosis (III or IV)

A minimal number of patients that are tBRCAm *and* gBRCA wt are expected to be randomised into this study. Assuming the number of progression events in this population is less than 20, these patients will be summarised with a Kaplan Meier of PFS by treatment. If the number of events is ≥ 20, this factor will be added to the forest plot (i.e. gBRCA and tBRCA mutated vs tBRCA mutated only).

Other baseline variables may also be assessed if there is clinical justification. For each subgroup, the HRs (olaparib: placebo) and associated CIs will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term, factor (subgroup) 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).

The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. The results observed in Phase II (D0810C00019) do not suggest that these factors will be predictive factors for a qualitatively different treatment effect.

If there are too few events available for a meaningful analysis of a particular subgroup (where there are less than 20 events per subgroup level no formal statistical tests will be performed), the relationship between that subgroup and PFS will not be formally analysed. In this case, only descriptive summaries will be provided.

No adjustment to the significance level for testing 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, 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 of Gail and Simon 1985.

A further analyses 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 central 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. A KM plot of PFS in this subset of patients will be presented by treatment group.

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 investigator 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 BICR assessed RECIST data to programmatically derive PFS. The HR and 95% Confidence Interval will be presented.

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

(d) Deviation bias (if meaningful to do)

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

- Did not have the intended disease or indication or
- Did not receive any randomised study treatment

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

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.

As a sensitivity, the analysis of PFS2 will be repeated in those patients whose gBRCAm status is confirmed by the central Myriad test. A KM plot of PFS2 in this subset of patients will be presented by treatment group.

The sensitivity analysis outlined for 12.2.2.1 will not be repeated for PFS2 with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary PFS2 is reversed.

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.

As a sensitivity, the analysis of OS will be repeated in those patients whose gBRCAm status is confirmed by the central Myriad test. A KM plot of OS in this subset of patients will be presented by treatment group.

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 Analysis of TFST, TSST, TDT endpoints

Time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST) and time to study treatment discontinuation or death (TDT) will be analysed at the same time as the primary analysis of PFS and using the same methodology and model. The HRs for the treatment effect together with 95% CIs will be presented. Kaplan Meier plots will be presented by treatment arm. In addition, the time between first progression and starting first subsequent therapy will be summarised.

Summary tables of first and second subsequent therapies by treatment arm will be provided, as well as response to first and second subsequent therapy by treatment arm.

Further analyses of these endpoints will be performed when the OS data are approximately 60% mature.

As a sensitivity, the analyses of TFST, TSST and TDT will be repeated in those patients whose gBRCAm status is confirmed by the central Myriad test. KM plots of TFST, TSST and TDT in this subset of patients will be presented by treatment group.

12.2.3.4 Analysis of time to earliest progression by RECIST 1.1 or CA-125 or death

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

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

No multiplicity adjustment will be applied as this is viewed as a supportive endpoints (to PFS).

12.2.3.5 Summary of Best overall RECIST Response (BoR)

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

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

12.2.3.6 Analysis of PRO endpoints

The analysis population for HRQoL data will be the subset of the FAS (ITT) set.

Change from baseline in TOI score will be regarded as the primary analysis of the FACT-O questionnaire and will be analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline in TOI score for each visit. The primary analysis will be to compare the average treatment effect from the point of randomisation for the first 24 months (which will include visit data obtained at baseline, day 29 (week 4), weeks 12, 24, 36, 48, 60, 72, 84, 96 and the discontinuation and follow-up visits if occurring within the first 24 months) unless there is excessive missing data (defined as >75% missing data). If the time to first subsequent chemotherapy when approximately 50% of placebo patients receive chemotherapy does not occur by 24 months post-randomisation then additional time periods will be analysed and will be included on supportive summaries and graphical displays as appropriate.

The MMRM model will include patient, treatment, visit and treatment by visit interaction as explanatory variables and the baseline TOI score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model; patient will be included as a random effect. The treatment by visit interaction will remain in the model regardless of significance. Calculation of a suitable adjusted mean estimate will be detailed in the SAP that will estimate the average treatment effect over visits which gives each visit equal weight. The adjusted mean estimates and corresponding 95% confidence intervals will be presented for the overall treatment comparison and by visit for each treatment group.

Descriptive statistics and graphs will be reported for the TOI by visits as well as change in these scores from baseline. These will also be reported for the physical well being (PWB), social well being (SWB), emotional well being (EWB), functional well being (FWB) and the ovarian cancer subscale (Additional Concerns) domains.

Summary tables of Trial Outcome Index (TOI) best change rates will be provided.

12.2.3.7 Health State Utility – EQ-5D-5L

Descriptive statistics will be reported for EQ-5D-5L health state utility values and the visual analogue score by visit, as well as change in these scores from baseline. Further details of the exploratory analysis will be outlined in the statistical analysis plan (SAP).

The scores for each of the EQ-5D-5L health state utility values and visual analogue will be summarised in terms of mean changes from baseline at each post-baseline assessment (with n, standard deviation, min, max presented). If less than 50% of the items in one health state are missing, the mean scores for the completed items will be used for imputation. If 50% or more of the items in one health state are missing, that subscale will be treated as missing.

12.2.3.8 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 switch. 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 placebo patients, splitting between those that have and haven't switched at the time of the analyses. Further detail will be provided in the SAP and Payer Analysis Plan.

12.2.4 Exploratory endpoints

Exploratory endpoints are covered by PRO endpoints. For analysis description please see Section 12.2.3.6.

12.2.5 Interim analyses

No interim analyses of PFS prior to the primary analysis will be performed, however additional analyses of PFS and/or OS may be performed to meet Regulatory Agency requests.

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 206 PFS events in the study would have 90% power to show statistically significant PFS at the 2-sided 5% level if the assumed true treatment effect were HR 0.62; this translates to a 8 month benefit in median PFS over 13 months on placebo (estimated from data reported by Alsop et al 2012) if PFS is exponentially distributed.

Approximately 344 patients will be recruited (2:1 ratio) so that data maturity for the PFS analysis is approximately 60%.

Assuming 18 months non-linear recruitment, 206 PFS events are expected to occur approximately 36 months after first subject in is enrolled in the study (FSI). This will be the primary analysis of PFS. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

At this time, an analysis of OS will also be performed. It is anticipated that approximately 100 OS events (29% maturity) will have occurred. Assuming that the true OS treatment effect is 0.85 and if this point estimate for the HR of 0.85 was observed, the 95% upper confidence limit (UCL) for the HR would be 1.29.

A further analysis of OS may be performed at approximately 60% maturity (~206 events); this is anticipated to occur approximately 80 months after FSI. Assuming that the true OS treatment effect is 0.85 and this point estimate for the HR of 0.85 was observed, the 95% UCL for the HR would be 1.13. Note that these estimates are based on the assumption that no confounding will occur. AstraZeneca anticipates potential confounding of OS data due to availability of PARP inhibitors for BRCA mutated ovarian cancer patients during follow up in this study, which are likely to disproportionately affect OS in one arm of the study (placebo-treated patients).

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

12.4 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. 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 site.

Name	Role in the study	Address & telephone number
	Clinical Development Manager responsible for the protocol at central R&D site	
	SDT Physician responsible for the protocol at central R&D site	
	Global Safety Physician	
	24-hour emergency cover at central R&D site	

13.1 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.

13.2 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product 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 investigational product 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 6.4.4 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 the PREGOUT is used to report the outcome of the pregnancy.

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