AstraZeneca

Statistical Analysis Plan

Drug Substance	Olaparib
Study Code	D081FC00001
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A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

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PAREXEL Study Statistician PPD _____ PPD
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Astra Zeneca Global Product Statistician

PPD

PPD

Date

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this study Statistical Analysis Plan.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
Baseline	Refers to the most recent assessment of any variable prior to first dosing with study treatment
BDRM	Blind data review meeting
bid	Bis in die (Latin for 'twice a day')
BICR	Blinded independent central review
BMI	Body mass index
BoR	Best overall RECIST response
BRCA	Breast cancer susceptibility gene
BRCA mutation	Breast cancer susceptibility gene mutation (see gBRCA mutation or gBRCAm)
CI	Confidence interval
CIF	Cumulative incidence function
CR	Complete response
CRF / eCRF	Case Report Form (electronic)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAE	Discontinuation of investigational product due to adverse event
DBP	Diastolic blood pressure
DBL	Database lock
DCO	Data cut-off
DCO1	Data cut-off for primary PFS analysis
DCO2	Data cut-off for final formal OS analysis

Abbreviation or special term	Explanation
CCI [redacted]	[redacted]
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full Analysis Set
gBRCA	Germline BRCA
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.
HR	Hazard ratio
HRQoL	Health-related quality of life
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
ITT	Intention to treat
KM	Kaplan-Meier
LD	Longest diameter
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
NA	Not applicable
NE	Not evaluable
NED	No evidence of disease
NTL	Non-target lesions
ORR	Objective response rate

Abbreviation or special term	Explanation
OS	Overall Survival
CCI	[redacted]
p.o.	Per os (by mouth, orally)
PD	Progressive disease
PFS	Progression-free survival
PFS2	Time from randomisation to second progression
PID	Percentage intended dose
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of life
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use modified RECIST version 1.1.
REML	Restricted maximum likelihood
RS	Raw Score
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SOC	System organ class
Study treatment	Olaparib or matching placebo
TCMD	Time to sustained clinically meaningful deterioration (in HRQoL)
TDT	Time from randomisation to study treatment discontinuation or death
TFST	Time from randomisation to first subsequent therapy or death
TL	Target lesions
TSST	Time from randomisation to second subsequent therapy or death
ULN	Upper limit of normal
VAS	Visual analogue scale

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
	31 Jan 2020 Version 6.0	• Inclusion of exploratory analyses from the supplemental SAP in the new full SAP version. • Updates required due to the 12 months extension of study per the CSP amendment CCI [redacted] • Extension of the multiplicity section to show revised calculation of the significance level for interim analysis of OS and final formal analysis of OS based on the observed number of events at DCO1 • CCI [redacted]	Y (Version 3.0, 30 Aug 2019)	CSP Amendment: CCI [redacted]
Other	10 Apr 2019 Supplemental SAP	Separate Supplemental SAP was written after DCO1 to plan the following additional exploratory analyses that had been decided after DB lock and unblinding: • Additional subgroup analysis for PFS and OS by CCI [redacted] • Extension of PFS subgroup analysis by calculating median PFS and assessment of imbalances between treatment groups in selected subgroups by calculating the HR for treatment group. • Calculation of CIs for median duration and median time to onset of objective response. • PRO analysis was extended to include the following scales: EORTC QLQ-C30 dyspnoea, diarrhoea, and constipation multi-item symptom scales • CCI [redacted]	N/A	Adding post-hoc analysis after DCO1

Other	14 Dec 2018 Version 5.0	• Change in definition for best response in HRQoL. • Additional exposure calculation for mean total daily dose. • CCI [redacted] • Additional statistics for treatment difference estimates in the change from baseline HRQoL analysis.	N/A	Analysis updates after BDR 2
Other	07 Aug 2018 Version 4.0	• Added analysis of time to sustained clinically meaningful deterioration in HRQoL.	N/A	Analysis updates after BDR 1
Statistical analysis method for the primary or secondary endpoints / Other	06 Nov 2017 Version 3.0	• Changes in line with changes and reductions to the TFL shells. • Update to the PRO analysis set definition. • Additional specification of important protocol deviations. • Logistic regression analysis for Objective Response Rate (ORR) added. • Remove selected OS analysis. • Updated time to second progression (PFS2) analysis section to confirm that PFS2 is based on investigator assessment. Censoring rules in case of two or more missed visits also added.	N/A	Updates following TFL revisions
Primary or secondary endpoints / Multiple Testing Procedure	29 May 2015 Version 2.0	In line with the Clinical Study Protocol (CSP) Amendment: • Removal of the interim superiority analysis (change to futility only) as per Regulatory Agency recommendation. This included recalculation of the number of events needed for the primary PFS analysis. • Change to the method used for Type 1 error adjustment for the interim and final analyses of overall survival as per Regulatory Agency recommendation. • Inclusion of additional subgroup analyses as per Regulatory Agency recommendation. • Standardisation of the analysis of patient reported outcomes to be in line with other studies in the olaparib programme and to ensure consistency within the protocol. • Minor clarifications for the derivation of statistical endpoints in line with AZ oncology statistical guidance.	Y (Version 2.0, 28 Feb 2015)	CSP amendment

Other	29 May 2015 Version 2.0	Further updates: • Additional detail to clarify the independent central review process for tumour scans. • Clarification of programming of time-to-event endpoints in line with AZ oncology statistical guidance, i.e. to add one day to avoid issues with censoring at Day 1. • Clarification that best objective response, objective response rate and disease control rate will be repeated using investigator-recorded assessment as well as blinded independent central review data. • Additional detail to describe summaries of duration of response and time to onset of response. • CCI • Further clarification of dose intensity calculations for olaparib. • Inclusion of interaction testing for progression-free survival. • Inclusion of overall survival subgroup analyses. • Correction of typographical errors and additional minor clarifications.	N/A	Further updates (not related to CSP amendment)
N/A	22 Sep 2014 Version 1.0	Initial approved SAP	N/A	N/A

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1. STUDY DETAILS

As described in the protocol.

1.1 Study Objectives

Study objectives will be addressed in patients with deleterious or suspected deleterious germline mutation in breast cancer susceptibility gene 1 and/or 2 (*BRCA1* and/or *BRCA2*) and metastatic pancreas cancer who have achieved disease control (absence of objective progression) after receiving a minimum of 16 weeks of first-line platinum-based chemotherapy.

Primary:

To determine the efficacy of olaparib maintenance monotherapy compared to placebo by progression-free survival (PFS), using blinded independent central review (BICR) according to modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; in the following referred to as RECIST.

Secondary:

1. To determine the efficacy of olaparib maintenance monotherapy compared to placebo by assessment of

- Overall survival (OS).
- 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 (olaparib or matching placebo) discontinuation or death (TDT).
- Objective response rate by BICR using modified RECIST criteria.
- Disease control rate (DCR) at week 16 by BICR using modified RECIST criteria.

2. To compare the effects of olaparib maintenance monotherapy compared to placebo on the health-related quality of life (HRQoL) as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 global quality of life (QoL) scale.

Safety:

To assess the safety and tolerability of olaparib maintenance monotherapy by assessment of adverse events (AEs), physical examination, vital signs including blood pressure, pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology.

Exploratory:

1. CCI

Parts of the exploratory analyses may not be part of the analysis described in this statistical analysis plan (SAP) and as such, may not be reported in the Clinical Study Report (CSR). If not, they will be reported separately by AstraZeneca.

1.2 Study Design

This is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in metastatic pancreatic cancer patients with germline BRCA (gBRCA) mutations (documented mutation in gBRCA1 or gBRCA2) that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) and whose tumours have not progressed on at least 16-weeks of first-line platinum-based chemotherapy.

Approximately 145 patients will be randomised (using an Interactive Voice Response System / Interactive Web Response System) in a 3:2 ratio to the treatments as specified below:

- olaparib tablets per os (p.o.) 300 mg twice daily.
- placebo tablets p.o. twice daily.

Eligible patients will be those patients with pancreas cancer previously treated for metastatic disease gBRCA mutated, who have not progressed following completion of at least 16 weeks of first-line platinum-based chemotherapy before randomisation. All patients must have a known deleterious or suspected deleterious germline BRCA mutation to be randomised. Determination of gBRCA mutation will be done before enrolment to the study at Myriad laboratories.

Patients with known gBRCA mutation prior to randomisation will enter the study based on these results (by considering all other eligibility criteria as well), but undergo a confirmatory gBRCA test post-randomisation, while patients with unknown gBRCA mutation will enter the study after confirmation of gBRCA mutation.

Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of last treatment) and study treatment will start as soon as possible but no less than 4 and no more than 8 weeks after the last chemotherapy dose. At the time of starting study treatment, all previous chemotherapy treatment should be discontinued.

Following randomisation, patients 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 and will continue treatment until objective radiological disease progression as per RECIST as assessed by the investigator and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

Once a patient has discontinued study treatment, the patient will go into survival follow-up and clinic visits will be reduced to every 8 weeks. Following discontinuation of study treatment, further treatment will be at the discretion of the investigator. It is anticipated (but

not required) that patients will be re-treated with their previous platinum-based regimen. Details of any further systemic anti-cancer treatment will be collected until death, loss to follow-up, or withdrawal of consent. In addition to their regular 8 weekly contacts, patients will be contacted in the 7 days following a specified day (data cut-off date [DCO]) to capture survival status. The survival follow-up frequency of 8 weeks will be followed until the time of the final formal OS analysis (DCO2). Thereafter, CCI data will be collected every 12 weeks until the CCI

Patients will have tumour assessments according to RECIST at baseline and every 8 weeks (±1week) up to 40 weeks and then every 12 weeks (±1 week) relative to date of randomisation until objective radiological disease progression according to modified RECIST criteria. RECIST will be modified to assess patients with clinical complete response (CR) at entry who will be assessed as having no evidence of disease (NED) until 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 in order to assess objective radiological progression of disease. Failure to do so may result in bias in the study results. Once a patient has progressed, the patient will be followed for second progression every 8 weeks and for overall survival until the final analysis. Patients will be contacted in the week following the DCO for primary PFS analysis (timepoint for final PFS analysis, DCO1), following the DCO for final formal OS analysis (DCO2) and following the DCO for CCI for each analysis of survival.

The final PFS analysis of the study will occur when approximately 87 PFS events have occurred (confirmed via the BICR, DCO1), although an interim PFS analysis for futility will be performed when 50% of the PFS events required for the final PFS analysis have occurred. Both interim and final PFS analyses will be based on BICR of disease progression by modified RECIST version 1.1; however, a sensitivity analysis will be performed using the investigator-recorded assessment.

An interim analysis of OS will be performed at the time of the final analyses of PFS (DCO1). A final analysis of OS will be performed when approximately 106 OS events have occurred (DCO2). CCI

Unblinded outputs for the futility analysis of PFS will be prepared by the International Drug Development Institute (IDDI). For the combined analysis of final PFS and interim OS, the study will be unblinded at PAREXEL. No measures for keeping team members blinded for the subsequent final OS analysis are required. For details on how the blinding is maintained refer to the "Blinding Maintenance Plan" for the study.

The study flow chart is in Appendix A: Study Flow Chart while the study schedule is in Appendix C: Study Schedule.

1.3 Number of Patients

The primary endpoint of the study is PFS. Approximately 145 patients will be randomised (3:2 ratio of olaparib:placebo) and the final PFS analysis will occur once approximately 87 PFS events (confirmed via a central review, DCO1) have occurred. A single interim PFS analysis for futility will be performed when 50% of the PFS events required for the final analysis (approximately 44 PFS events) based on BICR have occurred.

The study is sized assuming a true treatment effect that is a PFS hazard ratio (HR) of 0.54 at the final analysis, assuming 80% power and 2.5% alpha (1-sided), with 3:2 randomisation (olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median PFS for placebo.

Patients are to be followed for the final analysis of OS and PFS2 (when approximately 106 death events have occurred, DCO2). With 106 OS events the study has 80% power to show a statistically significant difference in OS at the 1-sided 2.5% level if the assumed true treatment effect is a HR 0.57; this translates to an approximate 6-month improvement in median OS over an assumed 8 month median OS on placebo, assuming OS is exponentially distributed.

Assuming that the study accrual period will be approximately 15 months, 87 PFS events are anticipated to be observed approximately 18 to 19 months after the first patient is randomised in the study. It is estimated that 44 PFS events will occur approximately 13 to 14 months after first patient in. It is estimated that 106 deaths will have occurred approximately 31 months after first patient in.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

Full Analysis Set

Intention to treat (ITT): The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received or discrepancy between local and Myriad gBRCA results. Patients who were randomised but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy endpoints will be summarised and analysed using the FAS on an ITT basis.

In addition, key sensitivity analysis of efficacy endpoints will be performed in the subgroup of patients in the FAS that have a gBRCA mutation confirmed by the Myriad test.

Safety Analysis Set

All patients who received at least one dose of randomised investigational product, olaparib or placebo, will be included in the safety analysis set. Throughout the safety results sections, all patients who received at least one dose of olaparib will be accounted for in the olaparib treatment group. Erroneously treated placebo patients (those randomised to placebo but

actually received at least one dose of olaparib) will be accounted for in the olaparib treatment group. Any mis-randomisations will be discussed on an individual basis and decisions will be documented at the blind data review meeting (BDRM) for the final analysis of PFS and at the data review meeting (DRM) for the final analysis of OS and PFS2.

Patient Reported Outcome Analysis Set

The analysis population for patient reported outcome (PRO) data will be a subset of the FAS (ITT) population who have evaluable baseline EORTC QLQ-C30 CCI [redacted] forms where evaluable means that at least one sub-scale baseline score can be determined from at least one of the two forms.

Table 1 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
Primary analysis: PFS	FAS (ITT), Myriad confirmed Breast cancer susceptibility gene mutation (gBRCAm) subgroup
Secondary analysis:	
OS, PFS2, TFST, TSST, TDT	FAS (ITT), Myriad confirmed gBRCAm subgroup
Objective response rate (ORR)	FAS (ITT) (patients with measurable disease at baseline)
Disease control rate (DCR), Duration of response (DoR)	FAS (ITT)
CCI [redacted]	[redacted]
CCI [redacted]	
[redacted]	[redacted]
Demography	FAS (ITT)
Safety Data	
Exposure, AEs, Laboratory measurements; ECGs, Vital signs, CCI [redacted], Physical examinations	Safety

2.2 Violations and Deviations

Important protocol deviations are those that could have a heavy influence on the interpretation of any analysis based on addressing the primary efficacy and secondary safety objectives of

the trial. This section will define important protocol deviations so that instances can be identified and reported in the CSR.

Major protocol deviations are deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis. This will include all important deviations to be reported in the CSR.

Major and important protocol deviations will be listed for the FAS analysis set. Important protocol deviations will be summarised by randomised treatment group for the FAS analysis set. None of the deviations will lead to any patients being excluded from any of the analysis sets described in Section 2.1.

A per-protocol analysis excluding patients with important protocol deviations is not planned; however, a 'deviation bias' sensitivity analysis will be performed excluding patients with those important deviations that may affect the efficacy of the trial therapy if >10% of patients:

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

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock or data freeze for the final analysis on PFS (DCO1) and will be documented prior to the study being unblinded and the analysis being conducted.

The full definition of important protocol deviations and any action to be taken regarding the exclusion of subjects (for the sensitivity analysis) are defined in the project-specific Protocol Deviation Specification. The dataset of protocol deviations that is received from the protocol deviation system will contain a variable DVACTION that can be used to identify patients to be excluded from the sensitivity analysis.

The following general categories will be considered important deviations from a statistical perspective and will be summarized, listed and discussed in the CSR as appropriate:

- Patients randomised but who did not receive olaparib/matching placebo.
- Patients who deviate from key study entry criteria (to be determined at the BDRM), which will be documented ahead of database lock.
- Baseline RECIST scan missing or > 28 days before start of study treatment.
- Baseline RECIST scan after randomisation.
- RECIST scan not performed according to protocol.

The categorisation of these as important deviations is not automatic and will depend on duration and the perceived effect on efficacy.

In addition to the programmatic determination of the deviations above, monitoring notes or summaries will be reviewed to determine any important post-entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified.

Mis-randomisations in terms of errors in treatment dispensing, will also be considered as important protocol deviations. A mis-randomisation is when a patient is not randomised or treated according to the randomisation schedule. It is envisaged that there will be 2 subcategories of this:

(a) Patients who receive no treatment whatsoever for a period of time due to errors in dispensing of medication. Note, this is not due to tolerability issues where patients may stop taking drug.

(b) The patient receives a treatment pack with a different code from their randomisation code. However, the actual treatment may still match the randomised treatment. For example, a patient is given randomisation code 0001, which according to the randomisation schedule is olaparib. However, at the randomisation visit they are given treatment pack 0003, but this still contains olaparib.

The summary will include all patients with a dispensing error but will also include information on how many of those patients received at least one dose of the wrong treatment (olaparib/placebo) at any time.

Patients who receive the wrong treatment at any time will be included in the safety analysis set as described in Section 2.1. During the study, decisions on how to handle mis-randomisations will be made on an individual basis with written instruction from the study team leader and/or statistician.

The following table summarizes the important deviations discussed above. The last column flags the deviations that if observed in >10% of FAS patients would lead to a sensitivity analysis. For the full specification please refer to the project-specific Protocol Deviation Specification.

Table 2 Important protocol deviations

PD term	Criteria to identify PD	Sensitivity analysis
Not the intended disease or indication	Relevant in- or exclusion criteria are not fulfilled.	Yes
Did not receive any randomised therapy	Patient was randomised and did not receive any study treatment.	Yes
Deviation from other key	Patients who deviate from key entry criteria other than	

entry criteria	the intended disease or indication.	
Baseline RECIST missing	RECIST scan on or before first dose of study treatment is missing.	
Baseline RECIST scan too early	Baseline RECIST scan taken more than 28 days before start of study treatment.	
Baseline RECIST scan too late	Baseline RECIST scan taken after randomisation.	
RECIST scan not performed according to protocol	RECIST scan not in scheduled visit window on >2 occasions post-baseline regardless of whether visits were consecutive or not.	
Wrong treatment kit but correct study drug	The patient receives a wrong treatment pack. Actual treatment matches the randomised treatment.	
Wrong treatment kit with incorrect study drug	The patient receives a wrong treatment pack. Actual treatment does not match the randomised treatment.	
Treatment interrupted	Subject did not receive study treatment for a period of 28 consecutive days or more due to errors in dispensing of medication or non-compliance. This excludes drug interruptions due to adverse events or due to tolerability issues.	
Subject took concomitant medications or therapies prohibited whilst receiving study medication	Subject took disallowed medications or therapies starting on or after first dose of treatment. Refer to details of medication types in section 7.7 of the CSP.	
Non-compliance with study treatment	Severe non-compliance with treatment reported by site monitor in IMPACT.	
Deviation from ICH-GCP	Deviation of ICH Good Clinical Practice (GCP) reported by site monitor in IMPACT	

The categories listed in the table can be identified using the protocol deviation reference IDs that are defined for each type of protocol deviation in the project-specific specification.

For the final analysis of PFS / interim analysis of OS, the final classification of deviations will be made at the BDRM prior to database lock or data freeze (DCO1) and all decisions including the requirement of a sensitivity analysis will be made whilst blinded to study

treatment allocation. Decisions made at the BDRM for the final analysis of PFS will be documented and approved by AstraZeneca prior to analysis and unblinding.

For the final formal analysis of OS (DCO2), new protocol deviations will be reviewed and classified at a DRM prior to DB lock. The study will be unblinded by that time, however, there is no sensitivity analysis planned for the analysis of OS. Also, for CCI [redacted] new protocol deviations will be reviewed and classified at a DRM prior to DB lock.

3. PRIMARY AND SECONDARY VARIABLES

At each visit patients will be assigned a RECIST visit response of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE) or NED depending on the status of their disease compared to baseline and previous assessments, based on the BICR. This will be repeated using the Investigator assessed RECIST data.

3.1 Derivation of RECIST Visit Responses

Patients with measurable or non-measurable disease or NED assessed at baseline by computed tomography (CT) / magnetic resonance imaging (MRI) will be entered in this study. RECIST has been modified to allow the assessment of progression due to new lesions in patients with NED at baseline (inclusion criteria #4).

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to modified RECIST version 1.1. It will also be used to determine if and when a patient has progressed in accordance with RECIST and also their best overall response.

Baseline radiological tumour assessments are to be performed no more than 28 days before start of study treatment and ideally as close as possible to the start of study treatment and prior to randomisation. Tumour assessments are then performed every 8 weeks (±1 week) up to 40 weeks and then every 12 weeks (±1 week) following randomisation until disease progression.

If an unscheduled assessment was performed and the patient had not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

At each visit, an overall visit response will be provided by the BICR and separately by the investigator - using the information from target lesions (TL), non-target lesions (NTL) and new lesions.

3.1.1 Target lesions

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (except lymph nodes which must have

short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved suitable for accurate repeated measurement) and these are referred to as TLs. If more than one baseline scan is recorded, then measurements from the one that is closest to and prior to randomisation will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Note: For patients who do not have measurable disease at entry (ie, no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTLs assessment and the absence/presence of new lesions (see Section 3.1.3 of the Clinical Study Protocol (CSP) for further details). If a patient does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

For patients with NED at baseline (ie, no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be NED.

Table 3 TL Visit Responses

Visit Responses	Description
CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also indicate an absolute increase of at least 5 mm.
NE	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
NA	No TLs are recorded at baseline.

Rounding of TL data

For calculation of PD and PR for TLs, percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

For a visit to be evaluable, all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded.
- A NTL visit response of PD is recorded.
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm from nadir, even assuming the non-recorded TLs have disappeared. Note: the nadir can only be taken from assessments where all the TLs had a longest diameter (LD) recorded, including non-missing TLs which have had intervention during the study and prior to any scaling of the measurements.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

Lymph nodes

For lymph nodes, if the size reduces to < 10 mm then these are considered non-pathological. However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10 mm and all other TLs are 0 mm, then although the sum may be > 0 mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

A CR can only be followed by CR, PD or NE. If a CR has occurred then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (ie, 0 mm or < 10 mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met ie, if a lymph node LD increases by 20% but remains < 10 mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (ie, 0 mm or < 10 mm for lymph nodes), then response will be set to NE irrespective of whether when referencing the sum of TL diameters the criteria for PD is also met.

- Step 3: If not all lesions meet the CR criteria and the sum of lesions meets the criteria for PD, then response will be set to PD.

- Step 4: If after steps 1 – 3 a response can still not be determined, the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure, this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure a value of 5 mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured. If a TL response of PD results, then this will be reviewed by the study team blinded to treatment assignment.

Irradiated lesions/lesion intervention

Previously irradiated lesions (ie, lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization), should be handled in the following way and once a lesion has had intervention then it should be treated as having had intervention for the remainder of the study, noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.

- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements, then scale up as described below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.

  Scaling will be based on the measurements at the nadir visit, to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-intervention lesions to the nadir sum of diameters excluding the lesions with interventions.

Table 4 Example of scaling

Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	Intervention
Sum	**29.3**	**26**

Lesion 5 has had an intervention at the follow-up visit.

The sum of lesions 1 to 4 at the follow-up is 26 cm. The sum of the corresponding lesions at baseline visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4 cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

- Step 3: If after both steps PD has not been assigned, then if appropriate, a scaled sum of diameters will be calculated (as long as ≤ 1/3 of the TLs have missing measurements), treating the lesion with intervention as missing, and PR or SD, then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or < 10 mm for lymph nodes) and the lesions that have been subject to intervention also have a value of 0 recorded. If scaling-up is not appropriate due to too few non-missing measurements then the visit response will be set as NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up where appropriate (as per step 2 above).

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 mm.

Change in method of assessment of TLs

Computed tomography (CT) and MRI are the only methods of assessment that can be used within the trial. If a change in method of assessment occurs between CT and MRI, this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (eg, CT changes to clinical examination), any affected lesions should be treated as missing.

3.1.2 NTLs and new lesions

At each visit an overall assessment of the NTL response should be recorded. This section provides the definitions of the criteria used to determine and record overall response for NTL at each visit.

The NTL response will be derived based on the overall assessment of NTLs as follows:

Table 5 NTL Visit Responses

Visit Responses	Description
CR	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
NE	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
NA	Only relevant if there are no NTLs at baseline.

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

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

New lesions will be identified on the electronic case report form (eCRF). The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present and should be treated as NE in the derivation of overall visit response.

'Symptomatic deterioration' is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs. Patients with symptomatic deterioration requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

3.1.3 Overall visit response

Table 6 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 6 Overall Visit Responses

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

NA is only relevant if there were no TL/NTL at baseline.

3.1.4 Independent review

A planned BICR of all radiological imaging data will be carried out using modified RECIST version 1.1 and these data will be used for the interim and primary analyses of PFS. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (PAREXEL Imaging) for central analysis. Prior radiotherapy and location of screening biopsy lesion reports will also be provided to the BICR to allow the selection of appropriate TLs. The imaging scans will be reviewed by 2 independent radiologists using modified RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response (ie, the response obtained overall at each visit by assessing TLs, NTLs and new lesions) data (for patients with TLs at baseline: CR, PR, SD, PD, NE; for patients with NTLs only: CR, SD, PD or NE; for patients with no disease identified at baseline: PD, NED, NE). If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD).

RECIST assessments/scans contributing towards a particular visit may be performed on different dates and for the central review the date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression, either for the adjudicated reviewer selecting PD or of the first reviewer where both select PD as time-point response and there is no adjudication.

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 modified RECIST 1.1 assessment conducted by the Investigator.

On an ongoing basis, patients who are determined to have progressed according to modified RECIST 1.1 criteria by the investigator will have scans centrally reviewed for confirmation of objective disease progression. Radiological scans will only be sent for BICR up until the date of RECIST progression determined by the investigator. However, if disease progression is not confirmed at BICR, an additional RECIST assessment will be requested at the next scheduled RECIST visit. After the final PFS analysis, BICR of scans will no longer be required, regardless of progression status.

Further details of the BICR will be documented in the BICR Charter.

3.2 Outcome Variables

For each patient, an overall RECIST visit response of CR, PR, SD, PD, NED, NE, will be determined from the BICR as described in Section 3.1.4 above. The outcome variables involving RECIST data, i.e. PFS, best overall response, ORR and DCR, will be derived using overall visit responses and relevant dates from the BICR (which is considered to be the primary RECIST dataset), unless otherwise stated.

Separately, investigator-assessed site measurements/assessments (TLs, NTLs, new lesions) will be used to programmatically derive an investigator assessment of overall visit response.

3.2.1 Progression-Free Survival

Progression-free survival is defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to disease progression (i.e. date of RECIST progression/death or censoring – date of randomisation + 1). 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 (prior to the missing visits). Given the scheduled visit assessment scheme, for the first 40 weeks from randomisation, two missing visits will equate to more than 18 weeks since the previous RECIST assessment, allowing an extra two weeks for early and late visits. After 40 weeks, two missing visits will equate to more than 26 weeks. If two missed visits occur over the period when the scheduled frequency of RECIST assessments changes (ie, from every 8 weeks to every 12 weeks), this will equate to more than 22 weeks (allowing for an early assessment at Week 32 and a late assessment at Week 52). Please refer to the appendix for a graphical display of the allowed time gap in RECIST assessments (Appendix D: Visualisation of Censoring Rule for Progression Free Survival).

The baseline RECIST assessment should be performed prior to randomisation but if an evaluable RECIST assessment occurs after randomisation but before treatment then this assessment will be used as the baseline 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 tumour assessment visits of randomisation (16 weeks plus 1 week allowing for a late assessment within the visit window).

If a patient has two missing visits between two evaluable RECIST assessments with outcome not equal to progression at the second evaluable RECIST assessment, but then subsequently progresses, the patient will not be censored when analysing for PFS. For example, if RECIST assessments were performed at week 8 with outcome SD, week 32 with outcome SD and week 40 with a progression event (weeks 16 and 24 were missed), the patient will be analysed from time of randomisation until progression event at week 40 without considering the interruptions.

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

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

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

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

(c) For both BICR data and investigational site assessments, 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 by the investigator and BICR 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 TLs (compared to previous minimum sum) and an absolute increase of > 5 mm, or an overall NTLs assessment of progression or a new lesion.

The primary analysis will be based on the programmatically derived PFS based on the BICR of the radiological scans, and using all scans regardless of whether they were scheduled or not. A sensitivity analysis based on the derived PFS based on investigator-recorded assessments will be carried out.

3.2.2 Overall Survival

Overall Survival is defined as the time from the date of randomisation until death due to any cause (i.e. date of death or censoring – date of randomisation + 1). 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. This analysis will be based on the "date subject last known to be alive" variable which is recorded within the survival status module of the eCRF (SURVIVE module).

Note: Survival calls will be made in the week following the date of 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. If a patient has died but the date of death cannot be determined, then the patient will be censored based on the last recorded date on which the patient was known to be alive (although every effort needs to be made to determine the date of death). The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. If the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly-available resources where it is possible to do so under applicable local laws.

3.2.3 Time from randomisation to second progression

The time from randomisation to second progression (PFS2) is defined as the time from the date of randomisation to the earliest of the second progression event as assessed by the investigator or death (ie date of PFS2 event or censoring – date of randomisation + 1). The

date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of objective radiological or symptomatic progression or death. The RECIST assessments will not be collected for assessment of PFS2. The date of the PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

Second progression status will be reviewed every 8 weeks following the investigator assessment of the first objective progression and status recorded (until DCO2). 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, ie, censored at the latest of the RECIST assessment or PFS2 assessment dates. If a patient progresses for the second time or dies after two or more missed visits, the patient will be censored for PFS2 at the time of the latest evaluable investigator – recorded assessment.

Censoring will need to be applied for some patients prior to the first progression and for others after the first progression, depending if the patient had a first progression at the time of analysis or not. The duration of two missed visits is depending on the respective visit schedule:

- If the patient was progression-free at the time of analysis, then patients will be censored as described for PFS (Section 3.2.1), i.e. using the latest RECIST scan.
- If the patient died in the absence of any progression after two or more missed visits, then the censoring visit rule as described for PFS (Section 3.2.1) needs to be applied.
- If a patient is alive and had only the first progression assessed at the time of analysis, then the censoring will be based on the latest investigator assessment of no progression in the follow-up phase. If there are no follow-up results recorded, then the date of the latest scan contributing to the investigator assessment of first progression will be used for censoring.
- If the patient had progressed once and then died or progressed for the second time after two or more visits, then those two or more missed visits equate to more than 18 weeks, since the patient is in the follow-up phase (16 weeks plus allowing an extra two weeks for early and late visits), i.e., if the latest follow-up assessment prior to second progression or death was are more than 18 weeks ago, then the patient is censored with the date of this last investigator assessment. If no follow-up results are recorded, and the investigator assessment of first progression is more than 18 weeks ago, then the date of the latest scan contributing to this first progression assessment will be used for censoring.

3.2.4 Time to first subsequent therapy or death

As a supportive summary to PFS, TFST will be assessed at the 30-day follow-up visit following study treatment discontinuation and then every 8 weeks until DCO2 / every 12 weeks after DCO2, in line with survival follow-up visits. The TFST is defined as the time from randomisation to the earlier of first subsequent cancer therapy start date following study treatment discontinuation, or death (i.e. date of first subsequent cancer therapy/death or censoring – date of randomisation + 1). 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 cancer therapy, ie, the last follow-up visit where this was confirmed.

3.2.5 Time to second subsequent therapy or death

As a supportive summary to PFS2, TSST will be assessed at the 30-day follow-up visit following study treatment discontinuation and then every 8 weeks until DCO2 / every 12 weeks after DCO2, in line with survival follow-up visits. The TSST is defined as the time from randomisation to the earlier of the second subsequent cancer therapy start date following study treatment discontinuation, or death (i.e. date of second subsequent cancer therapy/death or censoring – date of randomisation + 1). 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 second subsequent cancer therapy, ie, the last follow-up visit where this was confirmed.

3.2.6 Time to study treatment discontinuation or death

The TDT is defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death (i.e. date of study treatment (olaparib/placebo) discontinuation/death or censoring – date of randomisation + 1). 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. Patients who were randomised but never exposed to study treatment will be censored at day 1.

3.2.7 Best objective response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment (Table 6). It is the best response a patient has had following randomisation but prior to starting any subsequent cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorization of BoR will be based on the RECIST criteria using the following order of response categories: CR, PR, SD, NED (applies only to those patients entering the study with no disease at baseline), PD and NE. Patients entering the study with no measurable disease at baseline who would qualify for CR are considered as SD and summarized separately as "stable disease (complete response without measurable disease)".

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

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 7 weeks (ie, 8 weeks minus 1 week to allow for an early assessment within the assessment window), after randomisation. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For patients whose 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 ≤ 17 weeks (ie, 16 weeks +1 week to allow for a late assessment within the assessment window) after randomisation then BoR will be assigned to the PD category. For patients who die with no evaluable RECIST assessments, if the death occurred > 17 weeks (ie, 16 weeks +1 week) after randomisation then BoR will be assigned to the NE category.

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

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time following randomisation, prior to RECIST progression and prior to starting any subsequent cancer therapy.

3.2.8 Objective response rate

For each treatment group, the ORR is the number of patients with a BoR of CR and PR according to the BICR data divided by the number of patients in the treatment group with measurable disease at baseline where 'measurable' is defined by the BICR data. Only patients with measurable disease at baseline can achieve an objective response of CR or PR.

As supportive summaries, duration and time to onset of objective response in patients with an objective response (derived using BICR data) will be calculated using a Kaplan-Meier technique.

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint (using BICR data). The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a subject does not progress following a response, then the patient will be censored at the same timepoint that was used for the censored PFS analysis.

Time to onset of objective response will be defined as the time from randomisation to the date of first documented response.

ORR, duration of response and time to onset of objective response will also be calculated using investigator-recorded assessment, with 'measurable' disease at baseline defined according to investigator assessment.

3.2.9 Disease control rate

The DCR is defined as the percentage of patients who have at least one visit response of CR or PR or have demonstrated SD or NED for at least 15 weeks (ie, 16 weeks minus 1 week to allow for an early assessment within assessment window) prior to any evidence of

progression. In the case of SD and NED, follow-up assessments must have met the SD or NED criteria for a minimum interval of 15 weeks following randomisation. This will be calculated using BICR data, in addition to investigator-recorded assessment.

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3.4 Safety

Safety and tolerability will be assessed in terms of AEs (including serious AEs [SAEs]), deaths, laboratory data, vital signs, ECGs, physical examination, CCI [redacted] and exposure. These will be collected for all patients.

3.4.1 Adverse events

Adverse events and SAEs will be collected throughout the study, from informed consent until 30 days after the last dose of olaparib/placebo. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment should also be reported as an AE.

Adverse Event of special interest

Some AEs that follow clinical concepts are considered as adverse events of special interest (AESIs). They are grouped into the following three categories: Myelodysplastic syndrome / acute myeloid leukemia (MDS/AML), new primary malignancies and pneumonitis. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician will confirm the list of AEs of special interest (group terms and the specific preferred terms) and provide them for analysis. They will be confirmed at the BDRM prior to the final analysis for PFS and at the DRM prior to the final analysis of OS and PFS2.

3.4.2 Treatment exposure

Exposure will be defined as follows:

Total (or intended) exposure of olaparib/placebo:

- Total (or intended) exposure in days = last dose date - first dose date + 1

Actual exposure of olaparib/placebo:

- Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above. Dose interruptions are any periods when the patient does not take any treatment.

To calculate actual exposure, dose interruptions will include those where a patient forgot to take a dose.

Number of days on 300 mg olaparib/placebo bis in die (bid)

- Number of days on 300 mg olaparib/placebo bid = actual exposure for the dose assigned. Any days with changes in doses will not be counted.

Mean total daily dose per time period

- Sum of the total dose actually received in the time period of interest (considering interruptions and dose reductions) divided by number of days patient on dose for that time period (including interruptions and reductions).

Compliance will be assessed by calculating the actual exposure in days (total planned days - days of interruption) divided by the total exposure in days (last dose date - first dose date + 1) in percent. In addition, patient's individual drug accountability will be listed.

3.4.3 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation. Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression. Both will be derived using study treatment data up to the date of objective disease progression as defined by RECIST using the investigator site assessments. If the investigator considered that it was in the patient's best interest to continue study treatment past this time, this will not be included in the derivation of dose intensity.

RDI and PID will be defined as follows:

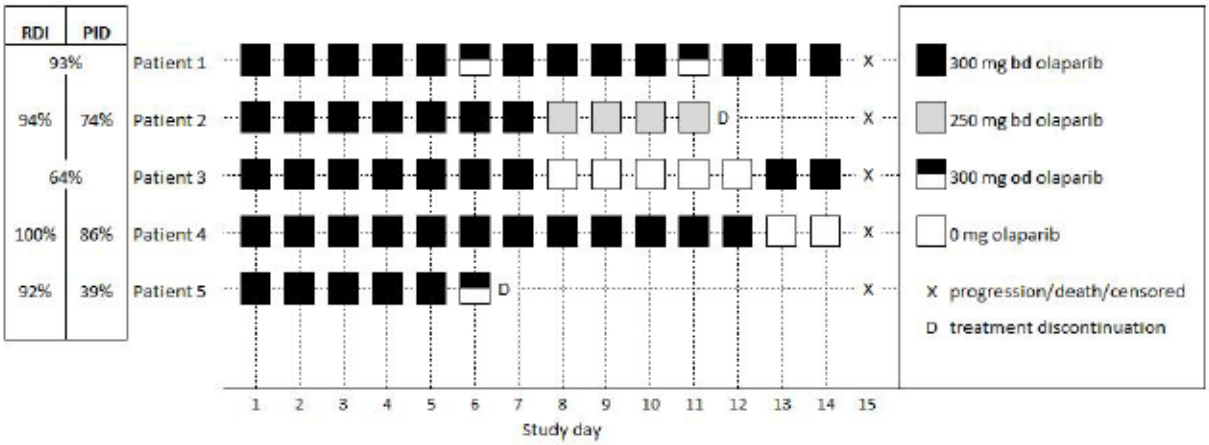
- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or the actual last day of dosing and D is the

intended (or planned) cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing.

- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended (or planned) cumulative dose up to progression (or a censoring event). D is the total dose that would be delivered, if there were no modification to dose or schedule.

For olaparib administered daily for the first two weeks of the cycle, the intended cumulative dose, D, will include all doses received up to midnight on the day of the last non-zero dose. Figure 1 provides examples of how dose intensity is calculated for olaparib.

Figure 1 Example of dose intensity calculations for olaparib



In this example, patients 1-4 progressed or were censored on Day 15. All four patients received less treatment than intended due to:

- Missed/forgotten doses (Patient 1)
- Dose reduction and early stopping (Patient 2)
- Dose interruption (Patient 3)
- Progression whilst on dose interruption (Patient 4)
- Early stopping (Patient 5)

CCI [redacted]

CCI [redacted]

3.4.4 Laboratory data

Laboratory data will be collected throughout the study, from screening to 30-day follow-up visit as described in Appendix C. Blood and urine samples for determination of pregnancy, haematology, clinical chemistry, and urinalysis will be collected as described in Section 5.2.1 of the CSP. For derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.4.9 below will be used.

3.4.5 Electrocardiograms

Electrocardiogram data will be collected during screening within 7 days prior to starting study treatment and when clinically indicated afterwards. For derivation of post baseline visit values considering visit window and how to handle multiple records present in any visit window, derivation rules as described in Section 3.4.9 below will be used.

3.4.6 Vital signs

Vital signs data including body temperature, height, weight, pulse and blood pressure will be collected as described in Appendix C. For derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.4.9 below will be used.

3.4.7 Physical examination

Physical examination data including 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 will be collected as described in Appendix C.

CCI [redacted]

3.4.9 General consideration for safety assessments

Time windows

Time windows will need defining for any presentations that summarise safety values by visit (ie. vital signs [incl weight and height], ECG, laboratory, and CCI [redacted]). The following conventions should also apply:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window should be based on the actual date and not the intended date of the visit.

- All unscheduled visit data should have the potential to be included in the summaries.

- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2, ie. the day after the first dose of study drug). The visits Screening, Cycle 1 Day 1, Treatment Discontinuation, 30-Day Follow-up and Survival Follow-up visits will be excluded from remapping. The equation to be used to calculate the time windows for each post-baseline visit is:

  Lower limit of interval=Upper limit of previous visit's time window +1

  Upper limit of interval=Nominal day at visit + ([nominal day at $visit_{i+1}$ - nominal day at $visit_i$]/2), where i = 3, 4, 5, 5.1, 5.2..., etc.

  If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.

  For example, the visit windows for vital signs data with 28 days between scheduled assessments are:

  – Day 29, visit window 2 – 42

  – Day 57, visit window 43 – 70

  – Day 85, visit window 71 – 98

  – Day 113, visit window 99 – 126

  – ...

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).

- Listings should display all values contributing to a time point for a patient.

- For visit-based summaries:

  – If there is more than one value per patient within a time window, then the closest value should be summarised, or the earlier in the event the values are equidistant from the nominal visit date. The listings should highlight the value for that patient that went into the summary table, wherever feasible.

  - To prevent very large tables or plots being produced that contain many cells with meaningless data, for each treatment group visit data should only be summarised if the number of observations is greater than the minimum of 20 and > 1/3 of patients dosed. For example, if 150 patients were dosed in the study (1/3*150 = 50), data at a particular visit would be summarised if the number of observations is greater than min (20, 50). This would be in each treatment group. Eg, if olaparib arm at Visit 6 has > 20 observations and placebo arm has < 20 observations, the visit data will be summarised for the olaparib arm but not the placebo arm. If both had < 20 patients, the data for that visit will be presented as 'NC' (Not Calculated). (This does not apply to PRO data.)

- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.

- Baseline will be defined as the last non-missing measurement prior to dosing with study treatment (olaparib or placebo). Any assessments made on day 1 will be considered pre-dose. If an assessment on day 1 is identified as baseline, then it will not be considered as "on treatment". Where safety data are summarised over time, study day will be calculated in relation to date of first treatment (olaparib or placebo).

Imputation of missing safety data

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (ie, below the lower limit of quantification) or "> x" (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

Imputation of missing age

- Age at randomisation: Age at randomisation (baseline) will be calculated from the date of birth. Due to country specific regulations the full date of birth will not be available for all patients. In this case the "age as collected" from the demographics CRF will be used instead.

- Age calculation after randomisation: If order to identify reference ranges for laboratory parameters during the study, the age of a patient needs to be calculated at the timepoint of the collection of the sample. If the date of birth of a patient is only partially collected, then the following rule will be applied: (a) if only day is missing, then calculate age using the first day of the month; (b) if day and month are missing, then calculate age using the first of July. Then use the maximum of this calculated age and of the age as collected at screening for identification of reference ranges. If the date of birth is completely missing, then age as collected will be used.

Imputation of missing dates

For **AEs**, imputation methods will be used on completely missing start dates. Missing AE stop dates are not imputed. Imputation for partial dates is not applicable because partial adverse event dates are not collected in this study. Imputed start dates are used to decide if an observation is treatment emergent and for calculation of the AE event rates. Data listings will show actual date values. Missing AE start dates will be imputed with the first dose date unless the end date indicates it started prior to first dose date, in which case impute the 1st January of the year where the AE stopped as the start date.

For **concomitant medications**, start and stop dates are captured on the CRF with no partial dates being entered in the CRF. If the drug started prior to study start, then this is indicated by a flag "Yes" and the start date is missing. If the treatment with the medication continues, then this is indicated by a flag "Yes" and the stop date is missing. For the analysis of medications, it is required to decide if the medication was taken during the time of study treatment. Such a medication may have started before, on or after the first dose of study drug and was taken in the time frame up to and including 30 days following the last dose of study drug. For patients on study treatment at the time of the PFS analysis, the DCO date will be used as the last dose of study drug.

Therefore, medications are considered as treatment emergent (taken during study treatment) if they:

- started on or before first dose and (stopped on or after first dose or are ongoing) OR
- started after first dose but prior to or on date of last dose plus 30 days.

The following conservative imputation rules will be applied:

- Start and stop date of medication present: apply the rules above
- Start date present but no stop date of medication: assume that medication is ongoing and apply the rules above.
- Start date missing and stop date is not missing and "treatment prior to study start" is "Yes": Temporarily set start date to the earliest of (date of first dose of study drug, stop date of medication) and apply the rules above
- Start date missing and stop date is missing and "treatment prior to study start" is "Yes": Temporarily set start date to the date of first dose of study drug, assume the medication is ongoing and apply the rules above
- Start date missing and stop date is not missing and "treatment prior to study start" is missing: Temporarily set start date to the earliest of (date of first dose of study drug, stop date of medication) and apply the rules above
- Start date missing and stop date is missing and "treatment prior to study start" is missing: Temporarily set start date to the date of first dose of study drug, assume the medication is ongoing and apply the rules above

3.5 Resource Use

Resource use outcome variables include the following:

- Total number of hospitalisations
- Length of hospital stay
- Reasons for hospitalisation
- Total number of ICU admissions
- Length of any time spent in an intensive care unit (ICU)
- Reasons for ICU admission

The length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date when occurred during hospital stay) and the start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). If the start of study drug is after the start of hospitalisation, then the start of study drug will be used instead (length of hospital stay = end date of hospitalisation – start date of study drug + 1). If a patient was never treated with study drug and the date of randomisation is after the start date of hospitalisation, then the date of randomisation will be used instead (length of hospital stay = end date of hospitalisation – date of randomisation + 1). For patients without an end date at the time of the PFS analysis, the date of death will be used if available; otherwise the DCO date will be used.

Sum of total duration of hospital stay will be considered for analysis if patient was admitted to hospital more than one time during study period.

Hospital and ICU admissions will be counted as a single event if a patient is re-admitted on the same day.

The length of ICU stay will be calculated using the same method as detailed above for the length of hospital stay. However, if the end date of the ICU stay is not available, but the end date of the corresponding hospitalisation period is given, then the end of the ICU stay will be imputed using this date, instead of using the DCO date.

4. ANALYSIS METHODS

4.1 General Principles

Efficacy data will be summarised and analysed using the FAS on an ITT basis while HRQoL data will be analysed using the PRO analysis set (see Section 2.1) and will compare the

treatment groups on the basis of randomised treatment, regardless of the treatment actually received. In addition, as sensitivity to the main analyses of PFS, PFS2, OS, TDT, TFST and TSST, analyses of these endpoints will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test.

Results of all statistical analysis will be presented using a 95% confidence interval (CI) and 2-sided p-value, unless specified otherwise. Median and corresponding 95% CI of time to event data (PFS, OS, PFS2, TFST, TSST, TDT) will be calculated using a Kaplan-Meier technique.

When assessing safety and tolerability, summaries will be produced based on the safety analysis set and will compare the treatment groups on the basis of treatment actually received. The safety data will be summarised descriptively and will not be formally analysed.

4.1.1 Presentation of results in summary tables

If not stated otherwise, tabulations will be presented by treatment group as follows:

- Olaparib 300 mg bid
- Placebo bid
- Total

Data listings will include at least the following details:

- Patient identifier
- Centre identifier
- Actual / randomised treatment group

Data listings will be sorted by treatment group (planned or actual) and patient ID, if not stated otherwise.

4.2 Analysis Methods

A single interim PFS analysis for futility will be performed when 50% of the final number of progression events has been reached (approximately 44 PFS events). A final PFS analysis will be performed when approximately 87 progression events have occurred (60% maturity) (DCO1). No further analyses of PFS are planned beyond this point.

One interim analysis for OS will be performed at the time of the final PFS analysis (approximately 87 PFS events). A final formal analysis of OS will be performed when approximate 106 death events have occurred (DCO2). CCI [redacted]

Individual efficacy response data will be listed in a by-patient listing.

A summary of the outcome variables to be analysed at each DCO is shown in Table 10 below.

Table 10 Timing of Statistical Analyses

Timing of analysis	Outcome Variable
Interim PFS when ~44 PFS events reported	PFS
Final PFS when ~87 PFS events reported (DCO1)	PFS, PFS2, TDT, TFST, TSST, OS, ORR, BoR, DoR and adjusted mean change from baseline in global HRQoL score.
Final formal OS when ~106 OS events reported (DCO2)	OS, PFS (investigator assessment), PFS2, TDT, TFST, TSST, and adjusted mean change from baseline in global HRQoL score.
CCI [redacted]	[redacted]

Safety variables will be analysed at each analysis time point.

There will be no further analyses done unless requested by health authorities.

The treatment comparison is olaparib 300 mg bid versus placebo.

The following table details which efficacy 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	**Primary analysis**: log-rank test using BICR data
	Key sensitivity analyses: log-rank test using BICR data in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
	Additional sensitivity analyses:
	1) Evaluation time bias analysis; log-rank test using BICR data
	2) Attrition bias analysis (using alternative censoring rules); log-rank test using BICR data
	3) Ascertainment bias analysis; log-rank test using investigator data

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

Endpoints Analysed	Notes
	4) Deviation bias analysis (if meaningful to do); log-rank test using BICR data
OS	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test data in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
	Supportive analysis: Kaplan-Meier (KM) plot of time to censoring for OS
PFS2	**Primary analysis**: log-rank test using investigator assessment of second progression
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TDT	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TFST	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TSST	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
ORR	**Primary analysis**: logistic regression using BICR data
	Sensitivity analysis: logistic regression using investigator data
Adjusted mean change from baseline in global HRQoL score	**Primary analysis**: mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit CCI [redacted]
Time to sustained clinically meaningful deterioration in HRQoL	**Primary analysis**: log-rank test **Supportive analysis**: attrition bias analysis (log-rank test using alternative censoring rules)

4.2.1 Multiplicity

In order to describe the nature of the benefits of olaparib maintenance treatment, PFS and OS will be tested at a 1-sided significance level of 2.5%.

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 be employed across the primary endpoint (PFS) and key secondary endpoint (OS).

A hierarchical testing strategy will be employed where PFS is tested first using the full test mass (full test mass = alpha 2.5% 1-sided) and the key secondary endpoint of OS will then be tested using a MTP with a recycling strategy (ie, the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 2).

The MTP is detailed below.

Figure 2 Multiple Testing Procedure

The OS will only be tested if the null hypothesis (of no difference) is rejected for PFS. One interim analysis for OS will be performed at the time of the final PFS analysis (approximately 87 PFS events) (DCO1). A final formal analysis of OS will be performed when approximately 106 death events have occurred (DCO2). CCI [redacted]

The Lan and DeMets approach that approximates the O'Brien & Fleming spending function will be employed to preserve the overall 1-sided type-I error rate of 2.5% (Lan and DeMets 1983). If the interim analysis for OS occurs at exactly 57% of the 106 OS events (60 OS events), statistical significance for OS will be declared if the null hypothesis for PFS is rejected and the observed p-value for OS is $p<0.003$, which equates to a HR ≤ 0.49. The significance level at the interim (DCO1) and the final formal analysis (DCO2) of OS will be determined based on the observed number of events at the time of the interim and the planned number of events at the final analyses. This will be documented in the minutes of the blind data review meeting prior to DB lock at DCO1. If the interim analysis for OS (DCO1) occurs at exactly 57% of OS events and the number of OS events at the final formal OS analysis is approximately 106 then the 1-sided significance level to be applied for the final formal OS analysis will be 2.4%. Statistical significance for OS would be declared if the observed p-value for OS is $p<0.024$, which equates to a HR ≤ 0.68. This plan was further revised as below.

DCO1 took place on 15th Jan 2019 at which time details of the alpha spending plan were updated. Based on the observed 71 OS events at the interim analysis, i.e. 67% of the 106 OS

events which are planned for the final analysis, statistical significance for OS was to be declared if the null hypothesis for progression-free survival (PFS) was rejected and the observed one-sided p-value for OS was $p<0.006$. Also, given that the number of OS events at the final analysis is planned as 106 the one-sided significance level to be applied for the final analysis will be $p<0.023$.

4.2.2 Primary variable - progression free survival

A summary of PFS will be prepared to present the number of patients with progression and no progression. Tabulation will detail the total number of progressions and no progressions, the number of patients with progression identified by RECIST (separately for TLs, NTLs, and new lesions) and death as well as details about non-progressed patients including the number of patients progression-free at time of DCO, lost to follow-up, withdrawn consent, and prematurely censored (RECIST or death) if they did not progress and if the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date. The summary will be presented by treatment group.

The PFS as defined in Section 3.2.1 will be analysed using a log-rank test for generation of the p-value and using the Breslow approach for handling ties in the following manner:

CCI [redacted]

By using the TEST-Statement within LIFETEST procedure the test statistics U and the covariance matrix will be averaged over the possible orderings of the tied failure times (SAS Lifetest 2008).

The HR and its CI will be estimated from the log-rank (U and V statistics) follows directly from the LIFETEST model as used above for calculation of p-values (Berry et al 1999 and Sellke et al 1983)

CCI [redacted]

CCI [redacted]

The log-rank test statistic, the HR (olaparib vs. placebo) together with its corresponding 95% CI and p-value will be presented (a HR less than 1 will favour olaparib).

The median and 95%-CI of PFS and the proportion of patients progression-free at 6 months, 12 months, 18 months, 24 months, 36 months and 48 months will be summarised and presented by treatment group. Further timepoints will be added as appropriate.

In addition, duration of follow-up will be summarised using median time from randomisation to date of censoring (date last known to be non-progressor) in censored (not progressed) patients only, presented by treatment group.

The following KM plots of PFS will be presented by treatment group. The KM plot will be prepared using LIFETEST procedure and selecting ODS graphics. The plot will identify censored patients using a different symbol and include patients at risk at specific time points:

- PFS
- PFS with censoring and event flags reversed

The assumption of proportionality will be assessed. The results of these model checks will not be presented in the CSR as part of the formal outputs; however, any deviation from this assumption will be considered in the interpretation. Note that in the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by producing plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation. The complementary log-log plot will be directly produced in SAS LIFETEST procedure using ODS graphics option PLOTS=(LLS) in the PROC-Statement. The graph will be assessed visually. Two parallel lines favour the proportionality assumption. To support the proportionality assessment a Cox proportional hazard's model will be constructed containing the interaction of treatment and the logarithm of PFS_time (treatment*log(PFS_time)). The p-value obtained from the Wald Chi-squared test for the time dependent covariate will be presented. The following SAS-code may be used:

A further analysis of PFS (using investigator assessed RECIST) was to be performed at the time of the final OS analyses, if requested by health authorities. A final decision was to be made at the BDRM for the final OS analysis. However, a decision was made after the analysis of PFS at DCO1 to carry out a full descriptive PFS analysis using investigator assessed RECIST at the time of the final OS analysis at DCO2. If patients are still on treatment at the time of DCO2 (i.e. investigator assessment of RECIST progression continues), then the analysis will be presented again at DCO3.

4.2.2.1 Progression-free survival sensitivity analyses

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 as for the primary analysis and the HR and associated 95% CI will be reported. A KM plot of PFS in this subset of patients will be presented by treatment group.

a) 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 their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

A by-patient listing will be produced similar to the PFS listing but including only patients who progressed but were censored for the primary analysis due to missing of two, or more, non-evaluable tumour assessments. The actual PFS times will be reported.

(b) Evaluation-time bias

A sensitivity analysis 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 log-rank test, as described for the primary analysis of PFS, will be repeated using the midpoint between the time of progression and the previous evaluable RECIST assessment to derive PFS time for patients with RECIST progression events. For patients whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules (Chen and Sun 2010). This approach will use the BICR RECIST assessments.

To support this analysis, the individual mean time difference between RECIST assessments (patient inter-assessment times) will be calculated and summarised using descriptive statistics.

(c) Ascertainment bias

The primary analysis of PFS (log-rank test) will be repeated using investigator assessed RECIST data. The HR and 95% CI will be presented. A KM plot of PFS based on the investigator assessed RECIST data will be presented by treatment group.

Ascertainment bias will be assessed through the use of two measures proposed by Amit (Amit, et al., 2011): the early discrepancy rate (EDR) and late discrepancy rate (LDR). The EDR represents the positive predictive value of Investigator assessment and quantifies the frequency with which the Investigators declare progression early relative to BICR within each arm as a proportion of the total number of Investigator assessed PD's. The LDR quantifies the frequency that the Investigators declare progression later than BICR as a proportion of the

total number of discrepancies within the arm. If the distribution of discrepancies is similar between the arms, then this suggests the absence of evaluation bias favouring a particular arm.

EDR and LDR are calculated as:

The EDR and LDR will be calculated for each treatment arm and the differential discordance around each measure will be defined as the rate on the experimental arm minus the rate on the control arm.

If there is an important discrepancy between the primary analysis using BICR assessments and this sensitivity analysis using investigator assessments, the proportion of patients with site but no central confirmation of progression will be summarised by treatment group and the primary analysis will be repeated for this subset of patients. The approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value, but only if an important discrepancy exists. Discrepancy between the primary analysis using BICR assessments and investigator assessments of progression will be discussed at the BDRM. The study team will decide whether the discrepancy between assessments is of importance and whether or not additional analyses are required.

A by-patient listing will be produced to present patients where at least one assessment differs between investigator and central reviews of RECIST progression.

(d) Deviation bias

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

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

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

The treatment status at progression by patients who have progressed / censored including the number of patients and percentage of on-treatment or discontinued will be tabulated. The number of days from treatment discontinuation to progression for patients who have discontinued treatment will be summarised descriptively. Data will be presented by treatment group.

Patients censored for progression at more than 14 weeks before the DCO ('censored > 14 weeks before DCO', 'censored <= 14 weeks before DCO') will be tabulated and presented by treatment group.

A by-patient listing will be produced including patients with an important deviation only.

4.2.2.2 Progression-free survival subgroup analyses

Subgroup analyses will be conducted comparing PFS between treatments. The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. KM plots will be produced for each subgroup according to treatment group.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 5 events in a subgroup in at least one treatment group), the results of the subgroup analysis (HR and 95% CI) will not be presented, however, all patients with non-missing subgroup data will be included in the Cox model used for the analysis (see below).

The following subgroups will be analysed for PFS:

- Previous chemotherapy (FOLFORINOX variants, gemcitabine/cisplatin, other); Reference=FOLFORINOX variants
- Type of previous chemotherapy (doublets, triplets, other); Reference=doublets
- Time on first-line treatment till randomisation (≤ 6 months vs > 6 months); Reference=≤6 months
- Best response on first-line treatment (SD vs PR/CR); Reference=SD

These will be determined from the "Metastatic Pancreas Cancer Therapy" (CAPRX2) module of the eCRF at screening by medical review.

- Presence or absence of biliary stent; Reference=Presence of biliary stent

This will be determined from the "Surgical History" (HISS) module of the eCRF at screening by medical review.

- Measurable versus non measurable disease / NED at baseline; Reference=non measurable disease / NED at baseline

This will be determined programmatically from the baseline BICR results.

- gBRCA mutation type (BRCA1, BRCA2, BRCA1/2 (both), non-gBRCAm); Reference=BRCA1

This will be determined programmatically from the Myriad central laboratory test results.

- Age at randomisation (>= 65 vs < 65); Reference=< 65
- Race (White vs Other); Reference=White
- Sex (Male vs Female); Reference=Male

These will be determined programmatically from the "Demography" (DEM) module of the eCRF at screening.

- ECOG performance status (normal activity, restricted activity); Reference=normal activity

The data will be determined from the "ECOG Performance Status" (PSTAT) module of the eCRF at screening.

Other baseline variables may also be assessed if there is clinical justification. A final decision will be made at the BDRM.

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 group, factor (subgroup) and treatment-by-factor interaction term. All patients with non-missing subgroup category data will be included in the Cox model. Statistics produced by the Cox model, i.e. HR/CI will only be displayed in subgroup categories with a sufficient number of events available (at least 5 events in both treatment groups), otherwise, only the total number of patients and events will be displayed. Reference cell coding will be used introduced by the PARAM=REFERENCE option in the CLASS-Statement. Individual reference levels will be defined using the REF= option within the CLASS-Statement for each subgroup. The treatment effect HRs for each treatment comparison along with their CIs will be obtained for each level of the subgroup from this single model. Analysis will be carried out using PHREG procedure in SAS in the following manner:

CCI [redacted]

The HRs and 95% CIs will be presented in an overview table as well as on a forest plot including the HR and 95% CI from the overall population (using the HR and 95% CIs from the primary analysis).

CCI

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 two-sided 10% significance level. If a covariate does not have more than 5 events per level in both treatment groups (of the covariate) it will be included as a covariate in the model but the covariate-by-treatment interaction term will be omitted. 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.

For all subgroups, median PFS time and 95% confidence intervals calculated using the Kaplan Meier method will be summarised by treatment group.

In order to assess the impact of imbalances between treatment groups in terms of the key prognostic variables best response on first-line treatment (CR/PR, SD), time on first-line treatment ($\leq$ 6 months, > 6 months), age group (< 65 years, $\geq$ 65 years), ECOG status at baseline (0 normal activity, 1 restricted activity), and previous chemotherapy (FOLFORINOX variants, Gemcitabine/Cisplatin, Other), a Cox proportional hazards model including only treatment group will be compared with a Cox proportional hazards model including treatment group and key prognostic variables. The hazard ratio for treatment group and 95% confidence intervals will be presented.

A by-patient listing will be produced for presenting individual PFS data.

4.2.3 Overall Survival

A summary of survival status at the time of analysis will be produced. This will summarise the number of patients who have died, who are still in survival follow-up, who are lost to follow-up or who have withdrawn consent. Results will be presented by treatment group.

Interim OS data as defined in Section 3.2.2 will be analysed at the time of the final analysis for PFS (DCO1) and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [> 5 deaths in both treatment groups], if not descriptive summaries only will be provided). A final formal analysis of OS will be performed when approximately 106 deaths have occurred (DCO2). CCI [redacted]

Median OS time and corresponding 95% CI will be summarised including the number of deaths, and survival at month 6, 12, 18, 24, 36 and 48. Further timepoints will be added as appropriate. Results will be presented by treatment group.

The analysis will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the central Myriad test.

The sensitivity analyses outlined for PFS in Section 4.2.2 will not be repeated for OS with the exception of a KM plot. Two KM plots will be produced. The first KM plot will show time to censoring of OS and the second KM plot will show time to censoring where the censoring indicator is reversed (median time to follow-up where events will be censored and previously censored patients will be treated as events). The first KM plot will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the central Myriad test.

OS data will be listed in a by-patient listing.

Similar subgroup analyses (except the interaction test) will be conducted comparing OS between treatments as detailed for PFS in Section 4.2.2.2, using the same methodology and model. KM plots will be produced for each subgroup according to treatment group. If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 5 events in a subgroup in at least one treatment group), the relationship between that subgroup and OS will not be formally analysed. In this case, only descriptive summaries (number of patients, number (%) of events, and KM plots) will be provided.

4.2.4 Time from randomisation to second progression

The status of PFS2 as defined in Section 3.2.3 will be summarised by the number and percentage of patients experiencing a PFS2 event and the type of progression (objective progression by RECIST, symptomatic progression or death). Results will be presented by treatment group.

The analysis of PFS2 will use the same methodology and model as the primary analysis of PFS. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

A KM plot of PFS2 will be provided by treatment group. A KM plot of the time to censoring where the censoring indicator of the PFS2 analysis is reversed will be produced (called median time to follow-up where events will be censored and previously censored patients will be treated as events).

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

The median and 95%-CI of PFS2 and the proportion of patients with no second progression at 6, 12, 18, 24, 36 and 48 months will be summarised and presented by treatment group. Further timepoints will be added as appropriate.

Days between second progression and last assessment prior to second progression will be summarised descriptively by treatment group.

A by-patient listing will be produced including details about time of second progression.

4.2.5 Time to first subsequent therapy or death

The TFST will be analysed using the same methodology and model as the primary analysis of PFS. The HRs for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group, together with status, median TFST and 95% CI for each treatment group.

As a key sensitivity, the analyses of TFST will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. In this subset of patients, median TFST and 95% CI will be reported by treatment group. In addition, a KM plot of TFST will be presented by treatment group.

The time between progression and starting subsequent cancer therapy will be summarised.

In addition, best overall RECIST response to first subsequent cancer therapy by treatment group will be provided.

Individual TFST will be presented in a by-patient listing.

4.2.6 Time to second subsequent therapy or death

The TSST will be analysed using the same methodology and model as the primary analysis of PFS. The HRs for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group, together with status, median TSST and 95% CI for each treatment group.

As a key sensitivity, the analyses of TSST will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. In this subset of patients, median TSST and 95% CI will be reported by treatment group. In addition, a KM plot of TSST will be presented by treatment group.

In addition, best overall RECIST response to second subsequent cancer therapy by treatment group will be provided.

Individual TSST will be presented in a by-patient listing.

4.2.7 Time to study treatment discontinuation or death

The TDT will be analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group, together with status, median TDT and 95% CI for each treatment group.

As sensitivity, the analyses of TDT will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. In this subset of patients, median TDT and 95% CI will be reported by treatment group. In addition, a KM plot of TDT will be presented by treatment group.

Individual TDT will be presented in a by-patient listing.

4.2.8 Best objective response and objective response rate

For each treatment group, BoR as defined in Section 3.2.7 will be summarised by n (%) for each category (CR, PR, SD, NED, PD, NE) based on the BICR data. This will also be summarised based on the investigator-assessed data. No formal statistical analyses are planned.

ORR as defined in Section 3.2.8 will be summarised descriptively, ie, number of patients (%) by treatment group, and using logistic regression, based on the BICR data, in patients in the FAS (ITT population) with measurable disease at baseline defined according to BICR. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 95% CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). If there are not enough responses for a meaningful analysis using logistic regression, then a Fisher's exact test will be presented.

ORR will also be summarised based on the investigator-assessed data in the FAS (ITT population) with measurable disease at baseline defined according to investigator assessment using the same methods as for the BICR data. Any patients who experienced CR or PR which was first observed whilst receiving subsequent therapy after discontinuation of olaparib will be identified and not treated as responders per definition of BoR in Section 3.2.7.

In addition, the duration and time to onset of objective response in patients with objective response (by BICR and by investigator assessment) will be summarised by treatment group.

95% confidence intervals for median duration and median time to onset of objective response in patients with objective response (by BICR and by investigator assessment) calculated using the Kaplan Meier method will be presented by treatment group.

BoR will be presented in a by-patient listing. In addition, a listing will be prepared including objective responders (confirmed CR or PR) only.

4.2.9 Disease control rate

The DCR as defined in Section 3.2.9 will be summarised (ie, n, %) by treatment group. The DCR will be presented based on the BICR data and also the investigator recorded data.

4.2.10 Target lesion summary and other efficacy

Target lesion size, and percentage change from baseline will be summarised by treatment group and time point using descriptive statistics. Lesion data according to BICR and also by investigator assessment will be listed in by-patient listings.

Subsequent cancer therapy relative to progression will be summarised using frequency counts and percentages. The tabulation will detail any patients receiving any further therapy for cancer by time of therapy ('After progression', 'Before progression', 'No progression'). Tabulation will include the number of patients where no subsequent cancer therapy was recorded as well. Data will be presented by treatment group.

4.2.11 Patient reported outcomes

The analysis population for PRO data will be the PRO analysis set as defined in Section 2.1. Derivations and rules for transformation of PRO data are defined in Section 3.3.

Impact of olaparib on HRQoL

The impact of olaparib on HRQoL will be assessed through an analysis of the global health status / QoL gathered from items 29 and 30 of EORTC QLQ-C30.

Descriptive statistics including change from baseline score will be produced by time point for the EORTC QLQ-C30 global health status / QoL score. Results will be presented by treatment group. Arithmetic mean (± standard deviation) plots of scores versus time point will be produced in linear scale.

Adjusted mean change from baseline in global QoL score will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and will be presented by treatment group. Only visits with at least 25% of non-missing values in both treatment arms (calculated separately by treatment arm) are included in the model. The study treatment discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include randomised treatment group, visit and treatment by visit interaction as explanatory variables and the baseline QoL score as a covariate along with a baseline QoL score by visit

interaction. Treatment, visit and treatment by visit interaction will be fixed effects in the model. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The following provides sample code for implementing the MMRM analysis:

where TRT is the randomised treatment group, VISIT is the visit, CFB is the change from baseline in the global QoL score, and BASE is the baseline global QoL score.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, and autoregressive.

The adjusted mean change from baseline estimates (obtained from LSMEANS-Statement as the calculated least square means adjusted for the random component of the model), standard error, and corresponding 95% CIs will be presented by visit for each treatment group. Corresponding plots over time will be presented.

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

A by-patient listing will be produced for the EORTC QLQ-C30 global QoL scale presenting raw scores (overall health and overall quality of life items) and the transformed score by time point.

As a supportive analysis, EORTC QLQ-C30 global QoL score improvement rate will be analysed using a logistic regression model. The model will include a binary variable as response (improvement=1; no improvement=0) and treatment group as an explanatory

variable in the MODEL-Statement together with the option CLPARM=PL to compute profile likelihood CIs and p-values. Explanatory variables will be introduced using a reference cell coding (option PARAM=REFERENCE) while the option REF= will be used to identify the reference. The following provides sample SAS code for implementing the analysis:

If the overall improvement rate is < 5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed). If the overall response rate is low (< 20%) a Fisher's exact test (for an example SAS code see below) will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

In addition, a summary table of EORTC QLQ-C30 global QoL score best overall QoL response will be provided (improvement, deterioration, no change).

Compliance

The EORTC QLQ-C30 and CCI compliance (overall compliance and by visit compliance, separately for each form) will be summarised and presented by treatment group.

4.2.12 Exploratory analyses

- CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]


CCI


CCI


CCI

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

4.2.13 Safety

Safety data will be summarised and listed only. No formal statistical analyses will be performed on the safety data. All safety data will be summarised by actual treatment group (olaparib or placebo). However, some listings such as AEs listings will display the actual dose the patient received at onset of an AE.

Adverse events

All AEs, both in terms of Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and Common Toxicity Criteria for Adverse Events (CTCAE) grade, will be listed and summarised descriptively by count (n) and percentage (%) for each treatment group. MedDRA dictionary will be used for coding. Any AE occurring before olaparib/placebo treatment (ie, before Study Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'.

The summary tables will include all AEs that occurred after the start of treatment up until the end of the 30 day follow-up period. The 30 day follow-up period will be defined as 30 days following discontinuation of olaparib/placebo treatment. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment will also be included in the AE listings, but not in the summary tables.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of severity and relationship to study drug. Frequencies

and percentages of patients reporting each PT will be presented (ie, multiple events per patient will not be accounted for apart from on the episode level summaries).

Summary information (the number and percent of patients by actual treatment) will be tabulated for:

- All AEs
- All AEs causally related to study medication
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to study medication
- AEs leading to dose modification of olaparib/placebo
- AEs leading to dose interruption of olaparib/placebo
- AEs leading to dose reduction of olaparib/placebo
- AEs with outcome of death
- AEs with outcome of death causally related to study medication
- All SAEs
- All SAEs causally related to study medication
- DAEs
- AEs leading to discontinuation of olaparib/placebo, causally related to study medication

An overall summary of the number and percentage of patients in each category will be presented.

In addition, a truncated AE table of most common AEs, showing all events that occur in at least 5% of patients overall will be summarised by PT, by decreasing frequency. This cut-off may be modified after review of the data. Also, a truncated AE table of most common non-serious AEs, showing events that occur in at least 5% of patients on the PT level in at least one treatment group will be summarised by SOC and PT, by decreasing frequency.

Each AE event rate (per 1000 patient years) will be summarised by system organ class (SOC) and also by PT within each SOC. The event rate will be calculated as the number of patients with an AE in that SOC or with that PT divided by the sum of the duration of therapy (for

patients without such an event) and the time to the AE (for patients with such an event) in each group multiplied by 1000. The denominator defines the time at risk for an event with:

- Duration of therapy (days) calculated as:
  MINIMUM([date of last dose + 30-day safety follow-up period], OS date, DCO) – date of first dose + 1

- Time to the AE (days) calculated as date of first occurrence of the AE – date of first dose + 1 (in days), imputed AE start dates can be used in case of missing start dates.

The formula for calculating the event rate for a specific PT is as follows:

CCI [redacted]

CCI [redacted]

CCI [redacted]

AEs will be assigned CTCAE grades (National Cancer Institute CTCAE version 4.0) and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, SOC, PT and actual treatment group. Tabulation will be repeated to present AEs with a CTCAE grade 3 or higher and separately those AEs, causally related to study treatment by SOC and PT. Fluctuations observed in CTCAE grades within the same PTs during study will be listed.

Tabulation of AEs causally related to study treatment will be summarised by SOC and PT and presented by treatment group.

Summaries of the number and percentage of patients with AEs leading to dose modification of olaparib/placebo and also separately with AEs leading to dose reductions and drug interruptions of olaparib/placebo will be presented by PT and treatment group.

A summary table will be prepared presenting AEs which started prior to first dose or > 30 days following date of last dose by SOC and PT. Data will be presented by treatment group.

Death

A summary of all AEs resulting in deaths will be provided with number and percentage of patients by actual treatment group, categorised as:

- Related to disease under investigation
- AE outcome=death
- Both related to disease under investigation and with AE outcome=death
- AE with outcome=death ≥30 days after last treatment dose
- Deaths ≥ 30 days after last treatment dose, unrelated to AE or disease under investigation
- Patients with unknown reason for death

In addition, AEs with outcome of death will be summarised. The following summary tables will be prepared and presented by treatment group:

- By SOC and PT
- Causally related to study treatment by SOC and PT
- Death will be listed as part of TLFs for part 11 of the CSR

Serious AEs

The following SAE summaries and listings will be prepared. Summaries will be presented by treatment group:

- By SOC and PT
- Causally related to study treatment by SOC and PT
- Listing of key information

Discontinuation

AEs leading to discontinuation of study treatment will be summarised by SOC and PT. In addition, AEs leading to discontinuation of study treatment, causally related to study treatment will be summarised by SOC and PT. Details of AEs leading to discontinuation will be presented in a by-patient table.

Listings

By-patient listings will be produced as following:

- A by-patient listing of AEs, including flags for AESIs
- A by-patient listing of AEs causally related to olaparib
- A by-patient listing of SAEs
- A by-patient listing of AEs with CTCAE grade 3 or higher (separately for causally related to olaparib)
- A by-patient listing of AEs leading to dose reduction or dose interruption
- A by-patient listing of AEs presenting any events that occur prior to dosing or starting more than 30 days after discontinuing therapy

Laboratory assessments

Laboratory data is collected by local laboratories. Results will be converted to standard units for reporting purposes. Reference ranges from the local laboratories are collected in the CRF and will be used to determine reference range indicators (low, normal, high). If the same parameter is found as measured in serum and in plasma, then the summaries will not distinguish between them (e.g. values from plasma Albumin and serum Albumin will be summarised under Albumin). If the same parameter is found as measured in serum and in plasma within the same patient, which would be a rare case, then the change from baseline will only be calculated for those post-baseline values using the same source, i.e. only within plasma or serum. If one patient has multiple toxicity grades, because they are derived separately from serum and plasma, then the maximum value of the two will be considered.

For all continuous laboratory assessments, absolute value, change from baseline and percentage change from baseline will be summarised using descriptive statistics at each scheduled assessment time by actual treatment group.

Shift tables for laboratory values (excluding electrolytes) from baseline to worst value on-treatment categorized using the common toxicity criteria (CTC) grading based on local reference ranges will be produced. On-treatment is defined as data collected up until the last dose of olaparib/placebo. For parameters with no CTC grading, shift tables from baseline to worst value on-treatment will be provided using normal ranges for categorization. Shift tables for urinalysis values from baseline to worst grade on-treatment will also be provided.

Box-plots of absolute values for continuous laboratory assessments will be presented, with AZ project defined reference ranges indicated.

A scatter plot of alanine aminotransferase (ALT) versus total bilirubin, both expressed as multiples of the upper limit of normal (ULN), will be produced with reference lines at 3×ULN

for ALT, and 2×ULN for total bilirubin. The scatter plot will be repeated for aspartate aminotransferase (AST) versus total bilirubin with reference lines at 3×ULN for AST, and 2×ULN for total bilirubin. In each plot, total bilirubin will be in the vertical axis.

Liver biochemistry test results over time for patients who show elevated ALT or aspartate aminotransferase (AST) (≥3xULN) and elevated total bilirubin (≥ 2xULN) (elevated results do not need to be present at the same visit), or a total bilirubin of ≥ 5xULN will be tabulated and plotted.

All laboratory summaries and listings will be presented by actual treatment group.

By-patient listings of laboratory assessments will be provided showing at least: laboratory parameters, actual time point, measurements/results, CTC grade (if available), and the change from baseline value (for continuous data) (if appropriate). In addition, a flag will indicate if the value was out of normal range, if appropriate:

- Laboratory reference ranges
- Haematology
- Serum chemistry
- Urinalysis
- Individual patient data with elevated ALT or AST plus total bilirubin
- Pregnancy report data

Electrocardiograms

If available, overall evaluation of ECG will be summarised by visit as normal, abnormal or borderline.

All ECG data will be listed by actual treatment group.

Vital signs

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, body temperature and weight) will be summarised by time point in terms of absolute values, changes from baseline and percentage changes from baseline at each scheduled measurement by actual treatment group. A shift table comparing baseline to maximum value on treatment will be summarised for SBP, DBP and pulse rate by actual treatment group, using the following normal ranges: SBP = 100 - 160 mmHg; DBP = 60 - 95 mmHg; pulse rate = 55 - 95 bpm.

Box plots for absolute values in SBP, DBP, pulse rate, body temperature, and weight will be presented.

Vital signs data will be listed.

Other

- Any concomitant procedures patients experiencing during the study will be listed in a by-patient listing
- Patients experiencing a Hy's Law incident will be tabulated and details will be included in by-patient listings. Hy's Law incidents are those cases where a patient shows an AST or ALT ≥ 3xULN or total bilirubin ≥ 2xULN. Please refer to Appendix D of the CSP for further instructions.

4.2.14 Demographic and baseline characteristics data

The following will be listed and summarised by randomised treatment group using the FAS analysis set:

- Listing of patients receiving the various batches of investigational product
- Listing of randomisation scheme and codes
- Patient disposition (including screening failures and reason for screening failure, reasons for patients prematurely withdrawing from study, patients with a mis-randomisation [treatment dispensing error] and patients who were unblinded, discontinuation of study treatment), to be repeated also for Myriad confirmed gBRCAm subgroup
- Important deviations including patients with a dispensing error and the number of patients received at least one dose of the wrong study treatment (see Section 2.2)
- Inclusion and exclusion from analysis populations; exclusions from full, safety and PRO analysis set
- Demographics (age in years, age group in years (<35, 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, >= 85), sex, race, and ethnicity), to be repeated also for Myriad confirmed gBRCAm subgroup
- Patient characteristics (baseline height [cm], baseline weight [kg], baseline body mass index [BMI] [kg/m²], weight group [< 70 kg, 70 kg to 90 kg, > 90 kg], BMI group [Normal (< 25), Overweight (25 - 30), Obesity (> 30)]), to be repeated also for Myriad confirmed gBRCAm subgroup
- Patient recruitment by country and centre
- All (allowed) concomitant medications on entry and during the study

- Disallowed concomitant medications on entry and during the study (defined at the BDRM)
- Disease characteristics at baseline including BRCA testing (local and Myriad, including a comparison of local versus Myriad results) and pathology at time of diagnosis, to be repeated also for Myriad confirmed gBRCAm subgroup
- Extent of disease
- Disease related medical history per CRF
- Relevant surgical history per CRF
- Pregnancy at baseline (entry)
- Physical examination at baseline (entry)
- Archival paraffin embedded tumour tissue or cytology sample
- Blood transfusion
- Previous radiotherapy and radiotherapy post randomisation (including current and subsequent radiotherapy)
- Post-discontinuation cancer therapy, defined as any therapy received after discontinuation of study treatment
- Patients who subsequently received a PARP inhibitor or entered a PARP inhibitor trial will be summarised and listed by treatment group according to line of subsequent therapy, ie, immediately after olaparib or as a later line, in addition to patients in the placebo arm who subsequently received olaparib
- Previous disease-related treatment modalities (metastatic pancreas cancer therapy)
- Previous non-disease-related treatment modalities
- Initial vomiting and nausea data will be listed only

WHO drug dictionary will be used for concomitant medication coding.

Patients who were unblinded (a) prior to disease progression and (b) prior to or on the day of treatment discontinuation will be listed.

Additional analysis for the prevalence of the gBRCA mutation in all screened patients will be done. The percentage of screened patients having the gBRCA mutation, as confirmed by Myriad, and with previously unknown gBRCA status will be calculated.

4.2.15 Treatment exposure

The following summaries related to study treatment will be produced for the Safety Analysis Set by actual treatment group:

- Total exposure of olaparib/placebo
- Actual exposure of olaparib/placebo
- Number of days on 300 mg olaparib/placebo bid = actual exposure for the dose assigned
- Reasons for dose reductions, dose interruptions, and dose modifications of olaparib/placebo. Dose reductions and dose interruptions will be based on investigator initiated dosing decisions. Dose interruptions/reductions due to "Subject Forgot to Take Dose" will be omitted from these summaries
- Number of dose reductions, dose interruptions, and dose modifications of olaparib/placebo that last for a period of three days or more
- PID and RDI of olaparib/placebo (entire intended treatment period)
- Mean total daily dose per time period

For patients on study treatment at the time of the PFS analysis, the DCO date will be used to calculate exposure.

Treatment compliance will be summarised by treatment group using descriptive statistics. Tabulation will be presented by actual treatment group.

All treatment information data will be listed:

- Study treatment compliance
- Administration of investigational product
- Duration of exposure
- Overdose report

5. INTERIM ANALYSES

A single interim PFS analysis for futility will be performed when 50% of the PFS events required for the final PFS analysis have occurred (approximately 44 PFS events) based on BICR. The interim analysis will be performed by an Independent Data Management

Committee (IDMC) and full details will be provided in the IDMC charter. Safety data including death rates will also be reviewed at this time.

The futility assessment will be based on the probability of eventually showing statistical significance for the primary endpoint when the number of PFS events required for final PFS analysis (n=87) is reached (Lachin 2005). The determination of this probability will be conditional on the observed data at the time of the interim analysis and on the assumed hazard ratio for the alternative hypothesis (PFS HR=0.54). If the probability is less than 20%, the IDMC will consider the option of declaring futility.

The exact figure used for the futility boundary will be calculated by AstraZeneca and sent to the IDMC at the time of the interim analysis, based on the number of events which have occurred at that time. As an example, if exactly 50% of the PFS events required for the primary PFS analysis have occurred at the time of the interim analysis (44 events), then the HR that corresponds to 20% conditional power for the interim analysis will be 1.02. Therefore, if the observed HR for PFS at the interim is more than 1.02, the IDMC will consider the option of declaring futility.

An interim analysis of OS will be performed at the time of the final analyses of PFS (~87 PFS events). A final formal analysis of OS will be performed when approximately 106 OS events have occurred.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The definition of the Patient Reported Outcome analysis set has been changed in order to add clarification. The previous definition required a patient to have "evaluable baseline EORTC QLQ-C30 CCI [redacted]". Now it has been decided to specify this in more detail by saying that it must be possible to determine at least one sub-scale baseline score from at least one of the two forms.

Analysis of time to sustained clinically meaningful deterioration in HRQoL has been added.

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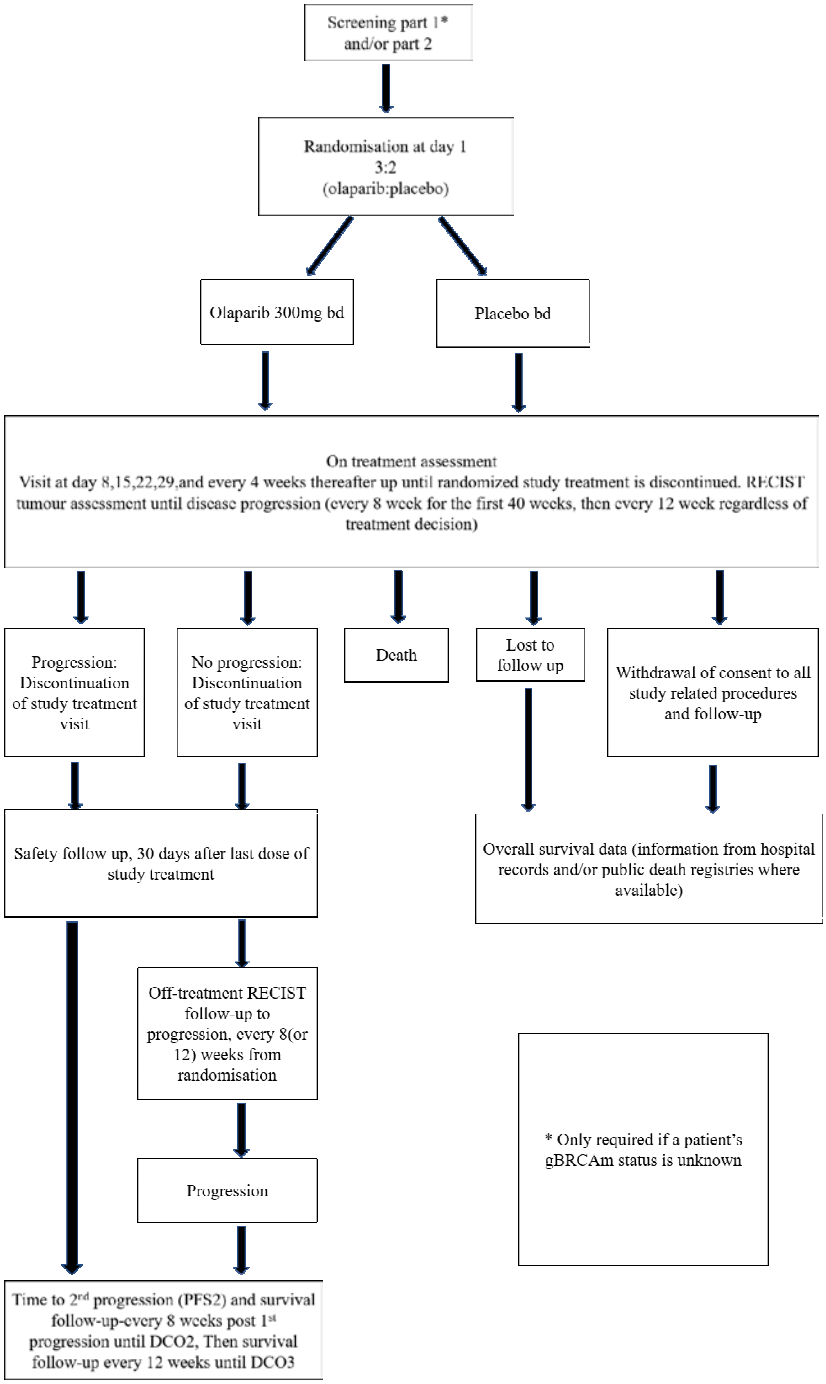
APPENDIX

Appendix A: Study Flow Chart

Figure 3 Study Flow Chart



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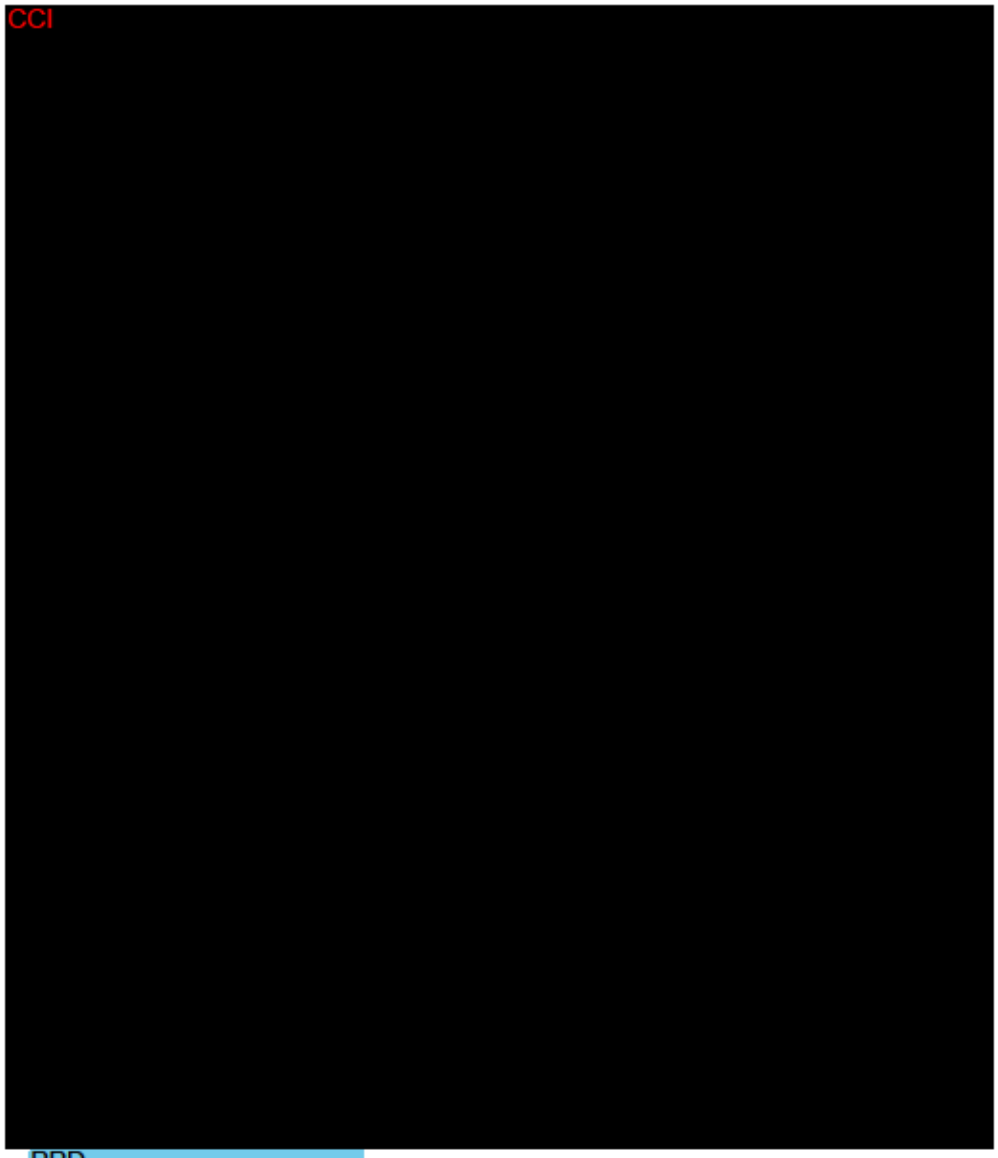

PPD

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Appendix C: Study Schedule

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up [v]**	
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			**Until DCO2**	**Between DCO2 & DCO3**
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**	**Every 12 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**
Informed consent	X	X										
Randomisation f			X f									
Demographics	X	X										
Medical and surgical history, including blood transfusions a		X										
Prior cancer therapies including radiotherapy		X										
Inclusion/exclusion criteria	X (all * criteria) b	X										

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	Screen PART 2 (All patients)	Treatment Duration						Study treatment discontinued	30-Day follow-up	Survival Follow-up [v]	
Cycle/ Visit			1 (28 days)				2	3+ (every 28 days)			Until DCO2	Between DCO2 & DCO3
Day		-28 to 0	1	8	15	22	29	57+			Every 8 weeks	Every 12 weeks
Visit window				±3d	±3d	±3d	±3d	±3d	±7d	±7d	±7d	±7d
Blood samples for gBRCA status c	X		X d									
Archival paraffin embedded tumour tissue or cytology sample e	X	X										
Concomitant medications		X	X	X	X	X	X	X	X	X		
CCI		[redacted]					[redacted]	[redacted]	[redacted]	[redacted]		
Vital signs		X g	X g				X	X	X	X		
Physical examination h		X					X	X	X	X		
ECG i		X	As clinically indicated									

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up [v]**	
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			**Until DCO2**	**Between DCO2 & DCO3**
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**	**Every 12 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**
Tumour assessment (modified RECIST) j		X (no more than 28 days before start of treatment) j	Every 8 weeks (± 1 week) until week 40 then every 12 weeks (±1 week), relative to the date of randomisation j						If patient does not have disease progression at the time of treatment discontinuation tumour assessments should be continued per the CSP schedule k			
Haematology/clinical chemistry		X	X l				X	X	X	X		

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	Screen PART 2 (All patients)	Treatment Duration						Study treatment discontinued	30-Day follow-up	Survival Follow-up [v]	
Cycle/ Visit			1 (28 days)				2	3+ (every 28 days)			Until DCO2	Between DCO2 & DCO3
Day		-28 to 0	1	8	15	22	29	57+			Every 8 weeks	Every 12 weeks
Visit window				±3d	±3d	±3d	±3d	±3d	±7d	±7d	±7d	±7d
Coagulation m		X	As clinically indicated									
Urinalysis n		X	As clinically indicated									
Pregnancy test o	X	X	X									
Biomarker blood sample p			X					X (only at progression)				
EORTC QLQ-C30 q		X					X	X	X	X		
CCI												

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up [v]**	
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			**Until DCO2**	**Between DCO2 & DCO3**
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**	**Every 12 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**
Adverse event r	SAEs related to study procedures only	X	X	X	X	X	X	X	X	X		
Study drug dispensing s			X				X	X				
Study drug return							X	X	X	X		
Subsequent cancer treatment t										X	X	X
Second progression assessment u											X u	
Survival status v											X v	X

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

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

c Patients must have a known deleterious or suspected deleterious *BRCA* mutation to be randomised to the study; this can be either a local lab result or a Myriad test result. Patients for whom their *gBRCA* status is already known, should be consented to the study within 28 days prior to day 1 of study treatment. Any patient who consents to study related Myriad CCI , must also have a blood sample taken at the same time for the purpose of developing and validating a CCI

d Samples to be taken on Day 1 only for patients with known *gBRCA* mutation who have not completed PART 1 Screening. The screening *gBRCA* test and method performed at site must be recorded in the eCRF.

e Collection of an archival tumour sample is requested, if available, for all patients. These samples will be collected from the site pathologist during the screening Part 1 for patients with unknown *gBRCA* status and screening Part 2 for patients with known local *gBRCA* test.

f Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of the last treatment) and treatment started as soon as possible but no less than 4 and no more than 8 weeks of the last chemotherapy dose. At the time of starting protocol treatment, all previous chemotherapy treatment should be discontinued.

g Vital signs performed on day 1 before every cycle. If vital signs assessed within 7 days before starting study treatment, it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

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

i ECG assessments to be completed within 14 days before starting treatment if patient is eligible following completion of all other PART 2 assessments. After screening, ECGs will only be required if clinically indicated.

j Baseline RECIST assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed no more than 28 days before start of study treatment and as close as possible to randomisation. A randomisation must be within 6 weeks of last chemotherapy. Treatment should be started as soon as possible but no less than 4 weeks and no more than 8 weeks after their last dose of chemotherapy. RECIST follow-up assessments will be performed every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) irrespective of treatment decisions. Follow-up assessment will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until disease progression assessed using modified RECIST criteria. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Prior to primary analysis for PFS, all scans will be submitted for independent review. If progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled visit.

k For patients who discontinue study treatment prior to disease progression, RECIST assessments will continue until objective disease progression (every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) relative to date of randomisation, until objective disease progression as defined by modified RECIST.).

l Haematology and clinical chemistry should be performed at screening and day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly.

m Coagulation test should be performed at screening and if clinically indicated.

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

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

p Mandatory blood samples for biomarker analysis to be taken prior to dosing on Cycle 1 Day 1 and at disease progression.

q CCI [redacted]

r Adverse events must be captured from time of consent. Only SAE's related to blood sampling for the Myriad gBRCA test will be collected at this visit.

s Continuous Olaparib 300mg/ placebo twice daily dosing. Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.

t All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them need to be recorded until end of study period (DCO3), plus the date of progression post discontinuation of study treatment, need to be recorded.

u Second disease progression (PFS2) assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. Subsequent therapy will be collected for these patients from the time of treatment discontinuation until end of study period (DCO3).

v The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients 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 (see Section 3.10 of the CSP). In addition to their regular 8 weekly contact, patients will be contacted in the 7 days following a specified date (data cut-off date) for each survival analysis until final formal analysis of OS (DCO1 & DCO2). Post DCO2 period, patients will be contacted every 12 weeks for survival status and in the 7 days following the specified date [redacted] CCI

Appendix D: Visualisation of Censoring Rule for Progression Free Survival