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

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

ClinicalTrials.gov Identifier: NCT03286842

Original SAP: 21 Nov 2017 (Version 1.0)
Amendment 1: 06 Aug 2018 (Version 2.0)
Amendment 2: 14 Sep 2021 (Version 3.0)

AstraZeneca

Statistical Analysis Plan

Study Code	D0816C00018
Edition Number	3.0
Date	14-Sep-2021

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

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

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

Study Statistician

_____ _____

Date

PPD (Parexel)

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

Global Product Statistician

PPD (AstraZeneca) Date

TABLE OF CONTENTS PAGE

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American joint committee on cancer
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BRCA1, BRCA2, BRCA1/2	Breast cancer susceptibility genes
CI	Confidence interval
cm	Centimetres
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CRR	Clinical response rate
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse event
DCO	Data cut-off
DCR	Disease control rate
DoCR	Duration of clinical response
DoR	Duration of response
d.p.	Decimal place
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ER	Estrogen receptor

Abbreviation or special term	Explanation
FAS	Full analysis set
gBRCAm	Germline BRCA1/2 mutation
HER2-ve	Human epidermal growth factor receptor 2 negative
INR	International normalised ratio
KM	Kaplan-Meier
LD	Longest diameter
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimetre
NCI	National Cancer Institute
NA	Not applicable
NE	Not evaluable
NTL	Non-target lesions
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PFS2	Time to second progression or death
PID	Percentage intended dose
PR	Partial response
PR	Progesterone receptor
PT	Preferred term
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
sBRCAm	Somatic BRCA1/2 mutation
SD	Stable disease
SOC	System organ class
TDT	Time to study treatment discontinuation or death

Abbreviation or special term	Explanation
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent treatment or death
TL	Target lesions
ULN	Upper limit of normal range
TSST	Time to second subsequent treatment or death
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	21-Nov-2017	Initial approved SAP.	N/A	N/A
Exploratory objectives. Consistency with TFL shells.	06-Aug-2018	CCI [redacted] Deleted reference to disclosure tables as per client request. Minor corrections.	Yes	See description
Protocol deviations.	14-Sep-2021	Updated section 2.2 protocol deviations due to regulatory intent of the study.	Yes	See description
Efficacy endpoints.		Added new subgroups for efficacy analyses. Additional analyses requested for the interim analysis and to support publications. Updates and additions to ensure the SAP is as required for regulatory intent. Consider protocol version 4 with changed criterion for final analysis. Updated SAP to reflect the TFL shells. Updated abbreviation table. Added new text around survival sweep.		
COVID-19 data.		Added new text for the handling and presentation of COVID-19 data.		
Subgroup analyses.		Added in text around repeating PFS subgroup analyses for subset of ER and/or PR positive patients.		
Aligning primary endpoint missing dates and censoring rules with AZ standards.		Updated imputation rules for missing dates and event censoring.		
Secondary endpoints.		Updated CRR/ORR section so that the denominator includes the full FAS population.	Yes	See description

1. STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the clinical study protocol (CSP). This SAP is based on version 4.0 of the CSP.

1.1 Study objectives

Primary Objective:

To evaluate the clinical effectiveness of olaparib treatment in human epidermal growth factor receptor 2 negative (HER2-ve) metastatic breast cancer patients in a real-world setting through assessment of progression-free survival (PFS) in germline BRCA mutated (gBRCAm) patients.

Secondary Objectives:

- To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of overall survival (OS) in gBRCAm patients.
- To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of time to use of subsequent therapies, second progression, and study treatment discontinuation in gBRCAm patients.
- To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of clinical response rate (CRR) and duration of clinical response (DoCR) in gBRCAm patients.

Safety Objective:

To evaluate the safety and tolerability of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-word setting.

Exploratory Objectives:

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

- CCI [redacted]
- CCI [redacted]

1.2 Study design

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

Olaparib will be administered to all patients in this single-arm study.

1.3 Number of patients

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

- Firstly, when approximately 160 gBRCAm patients have had a PFS event
- Secondly, when approximately 130 gBRCAm patients have died, at which point the PFS analysis will be updated

The sBRCAm patient cohort will also be assessed at these time points.

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

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

It is expected that approximately 20 sBRCAm patients will be enrolled.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Data from the germline and somatic BRCA mutated patient cohorts will be presented separately and combined, unless otherwise stated.

Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive at least one dose of olaparib. The FAS will be used for all efficacy and safety analyses.

All Patients Set

All patients screened will be included in this set, which will be used for listings of baseline data and for a small number of summary tables (e.g. patient disposition).

2.2 Violations and deviations

A list of all categories of protocol deviations with a classification of each protocol deviation as "not important" ("minor") or "important" ("major") is included in the Protocol Deviations Specifications document. Protocol deviations will be identified either programmatically based on the electronic case report form (eCRF) data or based on the medical review of data listings or based on monitoring notes. Protocol deviations will be reviewed regularly and also classified as related to Coronavirus disease 2019 (COVID-19) or not related to COVID-19.

A subset of the major protocol deviations will be considered as important.

The following general categories will be considered important protocol deviations. These will be listed and summarised and discussed in the clinical study report (CSR) as appropriate:

- Patients entered but who did not receive study treatment (Deviation 1).
- Patients who deviate from key entry criteria per CSP (Deviation 2):
    - Inclusion criteria 3, 4, 5, 6
    - Exclusion criteria 4, 5, 13
- Baseline RECIST scan > 42 days before first dose of study treatment (Deviation 3) (sBRCAm cohort only).
- No baseline RECIST 1.1 assessment on or before date of first dose of study treatment (Deviation 4) (sBRCAm cohort only).
- Received prohibited concomitant medications (including other anti-cancer agents) (Deviation 5). CSP section 7.7 describes medications that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle; the categorisation of these as important deviations is not automatic and will depend on a medical review of medication listings.

The final classification of deviations will be made prior to database lock or data freeze. Decisions made will be documented and approved by AstraZeneca prior to database lock.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Calculation or derivation of efficacy variables

In this real world study tumour evaluation is per institutional standard of care for the gBRCAm patients. The date of tumour assessment, method of evaluation (radiological response evaluation criteria in solid tumours [RECIST], radiological non-RECIST, clinical/symptomatic), radiological assessment (computed tomography [CT], magnetic resonance imaging [MRI], x-ray, ultrasound, bone scan, positron emission tomography [PET] scan, scintigraphy) and the investigators opinion of the patient status (responding, stable, progressing) is captured in the Tumour assessment eCRF page. RECIST assessment of tumour response is not mandated or captured and there is no requirement to confirm response for these patients.

For the sBRCAm patients, the RECIST tumour response data recorded in the Tumour evaluation eCRF pages based on the investigator's review of the imaging scans will be used to determine each patient's visit responses according to RECIST version 1.1. No central review will be performed.

3.1.1 Derivation of RECIST visit responses

For the sBRCAm patient cohort, baseline radiological tumour assessments performed within 6 weeks of first dose of olaparib are acceptable. Tumour assessments are then performed every 4 weeks up to week 12, then every 6 weeks up to week 48 and then every 12 weeks thereafter. In France and Germany, tumour assessments will occur every 4 weeks up to week 48, and then every 12 weeks thereafter.

Baseline values recorded after first dose of olaparib should not be used as the baseline assessment; although such assessments can be used in the calculation of progressive disease (PD).

At each visit, patients will be programmatically assigned an overall visit response of complete response (CR), partial response (PR), stable disease (SD) or PD depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

3.1.1.1 Target lesions (TL)

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is $\geq$ 10 millimetre (mm) in the longest diameter (LD), (except lymph nodes which must have short axis $\geq$ 15 mm) with CT or MRI and which is suitable for accurate

repeated measurements. A patient can have a maximum of five measurable lesions recorded at baseline with a maximum of two lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded then measurements from the one that is closest and prior to baseline 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 non-target lesions (NTLs) at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Table 1 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 1 Target lesions visit responses

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 the diameters of TL, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
PD	At least a 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5 mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
NE	Only relevant if any of the TLs were not assessed or NE 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.
Not applicable (NA)	No TLs are recorded at baseline.

Rounding of TL data

For calculation of PD and PR, for TLs the percentage changes from baseline and previous minimum should be rounded to one decimal place (d.p.) 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 then 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 LD recorded.

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

CR, PD or NE can only follow a CR. 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 (i.e. 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 i.e. 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 (i.e. 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 are 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 prior to database lock or data freeze. 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, then this will be indicated as such on the eCRF and a value of 5 mm will be entered into the database and used in TL calculations. However, a smaller value may be used if the radiologist has not indicated 'too small to measure' on the eCRF and has entered a smaller value that can be reliably measured. If a TL response of PD results, then this will be reviewed prior to database lock or data freeze.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. 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 / embolisation), should be handled in the following way and once a lesion has had intervention then it should be treated as having 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 in the 'Scaling' section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.

- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (i.e. if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, 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 mm (or <10 mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 mm (or <10 mm for lymph nodes) 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 (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)

If > 1/3 of TL measurements are missing (because of intervention) then the TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 mm for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥5 mm from nadir).

If ≤ 1/3 of the TL measurements are missing (because of intervention) then the results will be scaled up (based on the sizes 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-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of scaling

Lesion 5 is missing at the follow-up visit.

The sum of lesions 1-4 diameters at the follow-up visit is 26 centimetres (cm). The sum of the corresponding lesion diameters at the nadir visit is 26.8 cm. The sum of all lesion diameters at the nadir visit is 29.3cm.

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

$(26 / 26.8) \times 29.3 = 28.4$ cm

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤ 1/3 lesion assessments not recorded, the scaled up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

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

CT scan and MRI are the only methods of assessment that can be used within this 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.

3.1.1.2 NTLs and new lesions

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

NTL response will be derived based on the investigator's overall assessment of NTLs as follows:

Table 2 Evaluation of non-target lesions visit responses

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 NTL 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.

New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

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

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

New lesions will be identified via a Yes/No tick box. 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.

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 but should not overtly affect the derivation.

Symptomatic progression 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 progression' requiring discontinuation of olaparib without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

3.1.1.3 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 3.

Table 3 Overall visit response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	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
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	Non PD or NE or NA	No (or NE)	NE
NA	CR	No (or NE)	CR
NA	Non CR/Non PD	No (or NE)	SD
NA	NE	No (or NE)	NE

3.1.2 Progression-free survival

3.1.2.1 gBRCAm cohort

In gBRCAm patients, disease progression is based on investigator assessment, i.e. radiological (RECIST, non-RECIST) progression, or clinical/symptomatic progression, as long as progression can be documented.

PFS is defined as the time (days) from the date of the first dose of olaparib until the date of disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression (i.e. date of PFS event or censoring – date of first dose of olaparib + 1).

The eCRFs will capture each time a patient is assessed for progression regardless of the outcome of the assessment. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable progression assessment. If the patient has no evaluable progression assessments, they will be censored at study day 1.

The PFS time for gBRCAm patients will be derived based on the tumour assessment date as recorded in the Tumour assessment eCRF page, not visit dates.

3.1.2.2 sBRCAm cohort

In sBRCAm patients, disease progression is determined by RECIST version 1.1 (Eisenhauer EA, 2009).

PFS is defined as the time (days) from the date of the first dose of olaparib until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression (i.e. date of PFS event or censoring – date of first dose of olaparib + 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 post-baseline RECIST assessment prior to the missed visits (or censored at olaparib start date in case of no evaluable post-baseline scan prior to the missed visits). The allowed gap between the last previous evaluable post-baseline RECIST assessment (or olaparib start date in case of no previous evaluable post-baseline assessment) and the progression or death, for which the progression/death will still be counted as an event, will be defined as:

Allowed gap = 2*(scheduled time between scans) + allowed visit window
= 2*(4 weeks) + 1 week
= 9 weeks (63 days)
if there is no evaluable post-baseline scan prior to the progression or death.

Allowed gap = 2*(scheduled time between scans + allowed visit window)
= 2*(scheduled time between scans + 1 week)
= 10 weeks (70 days) for patients in the every-4-weeks schedule
= 12 weeks (84 days) for patients changing from every 4 to every 6 weeks
= 14 weeks (98 days) for patients in the every-6-weeks schedule
= 20 weeks (140 days) for patients changing from every 6 to every 12 weeks
= 26 weeks (182 days) for patients in the every-12-weeks schedule
if there is an evaluable post-baseline scan prior to the progression or death.

The first rule allows one missed visit directly after the olaparib start date and the next visit one week later than planned to consider the ±1 week visit window. The second rule allows one missing visit and considers that the previous scan may be 1 week earlier than planned and the progression visit 1 week later than planned, since the allowed visit window is ±1 week.

For a last previous evaluable scan at Week 4±1 the patient is still in the every-4-weeks schedule, for a last previous evaluable scan at Week 8±1 the patient changes from every-4-weeks to every-6-weeks, for a last previous evaluable scan from Week 12±1 to Week 36±1 the patient is still in the every-6-weeks schedule, for a last previous evaluable scan at Week 42±1 the patient changes from every-6-weeks to every-12-weeks, and for a last previous evaluable scan at Week 48±1 or later the patient is in the every-12-weeks schedule. The midpoints of the intervals from Week 4 to Week 8, Week 8 to Week 12, Week 36 to Week 42 and from Week 42 to Week 48 will be used to separate the three periods, and the allowed gaps between the last previous evaluable post-baseline RECIST assessment (or olaparib start date in case of no previous evaluable post-baseline assessment) and the progression or death will be defined as:

<u>All countries excluding France/Germany:</u>

Allowed gap =	
9 weeks (63 days)	if no evaluable post-baseline scan prior to the progression/death
10 weeks (70 days)	if last previous evaluable post-baseline scan < Week 6 (Day 42)
12 weeks (84 days)	if Week 6 (Day 42) ≤ last previous evaluable post-baseline scan < Week 10 (Day 70)
14 weeks (98 days)	if Week 10 (Day 70) ≤ last previous evaluable post-baseline scan < Week 39 (Day 273)
20 weeks (140 days)	if Week 39 (Day 273) ≤ last previous evaluable post-baseline scan < Week 45 (Day 315)
26 weeks (182 days)	if last previous evaluable post-baseline scan ≥ Week 45 (Day 315)

Since France and Germany have different visit schedules (every 4 weeks for the first 48 weeks and then every 12 weeks) the definition of the allowed gap changes as follows:

<u>France/Germany</u>

Allowed gap =	
9 weeks (63 days)	if no evaluable post-baseline scan prior to the progression/death
10 weeks (70 days)	if last previous evaluable post-baseline scan < Week 42 (Day 294)

18 weeks (126 days) if Week 42 (Day 294) ≤ last previous evaluable post-baseline scan < Week 46 (Day 322)
26 weeks (182 days) if last previous evaluable post-baseline scan ≥ Week 46 (Day 322)

Missed visits are only relevant immediately prior to a progression or death. If a patient missed two or more visits and has a SD, PR or CR immediately thereafter, then the missed visits can be ignored for the derivation of PFS.

The PFS for sBRCAm patients will always be derived based on scan/assessment dates not visit dates.

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

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

3.1.3 Time to first subsequent treatment or death (TFST)

TFST is defined as the time from the date of the first dose of olaparib to the earliest of the date of death or commencement of first subsequent anti-cancer treatment as recorded in the Time to subsequent cancer therapy eCRF page (i.e. date of death or commencement of first subsequent anti-cancer treatment - date of first dose of olaparib + 1). Any patient not known to have had a first subsequent anti-cancer therapy will be censored at the last date after the discontinuation of olaparib that the patient was known not to have received a first subsequent anti-cancer therapy (obtained from the Time to subsequent cancer therapy eCRF page). If a patient terminates the study for a reason other than death before first subsequent therapy, they will be censored at the earliest of their last known to be alive and termination dates.

If at least one subsequent therapy is recorded, but the start date of the first subsequent therapy is missing, then TFST will be censored at the last date after the discontinuation of olaparib the patient was known to have not started a subsequent therapy.

3.1.4 Clinical response rate and objective response rate

3.1.4.1 Clinical response rate

Response in gBRCAm patients is based on the investigator's assessment. The CRR is defined as the proportion of patients with at least one visit in which the investigator assessed the patient as responding. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of CRR. However, any responses, which occurred after a further anti-cancer therapy was received (as recorded in the Post study drug discontinuation cancer therapy eCRF page), will not be included in the numerator for the CRR calculation.

3.1.4.2 Objective response rate (ORR)

Response in sBRCAm patients must be based on RECIST 1.1. ORR is defined as the percentage of patients with a confirmed investigator-assessed response of CR or PR and will based on a subset of all treated patients with measurable disease at baseline per the site investigator. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue olaparib without progression, receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders (i.e. both visits contributing to a response must be prior to subsequent anti-cancer therapy for the patient to be considered as a responder).

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the two visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the two visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

3.1.5 Duration of clinical response and duration of response (DoR)

3.1.5.1 Duration of clinical response

For patients with a clinical response in the gBRCAm cohort, DoCR is defined as the time from the date of first response, until the date of documented progression or death (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death used for the PFS endpoint. The time of the initial response will be based on the tumour assessment captured in the eCRF.

If a patient does not progress following a response, they will be censored at the PFS censoring date.

3.1.5.2 Duration of response

For patients in the sBRCAm cohort, DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR that was subsequently confirmed.

If a patient does not progress following a response, they will be censored at the PFS censoring date.

3.1.6 Overall survival

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

OS is defined as the time from the date of the first dose of olaparib to the date of death from any cause (i.e. date of death – date of first dose of olaparib + 1). Patients who are not known to have died at the time of the analysis will be censored at the last date they were known to be alive.

If a patient is known to have died where only a partial death date is available then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:-

a. For Missing day only – using the 1st of the month

b. For Missing day and Month – using the 1st of January

c. This includes deaths where no partial death date was recorded, but the available survival data allows to conclude that the death date was within a month or within a year, i.e. last date known to be alive and first contact date when the patient is reported as dead are within the same month or same year.

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e. censored at the last known alive date.

3.1.7 Time to study treatment discontinuation or death (TDT)

TDT is defined as the time from the date of the first dose olaparib to the earliest of the date of death or discontinuation of olaparib. Patients who are alive and are still receiving olaparib will be censored at the last date their treatment was recorded as being administered.

3.1.8 Time to second progression or death (PFS2)

PFS2 is defined as the time from the date of the first dose olaparib to the earliest of the date of death or the progression event subsequent to that used for the primary variable PFS as recorded in the Tumour assessment for second progression eCRF page. Patients alive and for whom a second disease progression has not been observed will be censored at the last date they were known to be alive.

If a second progression was recorded, but the progression date is missing, then PFS2 will be censored at the date of the last evaluable tumour assessment for a second progression (PFS2 eCRF page) where a non-progression was assessed.

3.1.9 Time to second subsequent treatment or death (TSST)

TSST is defined as the time from the date of the first dose olaparib to the earliest of the date of death or commencement of the second subsequent anti-cancer treatment as recorded in the Time to subsequent cancer therapy eCRF page. Patients who are alive and have not been recorded as taking two subsequent anti-cancer treatments will be censored at the last date their treatment status was recorded. If a patient terminates the study for a reason other than death before second subsequent therapy, they will be censored at the earliest of their last known to be alive and termination dates.

If at least two subsequent therapies are recorded, and both the start date of the first subsequent therapy and the start date of the second subsequent therapy are missing, then TFST and TSST will be censored on the last date the patient was known to have not started a subsequent therapy.

If at least two subsequent therapies are recorded, the start date of the first subsequent therapy is known, but the start date of the second subsequent therapy is missing, then TSST will be censored on the latest of (1) last date the patient was known to have not started a second subsequent therapy and (2) one day after the start date of the first subsequent therapy.

3.1.9.1 Disease control rate at week 24:

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

3.2 Calculation or derivation of safety variables

3.2.1 Treatment exposure

Olaparib is taken daily. Hence, total (intended) exposure time (months) of olaparib will be calculated as follows:

- Total (or intended) exposure (months) = (earliest of (last dose date where dose > 0 mg, death date, DCO date) – first dose date + 1) / 30.4375

Actual exposure (months) of olaparib will be calculated as follows:

- Actual exposure = total exposure – total duration of dose interruptions in months (including days where dose = 0 mg), where total exposure will be calculated as above and a dose interruption is defined as any length of time where the patient has not taken any of the planned dose. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

For patients still on olaparib at the time of the interim analysis, the DCO date will be used to calculate exposure.

3.2.2 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. RDI will be defined as follows:

$$RDI\ (\%) = 100 \times \frac{d}{D}$$

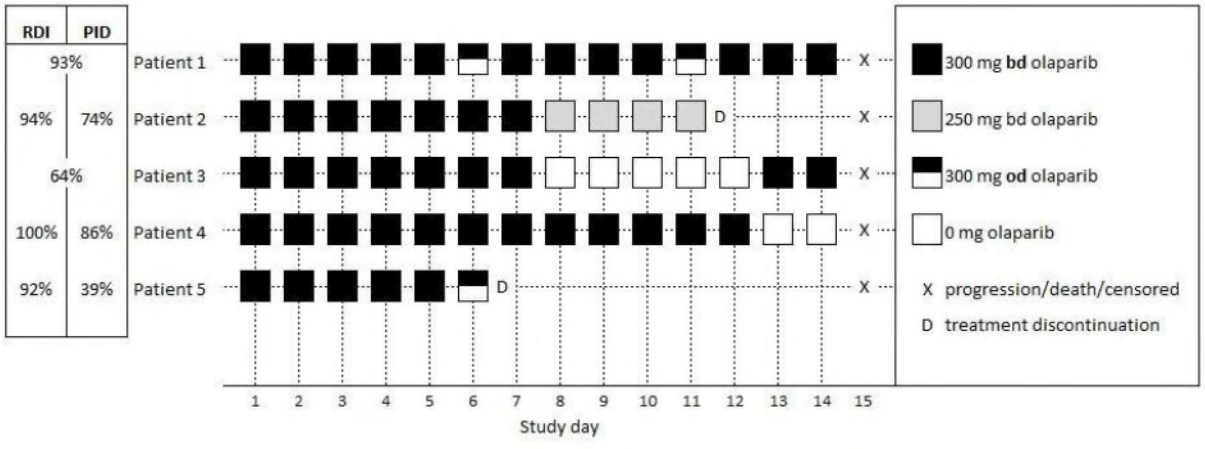
where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event, see section 3.1.2) or the actual last day of dosing and D is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing.

Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression and will be defined as follow:

$$PID\ (\%) = 100 \times \frac{d}{D}$$

where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended 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.

Figure 1 Example of dose intensity calculations for olaparib



In this example, patients 1 - 5 progressed or were censored on study day 15. All five 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)

Patient 1: RDI = PID = [(12 * 300 mg * 2) + (2 * 300 mg)] / (14 * 300 mg * 2) = 93%

Patient 2: RDI = [(7 * 300 mg * 2) + (4 * 250 mg * 2)] / (11 * 300 mg * 2) = 94%

PID = [(7 * 300 mg * 2) + (4 * 250 mg * 2)] / (14 * 300 mg * 2) = 74%

Patient 3: RDI = PID = (9 * 300 mg * 2) / (14 * 300 mg * 2) = 64%

Patient 4: RDI = (12 * 300 mg * 2) / (12 * 300 mg * 2) = 100%

PID = (12 * 300 mg * 2) / (14 * 300 mg * 2) = 86%

Patient 5: RDI = [(5 * 300 mg * 2) + (1 * 300 mg)] / (6 * 300 mg * 2) = 92%

PID = [(5 * 300 mg * 2) + (1 * 300 mg)] / (14 * 300 mg * 2) = 39%

3.2.3 Adverse events

Adverse events (AEs) (both in terms of the Medical Dictionary for Regulatory Activities [MedDRA] preferred terms [PT] and National Cancer Institute [NCI] Common Terminology Criteria for Adverse Event [CTCAE] grade) will be listed individually by patient.

A treatment-emergent AE (TEAE) is an AE with an onset date or a pre-existing AE worsening following the first dose of olaparib through to 30 days after the last dose of olaparib. Only TEAEs will be included in the AE summary tables. Any AE occurring before olaparib (i.e. before the administration of the first dose on 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'. However, any AE occurring before the administration of the first dose of olaparib on study day 1 that increases in severity after the first dose will be regarded as treatment emergent and thus will be included in the majority of summary tables.

For patient level summaries, if more than one AE is coded to the same PT for the same patient, the patient will be counted only once in summary tables using the most serious grading on causal relationship to olaparib.

3.2.4 Laboratory variables

Laboratory data will be collected throughout the study, from screening to the follow-up visits as per the study plan described in the CSP. These include blood samples for determination of haematology. For the definition of baseline and the derivation of post-baseline visit values considering visit window and how to handle multiple records, derivation rules described in section 3.4 will be used.

Change from baseline in haematology variables will be calculated for each visit on treatment and up to 30 days after last dose of olaparib. Common toxicity criteria (CTC) grades will be defined at each visit according to the CTC grade criteria using local or project ranges as required, after conversion of the laboratory result to corresponding project-wide preferred units.

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or on limits of range) and high (above range).

The maximum (or minimum) on-treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time.

Local reference ranges will be used for the primary interpretation of laboratory data at the local laboratory. Project reference ranges will be used throughout for reporting purposes. The denominator used in laboratory summaries of CTC grades will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTC criterion involves a change from baseline, evaluable patients would have both a baseline and at least one post-dose value recorded.
- If a CTC criterion does not consider changes from baseline, to be evaluable the patient needs only to have one post dose-value recorded.

3.3 Calculation or derivation of baseline variables

3.3.1 Age

If age is missing but date of birth is present, age will be calculated as follows (without rounding):

Age (years) = (study day 1 – date of birth) / 365.25

This will be determined from the date of birth (birth date in the Demographics eCRF page) and baseline visit ('visit 2' in the Date of visit eCRF page). If the day of birth is missing, the first day of the month will be imputed and if day and month are missing January 1st will be imputed.

3.3.2 Time from original diagnosis

Time from original diagnosis (months) will be calculated as follows:

Time from original diagnosis (months) = (study day 1 - original diagnosis date + 1) / 30.4375

If the original diagnosis day is missing, the first day of the month will be imputed, and if day and month are missing January 1st will be imputed.

3.3.3 Prior and concomitant medications

The World Health Organisation (WHO) Drug B3 dictionary will be used for concomitant medication coding.

Any medications taken by the patient prior to or during screening with a stop date prior to the first dose of olaparib will be considered prior medication.

Any medication taken by the patient at any time after the date of the first dose (including the date of the first dose) of olaparib up to 30 days after last dose will be considered concomitant medication. Any medication that started prior to the first dose of olaparib and ended after the first dose or is ongoing will be considered as both prior and concomitant medication.

For the purpose of inclusion in prior or concomitant mediation summaries, incomplete medication start and stop dates will be imputed as detailed in section 3.4.3.

3.3.4 Medical history

Relevant medical history (past and current) and relevant surgical history will be coded using the latest version of MedDRA.

3.3.5 Concomitant procedures/surgery

Concomitant procedures/surgery will be coded using the latest version of MedDRA. Any procedure occurring at any time after the date of the first dose (including the date of the first dose) of olaparib up to 30 days after last dose will be considered concomitant.

3.4 General considerations

3.4.1 Visit windows

Time windows will need defining for any presentations that summarise values by visit. The following conventions should also apply for all visits except for withdrawal, safety follow and long-term follow up visits, which will be presented separately:

- 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 data from visits as described in the visit schedule in the CSP and any other visits 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 study day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus one day.

- 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 value closest to the planned study day should be summarised, or the earlier in the event the values are equidistant from the planned study day.

3.4.2 Definition of baseline

Baseline will be defined as the last non-missing measurement prior to dosing with olaparib. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the CSP to be conducted before the first dose. Where safety data are summarized over time, study day will be calculated in relation to date of first dose of olaparib.

3.4.3 Missing data

Missing safety data will generally not be imputed. However, safety assessment values of the form of "<x" (i.e., below the lower limit of quantification) or >x (i.e., 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.

For missing medication and AE start dates, the following will be applied:

- If year is missing (or completely missing), then impute with the first study drug dose date unless the AE end date is prior to the first study drug dose date, in which case the AE start date is imputed with 01-Jan of the same year as the AE end date.

- If year is present and months and day are missing; or year and day are present and month is missing, impute as January 1st.

- If year and month are present and day is missing, impute day as first day of the month.

For missing medications and AE end dates, the following will be applied:

- If year is missing (or completely missing), do not impute.

- If year is present and month and day are missing; or year and day are present and month is missing, impute as December 31st.

- If year and month are present and day is missing, impute day as last day of the month.

- When the patient has died in the same month/year of partial stop date, use date of death.

For medications, a conservative approach will be followed and will be assumed to be concomitant unless the end date is before the first dose of olaparib. If the start and end dates are both missing it is considered concomitant.

In addition, for AEs, if for a partial start date, the AE start date could (when also considering the AE end date) potentially be on the first dose of olaparib date, the AE start date will be imputed with the first dose of olaparib date to assume a "worst case" scenario; e.g. AE from UNK-Jun-2017 to 23-Jul-2017 with the first dose of olaparib date 21-Jun-2017, then the AE start date will be imputed to 21-Jun-2017.

4. ANALYSIS METHODS

4.1 General principles

No hypothesis testing is planned for this single arm study.

The following general principles will be followed throughout the study:

- Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, maximum and first and third quartiles where required. Categorical variables will be summarised by frequency counts and percentages for each category. A category "Missing" will be added only if needed.

- Unless otherwise stated, percentages will be calculated out of the population total.

- The minimum and maximum will be reported to the same number of d.p. as the raw data recorded in the database. The mean, median, first and third quartile will be reported to one more d.p., and the standard deviation will be reported to two more d.p., than the raw data recorded in the database.

- Percentages will be presented to one d.p..

- SAS® version 9.3 will be used for all analyses.

- For time interval analyses in months, duration in months will be calculated as total duration in days / 30.4375.

- Study day 1 is defined as the date of first dose of olaparib. For visits (or events) that occur on or after first dose, study day is defined as (date of visit [event] - date of first dose of olaparib + 1). For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] - date of first dose of olaparib). There is no study day 0.

- In all summaries change from baseline variables will be calculated as the post-treatment value - baseline value. The percentage change from baseline will be calculated as [(post-baseline value - baseline value) / baseline value] ×100.

4.2 Analysis method

4.2.1 Analysis of the primary variable

The primary analysis will be based on assessment of disease progression using the FAS.

PFS will be summarised using the Kaplan-Meier (KM) method using the PROC LIFETEST SAS procedure, which will include a graph depicting the survival curve and estimates of median survival and associated 95% CI. Censored patients will be indicated. In addition, progression rates and 95% CIs at six monthly intervals will be estimated using the KM method.

The CI for the median will be calculated using the Brookmeyer-Crowley method.

The treatment status at progression of patients at the time of analysis will be summarised. This will include the number (%) of patients who were on olaparib at the time of progression, the number (%) of patients who discontinued olaparib prior to progression, the number (%) of patients who have not progressed and were on olaparib or discontinued olaparib. This will also provide the distribution of number of days prior to progression for the patients who have discontinued treatment.

For the sBRCAm cohort the detailed RECIST tumour assessment data will be listed.

Subgroup analysis

The primary endpoint will be summarised separately for each subgroup in the gBRCAm cohort as defined below:

- Evaluation method (RECIST, Non-RECIST, Clinical/Symptomatic, Not applicable). The evaluation method at the time of progression or at the last post-baseline tumour assessment for censored patients will be used. For patients without a post-baseline tumour assessment or who died without a progression the category "Not applicable" is used.

- Line of therapy (1st line i.e. no prior chemotherapy used in 1st line, but used as adjuvant/neoadjuvant vs 2nd line+ i.e. prior chemotherapy used in 1st line, +/- prior chemotherapy in adjuvant/neoadjuvant setting as collected in the Previous breast cancer chemotherapy eCRF page), showing the categories "1st line" and "2nd line+".

- Prior exposure to platinum-containing therapy, in the Previous breast cancer chemotherapy eCRF page (Yes vs. No). Category "Yes" will be further classified into "Adjuvant/Neo-adjuvant" and "First line".

- Line of therapy and prior exposure to platinum-containing therapy (1st line & Yes, 1st line & No, 2nd line+ & Yes, 2nd line+ & No)

- Prior exposure to anthracyclines and related substances (Yes, No)

- Prior exposure to taxanes (Yes, No)
- Prior exposure to hormonal therapy (Yes, No)
- Prior exposure to targeted therapy (Yes, No)
- Prior exposure to CDK4/6 inhibitor (including palbociclib and ribociclib) (Yes, No)
- Prior exposure to protein kinase inhibitors (Yes, No)
- Hormone status (Estrogen-receptor (ER) and/or progesterone-receptor (PR) positive vs. triple negative)
- Age at baseline group 1 (<65 vs. ≥ 65 years)
- Age at baseline group 2 (≤40, >40 – ≤50, >50 years)
- Hormone status and age at baseline group 2:
    - ER and/or PR positive & ≤40 years
    - ER and/or PR positive & >40 – ≤50 years
    - ER and/or PR positive & >50 years
    - Triple negative & ≤40 years
    - Triple negative & >40 – ≤50 years
    - Triple negative & >50 years
- Menopausal status at baseline (Pre-/Peri-menopausal, Post-menopausal, Not applicable)
- Hormone status and menopausal status at baseline:
    - ER and/or PR positive & Pre-/Peri-menopausal
    - ER and/or PR positive & Post-menopausal
    - Triple negative & Pre-/Peri-menopausal
    - Triple negative & Post-menopausal
- Region (Asia, Europe or North America)
- BRCA mutation type (BRCA1. BRCA2. Both)
- Metastatic site: Visceral (Yes, No). Visceral includes: brain/CNS, cardiovascular, respiratory, ascites, gastrointestinal, hepatic (including gall bladder), genitourinary, adrenal, pericardial effusion, peritoneum, other CNS, pancreas, spleen, esophagus, colon and liver.
- Metastatic site: Bone and locomotor (Yes, No)
- Metastatic site: Liver/hepatic (including gall bladder) (Yes, No)

- Metastatic site: Respiratory (Yes, No)

Only in case of missing values a separate category "Missing" will be added for a subgroup variable.

Kaplan-Meier plots will be created for each of the above subgroups. No formal statistical comparisons will be performed between the subgroups.

The PFS subgroup analysis will be repeated in the subset of ER and/or PR positive patients.

4.2.2 Analysis of the secondary variables

All efficacy data will be summarised based on the FAS.

4.2.2.1 Overall survival

OS will be analysed using KM methodology (PROC LIFETEST). A graph depicting the survival curve and estimates of median survival and associated 95% CI will provided together with OS rates at six monthly intervals. Censored patients will be indicated.

Summaries of the number and percentage of patients who have died, those who are censored, those still in survival follow-up, those lost to follow-up and those who have withdrawn consent will be provided. Overall survival for the gBRCAm cohort will also be summarised by the subgroups described in section 4.2.1, including the Kaplan-Meier plots per subgroup, excluding the evaluation method, which is not applicable for OS.

In addition, the duration of follow-up will be summarised:

- In censored patients who are alive at the last assessment before DCO only (excluding those who were lost to follow-up or who withdrew consent): Time from date of first dose of olaparib to date of censoring (date last known to be alive before the DCO).

- In all patients: Time from date of first dose of olaparib to the date of death (i.e. OS) or to the date of censoring for censored patients.

4.2.2.2 Other time-to-event endpoints

DoCR, DoR, TFST, TSST, TDT and PFS2 will be analysed using KM methodology. A graph depicting the survival curve and estimates of median survival and associated 95% CI will provided together with rates at six monthly intervals. Censored patients will be indicated. DoCR will be presented for the patients in the gBRCAm cohort and DoR for the patients in the sBRCAm cohort.

Summaries of the number and percentage of patients who received a subsequent anti-cancer therapy and a summary table of first (and second) subsequent anti-cancer therapies will be provided. Duration of clinical response for the gBRCAm cohort will be presented by the subgroups described in section 4.2.1 (without the Kaplan-Meier plots by subgroup), excluding the evaluation method, which is not applicable for DoCR.

4.2.2.3 Clinical response rate and objective response rate

CRR and ORR will be summarised as the proportion of patients as having a response using the number of all patients in the FAS as the denominator. Responses occurring after the start of subsequent anti-cancer therapy will not be included in the numerator. Exact binomial (Clopper C, 1934) 95% CIs will be calculated. CRR will be presented for the patients in the gBRCAm cohort and ORR for the patients in the sBRCAm cohort. CRR for the gBRCAm cohort will be presented by the subgroups described in section 4.2.1 (without the Kaplan-Meier plots by subgroup), excluding the evaluation method, which is not applicable for CRR.

4.2.2.4 Disease control rate

DCR at week 24 will be summarised as the proportion of patients with no evidence of progression (CR. PR, or SD) in the brain from the Brain assessment eCRF pages at or prior to week 24 using the number of patients with brain metastases at baseline (from the Brain metastases evaluation baseline eCRF page) as the denominator. Exact binomial (Clopper-Pearson) 95% CIs will be calculated.

4.2.3 Analysis methods of safety variables

All safety data will be summarised based on the FAS.

4.2.3.1 Exposure

The following summaries will be produced:

- Total (or intended) exposure to olaparib
- Actual exposure to olaparib
- Number of and reasons for dose interruptions of olaparib
- Number of and reasons for dose reductions of olaparib
- Number of and reasons for dose modifications of olaparib
- RDI and PID
- Time on study – defined as the earliest of the two dates
    - latest study assessment or olaparib dose date
    - study termination date

  minus first olaparib dose date + 1.

4.2.3.2 Adverse events

Only TEAEs (see section 3.2.3) will be summarised. Any AE occurring before the first dose of olaparib and AEs occurring more than 30 days after last dose (i.e. AE onset date > 30 days after date of last Olaparib dose) will be listed only and not included in the summaries.

An overall summary information table will be produced including the number and percentage of patients for each category below:

- All AEs
- All AEs causally related to olaparib
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to olaparib
- AEs with outcome of death
- AEs with outcome of death, causally related to olaparib
- All SAEs
- All SAEs causally related to olaparib
- AEs leading to discontinuation of olaparib
- AEs leading to discontinuation of olaparib, causally related to olaparib
- AEs leading to dose modification (either reduction or interruption) of olaparib
- AEs leading to dose modification of olaparib, causally related to olaparib
- AEs leading to dose reduction of olaparib
- AEs leading to dose reduction of olaparib, causally related to olaparib
- AEs leading to dose interruption of olaparib
- AEs leading to dose interruption of olaparib, causally related to olaparib

An overall summary of the number of episodes in each of the above categories will also be tabulated.

For each of these categories summaries will be presented by system organ class (SOC) and PT, with the exception of causally related AEs leading to dose modification or reduction or interruption and causally related AEs with outcome death.

A truncated AE summary table of most common AEs, showing all events that occur in at least 5% of patients will be summarised by decreasing frequency of PT.

AE and SAE event rates (i.e., exposure adjusted incidence of patients with an AE/SAE) will also be summarized by PT within each SOC. AE event rates will be calculated as the number

of patients with at least one event divided by the total time at risk, i.e. the number of days of total (or intended) exposure (see section 3.2.1) to olaparib summed over all patients. This rate is then multiplied by 1000 to present events per 1000 patient years.

The number of patients experiencing each AE will be summarised by SOC, PT and worst CTCAE grade.

Nausea and vomiting

Rates and worst CTCAE grade of nausea/vomiting, as identified by medical review of the AE unique terms, will be summarised over time and also according to whether the patient received antiemetic therapy, as identified by medical review of the concomitant medication terms, taking into account the worst CTCAE grade of nausea/vomiting at the time of administration.

Adverse events of special interest

Adverse events of special interest (AESI) for olaparib are:

- Myelodysplastic syndrome (MDS) / Acute myeloid leukaemia (AML)
- New primary malignancy (other than MDS/AML)
- Pneumonitis

Summaries of the above mentioned AESIs, after medical review of the AE unique terms, will include number (%) of patients who have:

- At least one AESI
- At least one AESI causally related to olaparib
- At least one AESI leading to discontinuation of olaparib

In addition, AEs, AEs with outcome of death and SAEs will be listed.

Anaemias and blood transfusions

AEs of anaemia will be summarised by worst CTCAE grade, showing also the number (and %) of affected patients who received a blood transfusion.

Other subgroups of AEs

The AE overview table will be repeated for the following subgroups of AEs, which will be defined based on the preferred terms:

- Anaemia grouped term
- Fatigue / asthenia grouped term

- Leukopenia grouped term
- Lymphopenia grouped term
- Nausea grouped term
- Neutropenia grouped term
- Thrombocytopenia grouped term
- Vomiting grouped term

COVID-19 adverse events

Confirmed / suspected COVID-19 infections are defined as adverse events occurring during the pandemic timeframe (post 11-Mar-2020) with preferred term and lower level term within the search criteria specified in the AZ Oncology Pandemic CSRHLD Table and Listing Templates v1.0.
COVID-19 associated AEs are confirmed / suspected COVID-19 infection AEs plus all other AEs of the same patient with onset in the period from <7 days prior to start until <30 days after start of a confirmed / suspected COVID-19 infection AE.

Patients with confirmed / suspected COVID-19 infection and patients with confirmed / suspected COVID-19 infection who died will be summarised.

Confirmed or suspected COVID-19 infection AEs, COVID-19 associated AEs and all AEs of patients with confirmed / suspected COVID-19 infection will be listed.

4.2.3.3 Deaths

A summary of deaths will be provided with number and percentage of patients, categorised as:

- Related to disease under investigation only (deaths ≤30 days after last olaparib dose)
- Related to disease under investigation only (deaths >30 days after last olaparib dose)
- AE with outcome = death only (AE onset ≤30 days after last olaparib dose)
- AE with outcome = death only (AE onset >30 days after last olaparib dose)
- Related to disease under investigation and with AE outcome=death (deaths ≤30 days after last olaparib dose)
- Related to disease under investigation and with AE outcome=death (deaths >30 days after last olaparib dose)
- Deaths >30 days after last olaparib dose, unrelated to AE or disease under investigation
- Patients with unknown reason for death

All deaths will be listed.

4.2.3.4 Laboratory evaluations

Laboratory data obtained up until the 30 day safety follow-up visit will be included in the summary tables. Absolute values and change from baseline for all continuous haematology laboratory parameters will be summarised by analysis visit.

Shift tables for change in CTCAE grade from baseline to the maximum post-baseline CTCAE grade will be produced for haematology parameters, considering both changes to the minimum post-baseline value (anaemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia) and changes to the maximum post-baseline value (increased haemoglobin, leukocytosis, increased lymphocyte count). The laboratory parameters for which CTC grade shift outputs will be produced are: haemoglobin, leukocytes, lymphocytes (absolute count), neutrophils (absolute count) and platelets.

Clinical chemistry results will be listed only as they are not mandatory at every visit.

Hy's law

To assess Hy's law criteria the following categories of maximum post-baseline ALT and AST will be tabulated versus categories of maximum post-baseline total bilirubin, based on multiples of the upper limit of the normal range (ULN):

- ALT <3*ULN
- ALT ≥3 – <5*ULN
- ALT ≥5 – <10*ULN
- ALT ≥10*ULN

- AST <3*ULN
- AST ≥3 – <5*ULN
- AST ≥5 – <10*ULN
- AST ≥10*ULN

- Total bilirubin <2*ULN
- Total bilirubin ≥2*ULN

Scatter plots will show ALT and AST versus total bilirubin as multiples of ULN. Data collected on the Hy's Law eCRF page will be listed.

4.2.3.5 Electrocardiogram (ECG)

ECG data will be listed only.

4.2.3.6 Vital signs

Vital signs data (blood pressure, pulse, temperature) will be listed only.

4.2.3.7 Pregnancy test

Positive pregnancy test results will be listed only.

4.2.3.8 Overdose results

Overdose data will be listed only.

4.2.4 Analysis methods of demography and baseline characteristics variables

4.2.4.1 Patient disposition

The total number of patients screened (and screen failures), patients enrolled, patients not assigned to olaparib, patients who received any olaparib, patients ongoing olaparib at DCO, patients who discontinued olaparib and the reason for discontinuation, patients ongoing in the study, patients who terminated study and reasons for termination will be summarised.

The reasons for not being enrolled will be summarised for screened but not enrolled patients.

The number and percentage of patients included in all the analysis populations and the number of patients recruited by region, country and centre will be also presented.

4.2.4.2 Protocol deviations

All identified important protocol deviations will be summarised for the FAS. This summary will be repeated for important protocol deviations related to COVID-19 and important protocol deviations not related to COVID-19.

Important protocol deviations (related or not related to COVID-19) and protocol deviations related to COVID-19 (important or not important) will be listed.

4.2.4.3 Demographics and other baseline characteristics

Demographic and baseline patient characteristics will be summarised for the FAS as follows:

- age (years)
    - as continuous variable
    - <50; ≥50 - <65; ≥65 - <75; ≥75
    - <65; ≥ 65
- sex
- race
- ethnicity
- weight (kg)

- as continuous variable
- <40, ≥40 - <70, ≥70 – <90, ≥90- <120, ≥120

Nicotine use, level of education and menopausal status will be summarised.

4.2.4.4 Medical/surgical history

All medical and surgical history will be summarised separately (number and percentage of patients) for the FAS by SOC and PT.

Breast cancer surgical history will be summarised using the eCRF categories.

4.2.4.5 Disease history

The following disease characteristics will be summarized for all patients in the FAS:

- Disease characteristics at baseline (time from original diagnosis, time from first diagnosis of metastatic disease, primary tumour laterality at diagnosis, histology type at diagnosis, primary tumour at diagnosis, regional lymph nodes at diagnosis, distant metastases at diagnosis, tumour grade at diagnosis, stage/ American Joint Committee on Cancer [AJCC] stage at diagnosis, ECOG)
- Extent of disease upon entry to study (evaluation method, radiological assessment, metastatic/locally advanced, site of metastatic disease)
- Previous disease-related treatment modalities by anatomical therapeutic chemical (ATC) classification and preferred group. Previous disease-related treatment modalities will also be presented by treatment status and preferred group as well as by patient regimen.
- Previous breast cancer therapy (chemotherapy, platinum compounds and other therapies)
- Receptor status for ER/PR (negative/positive)
- Receptor status for HER2 (negative/positive)
- Family history of cancer
- BRCA1/2 gene status (BRCA1/BRCA2/both)

4.2.4.6 Concomitant procedure/surgery

All concomitant procedures/surgeries will be summarised (number and percentage of patients) for the FAS by SOC and PT.

4.2.4.7 Concomitant medication

Concomitant medication will be summarised (number and percentage of patients) by ATC classification code for the FAS.

Moreover, the following concomitant medications or therapies will be summarized:

- Disallowed concomitant medications (see section 7.7 of the CSP and section 2.2 of the SAP)
- Post-study treatment (subsequent) anti-cancer therapies (post-study treatment medications are those with a start date after the last dose date of olaparib recorded in the Post study drug discontinuation cancer therapy eCRF page)
- First post-study treatment (subsequent) anti-cancer therapies

Prior medications will be listed only.

4.2.4.8 Covid-19 data

Discontinuations of study treatment or study due to COVID-19 will be summarised within the patient disposition table.

Important protocol deviations related to COVID-19 will be summarised separately, and all COVID-19 related protocol deviations will be listed.

The number of patients enrolled before and after the start of the COVID-19 pandemic will be summarised, together with the number of patients no longer in the study and ongoing in the study at the start of the pandemic.

The following COVID-19 study disruptions will be summarised:

- Study drug impacted by COVID-19
- Study treatment discontinuation due to COVID-19
- Study discontinuation due to COVID-19

Confirmed / suspected COVID-19 infections are defined as adverse events occurring during the pandemic timeframe (post 11-Mar-2020) with preferred term and lower level term within the search criteria specified in the AZ Oncology Pandemic CSRHLD Table and Listing Templates v1.0.

COVID-19 associated AEs are confirmed / suspected COVID-19 infection AEs plus all other AEs of the same patient with onset in the period from <7 days prior to start until <30 days after start of a confirmed / suspected COVID-19 infection AE.

Patients with confirmed / suspected COVID-19 infection and patients with confirmed / suspected COVID-19 infection who died will be summarised.

The following listings will be created:

- Patients affected by the COVID-19 pandemic
- Patients with reported issues in the Clinical Trial Management System due to the COVID-19 pandemic
- Demographics data for patients with confirmed or suspected COVID-19 infection
- Medical history for patients with confirmed or suspected COVID-19 infection
- Confirmed or suspected COVID-19 infection AEs
- COVID-19 associated AEs
- AEs of patients with confirmed or suspected COVID-19 infection

4.2.4.9 Other exploratory analyses for demographics and baseline characteristics

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

5. INTERIM ANALYSES

No formal statistical comparisons will be carried out in this single-arm trial.

An interim analysis will be performed when approximately 160 patients have had a PFS event. The following tables were produced:

- Patient disposition for all patients
- Reasons for not being enrolled for patients screened but not enrolled
- Demographic characteristics
- Disease characteristics
- Extent of disease

- Previous disease-related treatment modalities by ATC classification and preferred group / by patient regimen
- Previous breast cancer chemotherapy
- Previous breast cancer chemotherapy platinum compounds
- Previous breast cancer other therapies
- Demographics, disease characteristics, previous disease-related treatment modalities by ATC classification and preferred group and the subgroups described in section 4.2.1 will also be summarised by hormone status and menopausal status at baseline for the gBRCAm cohort.
- Summary of PFS
- PFS subgroup analysis
- PFS subgroup analysis for ER and/or PR positive patients
- DoCR for the gBRCAm cohort
- TFST
- TDT
- CRR for the gBRCAm cohort
- CRR subgroup analysis
- Duration of exposure and time on study
- Overall summary of AEs
- SAEs by SOC and PT
- Most common AEs
- AEs by SOC, PT and maximum reported CTCAE grade
- AEs of special interest
- AEs of anaemia and blood transfusions

The following figures were prepared for the interim analysis:

- Kaplan-Meier plots for PFS, DoCR, TFST, TDT for the gBRCAm cohort

- Kaplan-Meier plots for PFS by subgroups for the gBRCAm cohort.

The final analysis will be performed at the end of the study when approximately 130 patients have died, at which point the PFS analysis will be updated and all outputs described in this SAP will be produced.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable.

7. REFERENCES

Clopper C, P. E. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*, 26:404-413.

Eisenhauer EA, T. P. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, 42(2):228-427.

8. APPENDIX

Not applicable.

Document ID: 651086242 - Name at Publication: 234674 Statistical Analysis Plan 20210914 v3.0 clean.pdf
This document contains a total of 47 pages including any signature page/s.

PAREXEL International Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with PAREXEL International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: PPD
Title: PPD
Date: Tuesday, 14 September 2021, 05:08 PM GMT Standard Time
Meaning: Document contents approved.
==========