Statistical Analysis Plan	
Study Code	D081LC00002
Edition Number	SAP 2.0
Date	23Sept2024

A Randomized, Open-label Study to Assess the Efficacy and Safety of Olaparib Versus Enzalutamide or Abiraterone Acetate in Chinese Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have BRCA1/2 Mutations

(PROfound-CN)

A Randomized, Open-label Study to Assess the Efficacy and Safety of Olaparib Versus Enzalutamide or Abiraterone Acetate in Chinese Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have BRCA1/2 Mutations

(PROfound-CN)

Study Statistician

PPD (AstraZeneca) Date

A Randomized, Open-label Study to Assess the Efficacy and Safety of Olaparib Versus Enzalutamide or Abiraterone Acetate in Chinese Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have BRCA1/2 Mutations

(PROfound-CN)

Global Product Statistician

PPD (AstraZeneca) Date

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BICR	Blinded independent central review
bid	Twice daily (Latin: *bis die*)
BoR	Best objective response
BP	Blood pressure
BRCA	Breast cancer gene, i.e., BRCA1 and BRCA2
CI	Confidence interval
CR	Complete response
CRPC	Castration-resistant prostate cancer
CRF	Case report form
CRO	Contract research organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse events
DBL	Database lock
DCO	Data cut-off
DoR	Duration of response
d.p.	Decimal place
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFR	Evaluable for response
FAS	Full Analysis Set
HR	Hazard ratio

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
ICR	Independent central review
ICU	Intensive care unit
IP	Investigational product
IPCW	Inverse probability of censoring weighting
IPD	Important protocol deviation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LD	Longest diameter
LLOQ	Lower limit of quantification
LRCI	Likelihood ratio confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NE	Not evaluable
NED	No evidence of disease
NHA	New hormonal agent
NTL	Non-target lesion
OAE	Other significant adverse events
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'-diphosphoribose polymerase
PCS	Prostate cancer subscale
PCWG-3	Prostate Cancer Working Group 3
PD	Progressive disease
PID	Percentage intended dose
PFS	Progression free survival
PFS2	Second progression
PR	Partial response
PSA	Prostate specific antigen
RDI	Relative dose intensity

Abbreviation or special term	Explanation
RECIST	Response Evaluation Criteria in Solid Tumours
rPFS	Radiologic progression-free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS®	A commercially available integrated system of software products, commonly used for reporting and analysis of Clinical Studies
SD	Stable disease
SOC	System organ class
SSRE	Symptomatic Skeletal –Related Event
TFST	Time to first subsequent therapy or death
TL	Target lesion

AMENDMENT HISTORY

Category: Changes refers to	Date	Description of change	Change from CSP?	Rationale
Derivation on secondary endpoints	23Sept2024	OS derivation: Date of physical exam removed from censoring definition (section 3.2.3)	N/v3	Given physical exam is only captured when clinical indicated, and not mandatory to perform post-baseline
		DoR: Definition of DoR for unconfirmed response removed (section 3.2.5)	N/v3	To align with the study protocol which only includes confirmed ORR and to focus reporting on key analyses given the small sample size
		PFS2: Clarified PFS2 censoring rule for patients who did not receive study treatment (section 3.2.9)	N/v3	To clarify censoring definitions
Statistical analysis method for secondary endpoints	23Sept2024	CCI [redacted] Sensitivity analyses of rPFS focused on ascertainment bias (per BICR) (section 4.2.2.2)	Y/v3	To focus reporting of PFS on key analyses given the small sample size of the trial
		Clarified confirmed ORR and BoR based on BICR will be summarised only as primary analysis method (section 4.2.3).	N/v3	To focus reporting of response on the primary definition given the small sample size of the trial

		Removed reference to summaries of concordance (section 4.2.10.2). All response/DoR data will be listed (section 4.2.6)		
		Clarified that unless otherwise stated, analysis will not be performed if there are < 5 events/responses across both treatment	N/v3	To ensure analyses are performed based on a sufficient number of events/responses.
Data presentations	23Sept2024	Clarified reporting of decimal points in summary tables (section 4.1)	NA/NA	To align with latest TA SAP and AZ output standard
		PSA50 response: updated to be summarised in FAS population	N/v3	To align with the global PROFOUND study
		Removed vital signs and ECG summaries in patients who switch therapy	N/v3	Given, per CSP, vital signs and ECG is only captured when clinical indicated, and not mandatory to perform following treatment switching

		Clarified AE summarises require a sufficient number of events (ie. 5 events across both arm). Removed summary of AE possibly related to Olaparib and summaries of long term tolerability (Section 4.2.11.2) Summary table of most common AEs included. Clarified format of death summary table.	N/v3	Updated due to the small size sample size of the trial and to align with global PROfound reporting format.
Other	23Sept2024	Clarified that local lab range will be used for CTCAE grade derivation (section 4.2.11.6)	NA/NA	To align with AZ current project standard
		Updated the IPDs list to align with the Global PROFOUND study (section 2.2)	N/v3	To ensure alignment of reporting with the Global PROFOUND trial PD plan
		Updated terms of AESI	N/v3	To align with latest protocol
		Minor editorial clarifications/corrections made to text, tables and footnotes	NA/NA	For clarity and correct inaccuracies and to align with the wording in case report form
		Global Product Statistician transition from PPD to PPD	NA/NA	To update the name of statistician

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 3 of the CSP.

1.1 Study Objectives

1.1.1 Primary Objective

Table 1 Primary objectives

Primary objective	Primary outcome measures
To determine the efficacy (as assessed by rPFS) of olaparib in patients with mCRPC and deleterious or suspected deleterious BRCA1/2 mutations	rPFS by BICR assessment using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria

BRCA1/2 = Breast Cancer gene 1 or Breast Cancer gene 2; mCRPC = metastatic castration-resistant prostate cancer; PCWG3 = Prostate Cancer Working Group 3; rPFS = radiological progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

1.1.2 Secondary Objectives

Table 2 Key secondary objectives

Key secondary objectives	Key secondary outcome measures
To determine the efficacy (as assessed by ORR) of olaparib in patients with mCRPC and deleterious or suspected deleterious BRCA1/2 mutations	Confirmed ORR by BICR assessment in patients with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
To determine the efficacy (as assessed by OS) of olaparib in patients with mCRPC and deleterious or suspected deleterious BRCA1/2 mutations	Overall Survival (OS)

BRCA1/2 = Breast Cancer gene 1 or Breast Cancer gene 2; mCRPC = metastatic castration-resistant prostate cancer; ORR = Objective response rate; PCWG3 = Prostate Cancer Working Group 3; rPFS = radiological progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 3 Other secondary objectives

Other secondary objectives	Other secondary outcome measures
To further assess the efficacy of olaparib in patients with mCRPC and deleterious or suspected deleterious BRCA1/2 mutations	• Time from first dose to the first Symptomatic Skeletal –Related Event (SSRE)

Table 3 Other secondary objectives

Other secondary objectives	Other secondary outcome measures
	• Time from partial or complete response by BICR assessment in patients with measurable disease (RECIST 1.1) to progression (Duration of Response [DoR]) • Time from randomization to opiate use for cancer-related pain • Proportion of patients achieving a ≥50% decrease in PSA from baseline to the lowest postbaseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (PSA_{50} response) • Time from randomization to second progression by investigator assessment of radiological or clinical progression or death (PFS2)

BRCA1/2 = BRCA1 or BRCA2; mCRPC = metastatic castration-resistant prostate cancer; PSA = Prostate specific antigen; PFS2 = second progression; RECIST = Response Evaluation Criteria in Solid Tumors.

1.1.3 Safety Objectives

Table 4 Safety objectives

Safety objectives	Safety outcome measures
To evaluate the safety and tolerability of olaparib	• Adverse events (AEs)/ serious adverse events (SAEs) • Vital signs (including blood pressure and pulse) • Collection of clinical chemistry/haematology parameters • ECGs

ECG = Electrocardiogram.

1.2 Study Design

This randomized, multicenter, open-label study (PROfound-CN) is designed to assess the efficacy and safety of olaparib in Chinese men with metastatic castration-resistant prostate cancer (mCRPC) who have failed prior treatment with a new hormonal agent (NHA) and have tumor BRCA1/2 mutations.

Eligible patients will have histologically confirmed mCRPC; BRCA mutation (BRCAm) status will be confirmed by central testing of tumour tissue.

Approximately 42 patients will be randomized in a 2:1 ratio to olaparib 300 mg twice daily (bid) or to investigator's choice of either enzalutamide 160 mg once daily (qd) or abiraterone acetate (1000 mg qd plus prednisone 5 mg bid). Randomization will be stratified based on prior receipt of taxane chemotherapy (yes vs no) and presence of measurable disease at baseline (yes vs no).

1.3 Number of Patients

Approximately 700 patients will be screened to achieve approximately 42 randomly assigned to study intervention. Approximately 42 patients will be randmoized in a 2:1 ratio to olaparib tablets (300 mg orally bid) versus pre-declared investigator choice of either enzalutamide (160 mg orally od) or abiraterone acetate (1,000 mg orally od with 5 mg bid prednisone). The primary endpoint of the study is radiological progression-free survival (rPFS) as assessed by blinded independent central review (BICR).

The primary rPFS analysis will be performed when approximately 21 rPFS events have occurred (50% maturity). Assuming a true underlying rPFS hazard ratio (HR) of 0.35, exponentially distributed data and a median rPFS of 3.4 months on the investigator choice arm, this translates to a median rPFS of 9.7 months on the experimental arm ie a 6.3-month benefit. It is expected that the target sample size of 42 patients with 21 rPFS events have occurred (50% maturity) will have >90% probability to demonstrate the same trend of treatment effect (at least 50% retention of true HR, ie. HR <0.675) as that shown in the PROfound study.

With a recruitment period of approximately 17 months and a minimum follow-up period of 4 months assumed, it is anticipated that this analysis will be performed 21 months after the first patient has been randomized, taking into account study dropout.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

Enrolled analysis set

All patients who sign the ICF will be included in the enrolled analysis set. Disposition will be displayed using the enrolled analysis set.

Full analysis set (FAS)

The primary statistical analysis of the efficacy of olaparib in comparison to investigator choice of either enzalutamide or abiraterone acetate will include all patients who were randomized regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the full analysis set (FAS). Efficacy data (except for ORR, DoR and BoR) will be analyzed using the full analysis set. See Table 5 for details.

Evaluable for response (EFR) analysis set

This is a subset of the FAS, who have measurable disease at baseline as per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria. Measurable disease will be defined using the BICR assessment for analyses of BICR data, as well as using the investigator assessment data for analyses of investigator assessment ORR, DoR and BoR will be analyzed using the EFR set.

Safety analysis set

All patients who were randomized and received at least one dose of randomized study treatment will be included in the safety analysis set. If a patient receives at least one dose of olaparib study treatment they will be summarized in the olaparib arm for safety summaries (e.g. olaparib arm will include patients randomized to olaparib who receive at least one dose of olaparib or those patients randomized to investigator choice arm who receive at least one dose of olaparib study treatment in error at any time). If a patient randomized to olaparib receives only investigator choice of either enzalutamide or abiraterone acetate then they will be summarized as part of the investigator choice arm. Safety data captured on patients receiving investigator choice who have subsequently switched to olaparib upon progression will be summarized per the treatment at the time of the onset of safety condition or lab result and reported in a separate section.

Safety switch analysis set

All patients randomised to investigator choice, who received at least one dose of study treatment, who have subsequently switched to olaparib upon progression and received at least one dose of olaparib will be included in the safety switch analysis set.

Table 5 Summary of outcome variables and analysis sets

Outcome variable	*Analysis set*
Efficacy Data • rPFS • Overall survival • Time from randomization to first symptomatic skeletal–related event	*FAS*

Table 5 Summary of outcome variables and analysis sets

Outcome variable	*Analysis set*
• Time from randomization to opiate use for cancer-related pian • PSA_{50} Response • PFS2	
Efficacy Data • ORR • Duration of Response	*EFR*
Demography Data	*FAS*
Disposition	*Enrolled analysis set, FAS, Safety switch analysis set*
Safety data • Compliance and exposure • Adverse events • Laboratory measurements • Vital signs	*Safety analysis set, Safety switch analysis set*
• Concomitant medications	*FAS*

EFR = Evaluable for response; FAS = Full analysis set; ORR = Objective response rate; PSA = Prostate specific antigen; PFS2 = second progression; rPFS = radiological progression-free survival.

2.2 Protocol Deviations

The important protocol deviations (IPD) will be listed and summarised by randomized treatment group. None of the deviation will lead to any patients being excluded from the efficacy or safety analysis set. The following general categories will be considered important protocol deviations (please refer to protocol deviation (PD) plan for details):

- Patients who deviate from key inclusion criteria per the Clinical Study Protocol (CSP) (Deviation 1)
  1) Histologically confirmed diagnosis of prostate cancer.
  2) Candidate for treatment with enzalutamide or abiraterone acetate with documented current evidence of mCRPC where metastatic status is defined as at least 1 documented metastatic lesion on either bone scan or CT/MRI scan. Participants whose disease spread is limited to regional pelvic lymph nodes or local recurrence (e.g. bladder, rectum) are not eligible.
  3) Participants must have progressed on prior NHA (eg, abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or castration-

resistant prostate cancer (CRPC). Determination of progression is done per local investigator.

4) Deleterious or suspected deleterious BRCA1/2 mutation in tumor tissue
5) Eastern Cooperative Oncology Group (ECOG) performance status 0-2
6) Lack of provision of informed consent prior to study related procedures

- Patients who deviate from key exclusion criteria per the Clinical Study Protocol (CSP) (Deviation 2)

1) Other malignancy (including MDS and MGUS) within the last 5 years
2) Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator, or patients with congenital long QT syndrome
3) Previous treatment with DNA damaging cytotoxic chemotherapy, except if for non-prostate cancer indication and last dose > 5 years prior to randomization
4) Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment
5) Concomitant use of known strong CYP3A inhibitors or moderate CYP3A inhibitors. The required washout period prior to starting olaparib is 2 weeks
6) Concomitant use of known strong or moderate CYP3A inducers. The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents
7) Exposure to an investigational product within 30 days or five half-lives (whichever is the longer) prior to randomization

- Patient meets criteria for the discontinuation of the investigational product but was not discontinued from the study treatment per the CSP section 7.1 and potentially had major impact to patients' safety according to clinical judgement (Deviation 3)
- Patients randomized who received their randomized study treatment at an incorrect dose or received an alternative study treatment to that which they were randomized (Deviation 5.1, 5.2)
- Patients randomized but who did not receive olaparib/investigators choice of NHA (Deviation 5.6)
- Received prohibited other anti-cancer agents during study treatment period (Deviation 6.1)
- Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline. Study treatment should be discontinued and restarted per CSP (section 6.5) (Deviation 6.2)
- Patient randomized to investigators choice of NHA and switched to Olaparib before disease progression determined by BICR (Deviation 7.1)

- Persistently missing important protocol required safety assessments (hematology, liver function test, chemistry panel) and potentially having major impact to patient safety (clinical review on a case by case base) (Deviation 7.2)
- Baseline RECIST or Bone scan > 42 days before start date of randomized treatment. (Deviation 7.3)
- Missing baseline RECIST 1.1 or no bone scan assessment on or before date of randomization. (Deviation 7.5)
- Missing PI eCRF signature (Deviation 8)

The categorisation of these as IPDs is not automatic and will depend on duration and the perceived effect on efficacy and safety. 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. The final classification will be made prior to database lock and all decisions will be made whilst blinded to study treatment allocation.

For example, details of disallowed concomitant medication use will be reviewed by a physician using blinded data and may be determined as important.

A 'deviation bias' sensitivity analysis will be performed on the rPFS endpoint excluding patients with deviations that may affect the efficacy (deviation 1, 5.1, 5.2, 6, 7.3, 7.5) of the trial therapy if > 10% of patients in either treatment group have IPDs.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock, and will be documented prior to the primary analysis being conducted.

3. PRIMARY AND SECONDARY VARIABLES

The primary assessment of efficacy is rPFS by BICR, defined as disease progression according to RECIST 1.1 (for soft tissue disease) and/or PCWG-3 criteria (for bone disease), or death by any cause, whichever comes first. To ensure comparability, identical imaging techniques should be used for the assessment of response at baseline and throughout the study. Further details of the methods used to determine the RECIST response and PCWG3 progression are detailed below and also in Appendix E of the clinical study protocol. The primary analysis will be based on BICR of the radiological scans.

For efficacy analyses, when an event has occurred, every attempt will be made to establish the exact date of the event and enter this into the database. If this is not possible, partial dates will be accepted. If the date of event is not known, then the patient will have an imputed event date as the day of their last known alive event free date prior to date cut-off DCO.

For the date variables of historical data (i.e., any data referring to the period prior to the informed consent date), if the year is missing then the value will not be imputed. If the month

or day is missing, the value will be imputed: month will be imputed with June; day will be imputed as 15th.

3.1 Derivation of RECIST Visit Responses – malignant soft tissue

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

Baseline radiological tumour assessments are to be performed no more than 28 days before the date of randomization, and ideally as close as possible to the start of study treatment. Tumour assessments are then performed every 8 weeks (± 1 week), relative to the date of randomization, until objective radiological disease progression by BICR, even after the investigator has deemed objective disease progression, irrespective of treatment decision or dose interruptions.

If a patient has been deemed to have objective disease progression according to investigator assessment, but not by BICR, he is not eligible to switch to olaparib at that time. Patients should continue to receive randomized study treatment until progression determined by BICR.

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

3.1.1 Target lesions (TLs) – site investigator data

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. 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 randomization 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 TL 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.

Note: For patients who do not have measurable disease at entry (i.e. no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see section 3.1.3 for further details). If a

patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

Table 6 TL Visit Responses (RECIST 1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not evaluable (NE)	Only relevant in certain situations (i.e. if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable 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 percentage changes from baseline and previous minimum should be rounded to one 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.

If all TL measurements are missing then the TL visit response is NE. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

Lymph nodes

For lymph nodes, if the size reduces to < 10mm 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 < 10mm and all other TLs are 0mm then although the sum may be > 0mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

Only CR, PD or NE can 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. 0mm or < 10mm 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 < 10mm.

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm 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 (i.e. a pathological lymph node selected as TL has short axis > 10mm or the reappearance of previously disappeared lesion) or a new lesion appears, 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 then this will be indicated as such on the case report form and a value of 5mm 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 case report form and has entered a smaller value that can be reliably measured. If a TL response of PD results (at a subsequent visit) then this will be reviewed by the study team blinded to treatment assignment.

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. 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 (or <10mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10mm 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 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 ≥5mm 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 nadir TL sum including lesions 1-5 was 74 mm.

The sum of lesions 1-4 at the follow-up is 68 mm. The sum of the corresponding lesions at the nadir visit is 62 mm.

Scale up as follows to give an estimated TL sum of 81 mm:

68 x 74 / 62 = 81 mm

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 0cm.

Change in method of assessment of TLs

CT, MRI and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. 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 (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.1.2 Non-target lesions (NTLs) and new lesions – site investigator data.

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 7 NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive disease (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.
Not evaluable (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.
Not applicable (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 the presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

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 (excluding bone lesions). 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 (excluding bone lesions)' 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 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 – site investigator data

Table 8 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 8 RECIST 1.1 Overall visit responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD[a] or NE or NA	No (or NE)	**PR**
SD	Non-PD[a] 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**
NA	NA	No (or NE)	**NED**

[a] Non PD = CR or Non CR/Non PD.
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no TL and/or NTLs at baseline), NED = No Evidence of Disease (only relevant when there is no TL and NTL from baseline).

3.1.4 Bone Lesion Progression using PCWG3

Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment. If more than one baseline scan is recorded then measurements from the one that is closest and prior to randomization will be used.

All bone lesions (or sites of disease) should be identified at baseline. Their status should be followed at subsequent visits. At each visit an overall assessment of the bone lesion progression should be recorded by the Investigator.

Progression on a bone scan is identified using PCWG3 as follows:

- At the Week 8 scan:

  Two or more new metastatic bone lesions are observed on the first 8-week scan compared to the baseline assessment. The confirmatory scan, performed at least 6 weeks later and preferably no later than the next scheduled visit for a bone scan (ie, Week 16), must show two or more additional new metastatic bone lesions (for a total of four or more new metastatic bone lesions since the baseline assessment) for progression to be documented.

  Note - The first bone scan completed after baseline will be considered the '8-week scan' regardless if taken at week 8 or at an unscheduled assessment.

- After the Week 8 scan:

  Two or more new metastatic bone lesions are observed compared to the 8-week assessment. The confirmatory scan, performed at least 6 weeks later and preferably at the next scheduled visit for a bone scan, must show the persistence of or an increase in the number of metastatic bone lesions compared to the prior scan for progression to be documented.

The date of progression is the date of the scan that first documents the second lesion.

Table 9 provides the definitions for the visit bone progression status for bone lesions.

Table 9 Bone progression status

Non Progressive Disease (Non-PD)	No evidence of progression, or appearance of one new bone lesion, or non-fulfilment of the progression criteria including new lesions without confirmation of progression.
Progressive Disease (PD)	Bone lesions fulfilling the requirements for at least 2 new lesions and confirmation of progression.

Not Evaluable (NE)	Only relevant if no evaluable follow-up bone scan is available.

3.1.5 Blinded Independent Central Review (BICR) with RECIST 1.1 and PCWG3 criteria

A planned BICR of all radiological imaging data will be carried out using RECIST version 1.1 for soft tissue lesions and PCWG3 for bone lesions. 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 (CRO) for central analysis. The imaging scans will be reviewed by two independent radiologists using both RECIST 1.1 and PCWG3 and will be adjudicated, if required (i.e. two reviewers' review the scans and adjudication is performed by a separate reviewer in case of a disagreement in a timepoint assessment). For each patient, the BICR will define the overall visit response (i.e. the response obtained overall at each visit by assessing TLs, NTLs and new lesions) data and no programmatic derivation of visit response is necessary. RECIST assessments/scans contributing towards a particular visit may be performed on different dates and for the central review the date of progression for each reviewer will be provided based on the earliest of the scan dates of the component that triggered the progression. The records from the selected reviewer will be used to report all BICR information including dates of progression, visit response, censoring and changes in target lesion dimensions. Endpoints (of ORR, rPFS and DoR) will be derived programmatically from this information.

The independent review charter contains the details of the BICR conducted by the AstraZeneca- appointed CRO and has been developed in advance at the start of the study. The BICR will provide RECIST measurements and response and PCWG3 progression status for each visit (i.e. for visits where progression is/is not identified) for each patient at the time of the primary DCO. After the primary rPFS analysis, BICR review of scans will no longer be required.

3.2 Efficacy Variables

3.2.1 Radiological Progression free survival (rPFS)

The analysis of the primary endpoint rPFS will be based on tumor assessments determined by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria. There is no plan for BICR to read any scans dated after the date of DCO for the primary analysis. There will be no need to request confirmation of BICR PD after this time point, and the investigator assessed radiographic progression will prevail. A sensitivity analysis based on the programmatically derived rPFS based on investigator recorded assessments will be performed.

Radiological progression-free survival is defined as the time from randomization until the date of objective disease progression (soft tissue or bone) or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives

another anti-cancer therapy prior to progression (i.e. date of rPFS event or censoring – date of randomization + 1).

Patients who have not progressed (defined as CR, PR or SD by RECIST 1.1 for soft tissue disease, or Non-PD for bone disease) or died at the time of analysis will be censored at the time of the earliest date of their last evaluable RECIST 1.1 assessment (taking the latest target lesion, non-target lesion or new lesion scan date) or bone scan assessment that showed Non-PD. Else the latest of the previous RECIST1.1 assessment and bone scan if done at the same visit.

However, if the patient progresses or dies immediately after 2 or more consecutive missed visits for either soft tissue or bone assessments, the patient will be censored at the earliest of the previous RECIST 1.1 assessment (taking the latest target lesion, non-target lesion or new lesion scan date) or previous bone scan assessment prior to the two consecutive missed visits (if RECIST and bone scan done at different visits) (Note: NE visit is not considered as missed visit). Else the latest of the previous RECIST1.1 assessment and bone scan if done at the same visit. If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline (in which case their date of death will be used).

With 8 weekly scheduled scans, the allowable interval from the previous radiographic assessment (earliest of the previous RECIST 1.1 assessment or previous bone scan assessment) equates to 18 weeks (126 days), allowing for early and late visits (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment), or 17 weeks if immediately after the baseline scan (as no need to allow for an early assessment).

The rPFS time will always be derived based on scan dates not visit dates.

When the Investigator is in doubt as to whether PD has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

CT/MRI and bone scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- For BICR (RECIST 1.1 and PCWG3) assessments, 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 the reviewer with the earliest date of progression if there is no adjudication for BICR data.
- For investigator assessments, the date of progression will be determined based on the earliest of the dates of the component that triggered the progression
- For BICR and investigator assessments, when censoring a patient for rPFS, the patient will be censored at the earliest of the of the previous RECIST 1.1 assessment (taking

the latest target lesion, non-target lesion or new lesion scan date) or previous bone scan assessment.

Table 10 provides the definitions how the visit responses for soft tissue (according to RECIST1.1 criteria) and bone progression status (according to PCWG3 criteria) are combined to give an overall radiological objective visit response.

Table 10 Overall radiological visit response

Overall visit soft tissue response (RECIST 1.1)[a]	Bone progression status (PCWG3)[b]	Bone lesions at visit Present/Absent[c]	Overall radiological visit response
CR	Non-PD	Absent	**CR**
CR	Non-PD	Present	**PR**
CR	NE	-	**PR**
PR	Non-PD or NE	Any	**PR**
SD	Non-PD or NE	Any	**SD**
NED	Non-PD	Any	**Non-PD**
NED	NE	Any	**NE**
NE	Non-PD or NE	Any	**NE**
PD	Any	Any	**PD**
Any	PD	Any	**PD**

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable (if an assessment is missing, it will be considered NE), NED = No Evidence of Disease (only relevant if there were no TL and NTLs at all visits)

[a] See section 3.1.3.

[b] See section 3.1.4.

[c] To be categorised as 'absent' at a follow-up visit a patient must have no bone lesions at baseline and no new bone lesions at each visit up to an including this visit.

In order to derive an overall radiological response, the BICR RECIST 1.1 and PCWG3 assessments will be merged by the BICR visit number. The investigator assessments cannot be merged by visit number, they will instead be merged using windows around the protocolled visit schedule as described in the ADaM specification.

3.2.2 Objective Response Rate (ORR)

For patients in the EFR analysis set (who have measurable disease at baseline determined by BICR), objective response rate assessed by BICR (RECIST 1.1 and PCWG3), is defined as the number (%) of patients with at least one visit response of CR or PR, in their soft tissue disease assessed by RECIST 1.1, in the absence of progression on bone scan assessed by PCWG3. For each treatment group, the objective response rate (ORR) is the number of patients with a CR and PR divided by the number of patients in the treatment group .

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 randomized treatment 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 in the ORR.

In patients without a confirmed response, an unconfirmed response of CR/PR means that a response of CR/PR is recorded but either no confirmation assessment is performed or a confirmation assessment is performed but response is not confirmed.

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a confirmed responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best confirmed response of CR will be assigned.

Overall response rate based on soft tissue will be defined on the basis of RECIST 1.1 only. ORR will also be calculated based on investigator assessment using the EFR analysis set with measurable disease at baseline determined by investigator assessment.

3.2.3 Overall survival (OS)

Overall survival is defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of randomization + 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 (SUR_DAT, recorded within the SURVIVE module of the eCRF).

Note: Survival calls (if agreed to by the patient and in compliance with local data privacy laws/practices) will be made following the date of DCO for the applicable analysis (these contacts should generally occur within 7 days of the DCO). 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. Death dates may be found by checking publicly available death registries.

For any OS analysis performed prior to the final DCO, in the absence of survival calls being made or if the SURVIVE module is not completed for a particular patient, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on-treatment. The last date for each individual patient is defined as the latest among the following dates recorded on the case report forms (CRFs):

- AE start and stop dates
- Admission and discharge dates of hospitalization
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Date of ECG
- Disease assessment dates on RECIST CRF
- Disease assessment dates on BONESCN CRF
- Date of symptomatic skeletal related event assessment
- Start and stop dates of concomitant medication
- End of study date (only if the disposition is not “lost to follow up”)

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

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.

3.2.4 Time to first Symptomatic Skeletal –Related Event (SSRE)

Time from randomization to first symptomatic skeletal–related event as defined by any of the following or a combination:

- Use of radiation therapy to prevent or relieve skeletal symptoms
- Occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral, resulting from minimal or no trauma). Radiologic documentation is required.
- A pathological fracture, as determined by investigator, is defined as associated with low or no trauma and deemed to have occurred at a site of bone metastasis
- Occurrence of spinal cord compression. Radiologic documentation required
- Orthopedic surgical intervention for bone metastasis

Patients who have not experienced any of the above conditions will be censored at time of death, or time of last SSRE assessment.

3.2.5 Duration of response (DoR)

For patients in the EFR analysis set (who have measurable disease at baseline determined by BICR) and have a confirmed response (CR or PR as described in section 3.2.2), duration of response (DoR) will be defined as the time from the date of first documented confirmed response until date of documented progression or death in the absence of disease progression (i.e. date of rPFS event or censoring – date of first confirmed response + 1). The end of response should coincide with the date of progression or death from any cause used for the rPFS endpoint.

The time of the first confirmed response will be defined as the latest of the dates contributing towards the first visit response of confirmed PR or CR. The end of response will be defined as the date of progression or death from any cause used for the rPFS endpoint. If a patient does not progress following a response, then their duration of response will use the rPFS censoring date as the date at which that patient is censored for DoR. However, if the date of rPFS censoring is on or before the date of the first confirmed response then the patient will be censored at Day 1 for DoR.

The time to response is the time from randomization to the first onset of a confirmed objective tumor response (i.e. date of first confirmed response – date of randomization + 1).

3.2.6 Time to Opiate Use for Cancer Pain

Time to Opiate use is defined as the time from the date of randomisation until the date of opiate use for cancer-related pain on patients who have not received any opiates at baseline. Paitents who have not received opiates during the study or died prior to receiving opiates will be censored at the last study assessment date prior to DCO where no opiate use was recorded.

3.2.7 Prostate Specific Antigen (PSA) Response

A patient will be regarded as having a single PSA visit response if their PSA level at any post-dose visit is reduced by 50% or more compared with baseline.

A patient will be regarded as having a confirmed PSA response if they have a reduction in PSA level of 50% or more compared with baseline that is confirmed at the next assessment at least 3 weeks later (i.e., decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 3 weeks apart).

For patients who receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy), data will only be included until the start date of the subsequent anti-cancer therapy. All patients in FAS will be included, regardless of having a baseline PSA measurement. For the calculation of PSA responses, 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".

3.2.8 PSA changes on continuous scale

PSA changes on a continuous scale will be evaluated in patients in the FAS who have a valid baseline and post-baseline PSA measurement. Patients without a baseline PSA measurement and/or a post-baseline PSA measurement will be excluded from the analysis. For patients who receive a subsequent anti-cancer therapy (excluding radiotherapy), data will only be included until the start date of the subsequent anti-cancer therapy.

- PSA levels will be evaluated in terms of percentage change from baseline which will be derived for each post baseline visit where PSA data are available:
- Percentage change from baseline = [(post-dose PSA level – baseline PSA level) / baseline PSA level] *100
- Best percentage change from baseline in PSA will be derived as the biggest reduction in PSA level compared with baseline (or the smallest increase in the absence of a reduction) taking account of all PSA values collected for each patient.

For the calculation of PSA changes on a continuous scale, 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".

3.2.9 Time from randomisation to second progression or death (PFS2)

Second progression is based on investigator assessment according to local standard clinical practice and includes radiological, symptomatic progression (but not PSA progression) and clinical progression or death. Second progression status is reviewed every 12 weeks following the progression event used for the primary variable rPFS (ie, first progression) and the start of the next-line anticancer therapy (excluding radiotherapy). Based on two 12-weekly visits plus two allowed 2 week visit windows, a second progression investigator assessment is not

evaluable if it was greater than 196 days since last evaluable visit; where the last evaluable visit is the later of the first progression date and any evaluable second progression assessment. In addition, if next-line anticancer therapy has not started a second progression assessment is not evaluable and is censored at the date last known not to have received a subsequent therapy.

The time to PFS2 is defined as the time from date of randomisation to date of second progression on next-line (immediately after study treatment) anticancer therapy (excluding radiotherapy) or death, whichever occurs earlier (i.e. date of PFS2 event or censoring – date of randomisation + 1). If a patient had a first progression (radiological progression) and did not receive any next-line anticancer therapy, the second progression would not be counted as a PFS2 event. This is because the second progression would still be a marker of the effect of the first treatment (i.e. study treatment). If a patient had a first progression (radiological progression) which was censored due to 2 missed visits (i.e. was censored for the rPFS primary end-point), did receive next-line anticancer therapy, and subsequently a second progression was recorded by the investigator, then the patient will be counted as a PFS2 second progression event. If death occurs within 196 days of first progression (radiological progression), or within 196 days of the last evaluable second progression assessment, the death will be a PFS2 death event irrespective of whether next-line anticancer therapy has started.

Patients alive and for whom a second progression has not been observed should be censored at the earliest of: date of study termination, date last known alive, DCO or, if a patient has not had a first subsequent therapy, the date last known not to have received a first subsequent therapy.

However, if the patient experiences a second progression that is not evaluable, or dies immediately after two or more visits where there was no evaluable PFS2 assessment, the patient will be censored at the time of the later of the first progression date and the latest evaluable second progression assessment.

Also, if the patient died in the absence of any progression after two or more consecutive missed visits, then the censoring visit rule as described for rPFS (in section 3.2.1) should be applied.

Patients not receiving randomised treatment would have time to PFS2 calculated as time from date of randomisation to the initial therapy or death.

3.3 Safety Variables

3.3.1 Exposure and dose interruptions

Study drug exposure (days) for olaparib will be defined as time from first dose of olaparib, up to and including the, last day of dosing of olaparib. Exposure to investigators choice of enzalutamide or abiraterone acetate will be calculated in the same way using enzalutamide or abiraterone acetate only. Exposure to prednisone/prednisolone will not be calculated.

Exposure (i.e. duration of treatment) will be defined as follows:

Total (or intended) exposure of olaparib/investigators choice of NHA:

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

Exposure to olaparib for patients randomised to investigator choice of treatment, who have subsequently switched to olaparib upon progression will be defined as:

- Total (or intended) exposure = min(last dose date of Olaparib where dose>0 mg, date of death, date of DCO) – first dose date of olaparib + 1.

Actual exposure of olaparib/investigators choice of NHA:

- Actual exposure = intended exposure – total duration of dose interruptions, where intended 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 daily dose.

The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Missed or forgotten doses

Missed and forgotten doses should be recorded on the EX, EX1 and EX2 module for Olaparib, enzalutamide and abiraterone respectively as a dose interruption with the reason recorded as "Subject forgot to take dose". These missed or forgotten doses will not be included as dose interruptions in the summary tables but the information will appear in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

Patients who permanently discontinue during a dose interruption

If a patient permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded on DOSDISC, DOSDISC1 and DOSDISC2 will be used in the programming.

Safety Follow-up

- Total Safety Follow-up = min((last dose date +30 days), date of withdrawal of consent, date of death, date of DCO) – first dose date +1

3.3.2 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% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the or the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule.

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

- PID = 100% * 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.

Intensity of olaparib, enzalutamide, and abiraterone acetate will be summarised separately. The intended cumulative dose is defined as 300mg olaparib twice daily, 160mg enzalutamide once daily and 1000mg abiraterone acetate once daily.

3.3.3 Adverse events

The definitions of adverse events (AEs) and serious AEs (SAEs) are given in Sections 8.3 of the clinical study protocol. AEs and SAEs will be collected throughout the study, from date of informed consent until 30 days after the last dose of study treatment. Events will be defined as treatment emergent if they onset, or worsen (by investigator report of a change in intensity), during the treatment period as defined in the protocol. The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (using the CTCAE version 5.0).

Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and 'Discontinuation of Investigational Product due to Adverse Events' (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

AEs of special interest

Adverse events of special interest (AESI) are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI may be serious or non-serious. Adverse events of special interest for olaparib are:

- Important Identified Risks of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)

- Important potential risk of New primary malignancy (other than MDS/AML)
- Potential risk of Pneumonitis

Other categories may be added as necessary or existing terms may be merged. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician will review the AEs of interest and identify which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to database lock (DBL) to ensure any further terms not already included are captured within the categories.

3.3.4 Concomitant medications

Concomitant medications will be classified according to the current version of the WHO Drug Dictionary.

Concomitant medications will be classed as either:

- Concomitant medications starting prior to first dose (pre-study)
- Concomitant medications starting on or after first dose date and up to up to 30 days following discontinuation of randomized treatment or the day before switching to Olaparib (on study). Medications that start on the same day as the first dose of study treatment will be assumed to occur after study treatment has been administered, and be classified as on-study.

3.3.5 Laboratory assessment

Blood samples for determination of clinical chemistry, hematology and coagulation will be taken at each scheduled visit and urine samples to determine urinalysis will be taken at screening and Day 1 visits. The laboratory parameters to be collected are given in Section 8.2.4 of the protocol.

3.3.6 Vital Signs

Vital signs, including blood pressure (BP) (mmHg), pulse rate (beats/minute), body temperature (°C) and weight (kg), will be assessed at screening, baseline and as clinically indicated and will be summarized at baseline. Changes in vital signs should be recorded as an AE, if applicable.

3.3.7 Physical examination

Physical examination assessments will be performed at screening, day 1 and as clinically indicated.

3.3.8 Electrocardiogram (ECG)

Resting 12-lead ECGs will be performed within 7 days prior to starting study treatment and when clinically indicated. Measurements should be taken after the patient has been rested in a semi-supine position for at least 5 minutes. The following ECG variables will be collected:

ECG heart rate, PR duration, QRS duration,QT duration, QT interval corrected by Fridericia's formula (QTcF) and overall ECG evaluation.

All ECGs will be assessed locally to determine whether they are clinically significantly abnormal / not clinically significantly abnormal. The overall evaluation of an ECG will either be "normal" or "abnormal" with abnormalities categorized as either "clinically significant" or "not clinically significant. If there is a clinically significant abnormal finding, it will be recorded as an AE by the Investigator.

3.3.9 Analyses for crossover patients

Summary tables from the AEs sections described above, including causally related AEs, AEs leading to death, AEs leading to dose modification, serious AEs and AESIs, will be repeated for crossover patients only.

The AE summary tables for crossover patients will include all AEs that occurred or worsen after the start of crossover 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 treatment.

In addition to AE summaries, summaries of clinical laboratory parameters and vital signs will be repeated for crossover patients only.

4. ANALYSIS METHODS

4.1 General Principles

This study is comparing olaparib to investigators choice of NHA. Results of statistical analyses will be presented using corresponding 2-sided 95% confidence intervals and 2-sided p-values, where appropriate.

The hypothesis of interest with regards to the primary endpoint, rPFS assessed by BICR per RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria, is:

- H0: No difference between olaparib and investigator choice of enzalutamide or abiraterone acetate.
- H1: Difference between olaparib and investigator choice of enzalutamide or abiraterone acetate.

No formal testing of hypotheses will be performed as the study is designed to demonstrate the same trend of treatment effect in Chinese men as that shown in the PROfound study, and thus no adjustment for multiplicity will be made and all p-values generated will be regarded as descriptive.

The DCO date for the statistical analysis for the primary objective of the study will be when approximately 21 rPFS events are expected to have occurred (50% maturity).

The below mentioned general principles will be followed throughout the study:

- All analyses and reporting are by treatment arm.
- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles minimum, and maximum. For log-transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group. Overall totals will be calculated for baseline summaries only.
- For continuous data, the mean,median and standard deviation will be rounded to 1 additional decimal place compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- P-values are presented to 3 decimal places and p-values less than 0.001 are presented as <0.001 in Tables, Figures and Listings (TFLs).
- In general, unless otherwise stated, analysis will not be performed if there are < 5 events/responses across both treatment arms. Descriptive summaries may still be provided.
- SAS® version 9.4 or later will be used for all analyses.

In general, for efficacy endpoints the last observed measurement prior to randomisation will be considered the baseline measurement. However, if an evaluable assessment is only available after randomisation but before the first dose of randomised treatment then this assessment will be used as baseline. For safety endpoints the last observation before the first dose of study treatment will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

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 protocol to be conducted before the first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value - baseline value) / baseline value x 100.

Efficacy data will be summarised and analysed based upon the FAS. Safety and treatment exposure data will be summarised based upon the safety analysis set. Study population and demography data will be summarised based upon the FAS.

4.2 Analysis Methods

Table 11 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints Analysed	Notes
Radiologic progression-free survival	• Primary analysis stratified log-rank test based on BICR [RECIST 1.1 and PCWG3] assessments and stratified in accordance with the pooling strategy defined in section 4.2.2 • Hazard ratio using Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with progression or death events using Kaplan-Meier (KM) method.
rPFS sensitivity analysis • Ascertainment bias •	• Stratified log-rank test stratified in accordance with the primary pooling strategy • Hazard ratio using Cox proportional hazards model with ties=Efron and the stratification variables determined by the pooling strategy as covariates • KM plot
CCI [redacted]	[redacted] o

Endpoints Analysed	Notes
Confirmed objective response rate • BICR assessment using RECIST and bone scan data • BICR assessment using RECIST soft tissue only • Investigator assessment using RECIST and bone scan data • Investigator assessment using RECIST soft tissue only	• Odds ratio using logistic regression adjusted for prior taxane. If there are not at least 5 responses across both treatment groups, then a Fisher's exact test using mid p-values will be used.
Overall Survival	• Stratified log rank test stratified in accordance with the primary pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.
Time to first Symptomatic Skeletal-Related Event	• Stratified log-rank test stratified in accordance with the primary pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.
Time to Opiate use for Cancer related Pain	• Stratified log-rank test stratified in accordance with the primary pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.

Prostate Specific Antigen (PSA) Response	• Summarized using descriptive statistics
	• Waterfall plots
	  ○ Best percentage change from baseline
	  ○ Percentage change from baseline at Week 12
	• Confirmed PSA best response presented with 95% CIs

Endpoints Analysed	Notes
Time from randomization to second progression or death	• Stratified log-rank test stratified in accordance with the primary pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.

4.2.1 Multiplicity

There's no adjustment for multiplicity for this study.

4.2.2 Analysis of the primary efficacy variable (rPFS)

The primary analysis of radiologic progression-free survival will be performed when approximately 21 rPFS events (50% maturity) have occurred based on BICR (RECIST 1.1 and PCWG3) assessment.

The primary analysis will be based on the BICR assessment of rPFS using all scans regardless of whether they were scheduled or not. The hypothesis of superiority of olaparib compared to investigator choice will be tested using a log rank test with the Breslow method for handling ties, stratified by the variables determined by the pooling strategy described below.

The effect of olaparib versus investigator choice of NHA will be estimated by the HR and corresponding 95% confidence interval. This analysis will be performed using a Cox Proportional Hazards Model with the Efron approach being used for handling ties and the stratification variables determined by the pooling strategy being used as covariates. The 2-sided 95% confidence intervals will be calculated using the profile likelihood method and a HR less than 1 will favour olaparib.

Any patients mis-stratified in the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will be included in the stratified log rank test using the baseline data collected in the IVRS/IWRS.

It is expected that there may not be enough rPFS events in each strata (where strata are defined as categories formed from – prior taxane * measurable disease * treatment) to allow a meaningful analysis, if any stratum for either treatment arm contains less than 5 events, then a pooling strategy will be employed. The order of preference for pooling will be (prior taxane * treatment), (measurable disease * treatment), unstratified. Prior taxane and measurable disease will use data collected via IVRS.

All sensitivity analyses and secondary endpoints (except for ORR which only includes prior taxane) will be conducted in accordance with the primary pooling strategy for the analysis of rPFS. If a model does not converge when using the stratification variables from the primary pooling strategy then this will result in collapsing of strata in line with the pooling strategy

until the minimum 5 event criterion is achieved. Unstratified analyses will be conducted for any secondary endpoints that still do not conform to the 5-event rule per stratum.

Kaplan-Meier (KM) survival curves (product-limit estimates) of rPFS will be presented by treatment group, together with a summary of associated statistics (median rPFS time, and survival rate estimates at appropriate timepoints). Summaries of the number and percentage of patients experiencing an rPFS event, and the type of event (RECIST progression, PCWG-3 progression, both or death) will be presented along with the median rPFS for each treatment arm.

The assumption of proportionality will be assessed. Note that in the presence of nonproportionality, 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 (adding a treatment-by-time or treatment-by-ln(time) interaction term) to assess the extent to which this represents random variation. If qualitative non-proportionality is observed then using stratification rather than covariate adjustment will be considered.

4.2.2.1 CCI [redacted]

CCI [redacted]

4.2.2.2 PFS sensitivity analyses

Sensitivity analyses may be performed to assess the possible presence of time-assessment bias (i.e., differential assessment times between treatment groups). Summary statistics for the number of weeks between rPFS time and the last evaluable assessment prior to progression will be presented for each treatment group. For all sensitivity analyses, the same methodology and model will be used as per the primary rPFS analysis, including stratification factors in accordance with the final pooling strategy. The HR and associated 95% CI will be reported. Median rPFS will be presented by treatment group.

The following sensitivity analyses will be evaluated:

(a) Ascertainment bias

Ascertainment bias will be assessed by analysing the investigator assessment data. The stratified log rank test will be repeated on rPFS using the investigator assessment data based upon RECIST1.1 and PCWG3. The HR and CI will be presented.

If there is an important discrepancy between the primary analysis using the BICR data and this sensitivity analysis using investigator assessment data then the proportion of patients with site but no central confirmation of progression will be summarised; such patients have the potential to induce bias in the central review due to informative censoring. An approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value (Fleischer et al 2011), but only if an important discrepancy exists.

Disagreements between investigator and central reviews of RECIST1.1 and PCWG3 progression will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of central review declared progressions before the investigator review as a proportion of all central review progressions and the late discrepancy rate which is the frequency of central review declared progressions after the investigator review as a proportion of all discrepancies.

4.2.3 Objective response rate (ORR)

Objective response rate will be assessed based on BICR assessed RECIST and bone scan data (using all scans regardless of whether they were scheduled or not) in patients in the EFR analysis set (patients with measurable disease at baseline determined by BICR). Both confirmed ORR and unconfirmed ORR will be listed.

Confirmed ORR will be compared between olaparib and investigator choice using a logistic regression model adjusting for previous taxane (yes, no) collected via IVRS. The results of the analysis will be presented in terms of an odds ratio, with an odds ratio greater than 1 favouring olaparib, together with the associated 95% profile likelihood CI (e.g. using the option 'LRCI' in SAS procedure GENMOD) 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 at least 5 responses across both treatment groups then a Fisher's exact test using mid p-values will be presented. The mid-p-value modification of the Fisher exact test amounts to subtracting half of the probability of the observed table from Fisher's p-value.

Fisher's exact test mid p-value = Two sided p-value – (Table probability ÷ 2)

Summaries of number (%) of patients with a tumor response (BICR and investigator assessment of CR or PR) will be presented.

Best objective response (BOR) will be assessed based on BICR assessed RECIST and bone scan data in patients in the EFR analysis set in the full analysis set. For each treatment group BOR will be summarised by n (%) of patients for each category (CR, PR, SD, PD and NE), no formal statistical analyses for BOR are planned. For patients with a BOR of SD, the number and percentage of patients who had an unconfirmed response of CR/PR will be displayed. BOR will be repeated based on soft tissue response only using RECIST 1.1.

4.2.4 Overall survival (OS)

CCI [redacted] As there's no adjustment for multiplicity will be made and all p-values generated will be regarded as descriptive for this study, there's no alpha spending for this interim OS analysis. The final analysis of OS will occur upon achieving approximately 25 deaths (60% maturity).

The p-value will be based on the stratified log rank test stratified in accordance with the pooling strategy described in section 4.2.2. HR and 95% CI will be based on the Cox model.

A KM plot of OS will be presented by treatment group. Summaries of the number and percentage of deaths and those alive and censored will be provided along with median time to death for each treatment arm.

4.2.4.1 CCI

[redacted]

4.2.5 Time to first Symptomatic Skeletal-Related Event (SSRE)

Time to SSRE will be analyzed using the same methods as in the analysis of the primary endpoint rPFS.

A KM plot of time to SSRE will be presented by treatment group. Summaries of the number and percentage of patients with symptomatic skeletal related events and those who are censored will be provided along with median time to symptomatic skeletal related events for each treatment arm.

4.2.6 Duration of response (DoR)

Duration and onset of response in responding patients will be listed for patients in the EFR analysis set (patients with measurable disease at baseline determined by BICR).

4.2.7 Time to Opiate use for Cancer related Pain

Time to opiate use will be analyzed at the time of the primary rPFS analysis using the same methods as in the analysis of rPFS. The, p-value will be based on the stratified log rank test stratified in accordance with the pooling strategy described in section 4.2.2 HR and 95% CI will be based on the Cox model.

A KM plot of time to opiate use will be presented by treatment group. Summaries of the number and percentage of patients using opiates will be provided along with median time to opiate use for each treatment arm.

4.2.8 Prostate specific antigen (PSA) response

Proportion of patients achieving a PSA response and patients with a confirmed PSA response will be presented with 95% CIs. Best PSA percentage change from baseline will be summarized as continuous variables using descriptive statistics and will be graphically displayed using waterfall plots. In addition percentage change from baseline at Week 12 will be summarized as continuous variables using descriptive statistics and will be graphically displayed using waterfall plots.

For the Week 12 visit, a window of +/- 7 days will be applied to the scheduled visit Day 85. If there is more than one value per patient within the time window, then the closest value to the scheduled visit date will be summarised.

4.2.9 Time from randomisation to second progression or death (PFS2)

Time from randomisation to second progression (PFS2) or death will be analysed using identical methods as outlined for rPFS and adjusting for the same set of covariates, but no subgroup analysis will be performed. The HR for the treatment effect together with its 95% CI will be presented. Medians and Kaplan-Meier plots will be presented to support the analysis.

4.2.10 Concordance between BICR and investigator assessments

Concordance between BICR and investigator assessments for rPFS will be summarised by concordance status (concordant or discordant) and type of concordance (according to timing) by treatment group and overall.

The concordance rate will be derived as the proportion of patients where BICR and investigator have agreed on rPFS status (event or censored).

4.2.11 Safety

4.2.11.1 General considerations for safety assessments

Time windows will be defined for any presentations that summarise values by visit. The following conventions will apply:

- The time windows will be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window will be based on the actual date and not the intended date of the visit.
- All unscheduled visit data 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). 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 laboratory assessment data (with 4 weeks between scheduled assessments) are:
    - Day 29, visit window 2 – 42
    - Day 57, visit window 43 – 70
    - Day 85, visit window 71 – 98
- 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 to the scheduled visit date will be summarised, or the earlier, in the event the values are equidistant from the nominal visit date. The listings will highlight the value for the patient that contributed to the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date
  - To prevent very large tables or plots being produced that contain many cells with meaningless data, for each treatment group, visit data will only be summarised if the number of observations is greater than 1/3 of patients dosed
- For summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.
- Baseline for safety assessments will generally be the last value obtained prior to the first dose of study medication. Alternatively, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average can be taken as a baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment.

The following considerations are made for missing safety data, diagnostic dates and AE dates:

- 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. Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.
- For missing diagnostic dates, if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.
- For missing AE/concomitant medication start dates, the following will be applied
  a. Missing day- Impute the 1st of the month unless month is the same as month of the first dose of study drug then impute first dose date

b. Missing day and month -Impute 1st January unless year is the same as first dose date then impute first dose date

c. Completely missing-impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date

- For missing AE/concomitant medication end dates, the following will be applied:

  a. Missing day - Impute the last day of the month

  b. Missing day and month – impute 31st December Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

  c. Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing, then assume that AE is still present/medication is still being taken (i.e. do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.

If the imputed AE end date is before the AE start date the end date will set equal to the start date.

The imputation of dates will be used to decide if an observation is treatment emergent for adverse events or concomitant medications. The imputed dates are not used to calculate durations. Where partial dates occur, listings will contain the date collected in the partial form.

For laboratory data in particular, the following additionally applies:

- Numerical summaries should provide the mean, standard deviation, median, minimum, maximum, and lower and upper quartile for visit based tabular summaries.

4.2.11.2 Adverse events (AEs)

Adverse events will be summarized by treatment group. Separate summaries will be produced for Olaparib post switch from investigator choice. All AEs, both in terms of MedDRA preferred term and CTCAE grade, will be listed and summarised descriptively by count (n) and percentage (%) and treatment group. MedDRA dictionary will be used for coding. Any AE occurring before olaparib/investigators choice of NHA (i.e., 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’.

An overall summary of the number and percentage of patients in each category will be presented as will an overall summary of the number of episodes in each category. Frequencies and percentages of patients reporting each preferred term will be presented. Total number of events will also be reported separately.

All reported AEs will be included in listings along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of severity and relationship to study drug. A separate listing will be produced for AEs that are on-going in patients who switch from investigator choice to olaparib at the start date of olaparib.

Summary information (the number and percent of patients by treatment) will be tabulated by system organ class (SOC), preferred term and treatment group if there are sufficient number of events (i.e. 5 events across both treatment arm), else they will be listed for:

- All AEs
- All AEs possibly related to olaparib/ investigators choice of NHA
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to olaparib/ investigators choice of NHA
- AEs with outcome of death
- AEs with outcome of death causally related to olaparib/ investigators choice of NHA
- All SAEs
- All SAEs causally related to olaparib/ investigators choice of NHA
- AEs leading to discontinuation of olaparib/ investigators choice of NHA
- AEs leading to discontinuation of olaparib, causally possibly related to olaparib/investigators choice of NHA
- AEs leading to dose reduction of olaparib/ investigators choice of NHA
- AEs leading to dose interruption of olaparib/ investigators choice of NHA
- Other significant AEs
- Other significant AEs causally related to olaparib/ investigators choice of NHA
- AE's for COVID-19 infection

Key patient information tables will be produced for:

- AEs with outcome of death
- All SAEs
- AEs leading to discontinuation of olaparib/ investigators choice of NHA

- AE's for COVID-19 infection
- Other significant AEs

Each AE event rate (per 1000 patient years) will also be summarised by preferred term within each system organ class. For each preferred term, the event rate will be presented and will be defined as the number of patients with that AE divided by the sum of the duration of therapy (for patients without the event) and the time to the AE (for patients with the event) in each group multiplied by 1000.

Additionally, the most common AEs, which are those AEs that occur in at least 10% of patients in any treatment group, will be summarised by PT, by decreasing frequency based on the total number of AEs in Olaparib arm. This cut-off may be modified after review of the data.

Adverse events will be assigned CTCAE grades (National cancer institute CTCAE version 5.0) and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, SOC, preferred term and actual treatment group. Fluctuations observed in CTCAE grades during study will be listed.

AEs which started prior to first dose or > 30 days following date of last dose will be listed only.

Deaths

A summary of deaths will be provided with number and percentage of patients by actual treatment group categorised as:

- Related to disease under investigation only ⩽30 days after last treatment dose
- AE outcome=death only ⩽ 30 days after last treatment dose
- Both related to disease under investigation and with AE outcome=death ⩽ 30 days after last treatment dose
- AEs with outcome of death only (AE start date falling after 30 days follow-up)
- Related to disease under investigation only (death after 30 days follow-up)
- Both related to disease under investigation and with AE outcome=death (death > 30 days after last treatment date)
- Unrelated to AE or disease under investigation (death > 30 days after last treatment date)
- Patients with unknown reason for death
- Other deaths (not captured above)

Causally related adverse events with an outcome of death will be summarised for the number and percentage of patients by SOC, preferred term and actual treatment group. Causally

related serious adverse events will be summarised for the number and percentage of patients by SOC, preferred term and actual treatment group.

Adverse events leading to discontinuation of olaparib/ investigators choice of NHA will be summarised for the number and percentage of patients by SOC, preferred term and actual treatment group.

Causally related adverse events leading to discontinuation of olaparib/investigators choice of NHA will be summarised for the number and percentage of patients by SOC, preferred term and actual treatment group. In addition, AEs with outcome of death, SAEs, OAEs, AEs leading to discontinuation of treatment and AEs causally related to olaparib/investigators choice of NHA will be listed in key patient information tables.

Listings of AE data will also be produced.

4.2.11.3 Adverse events of special interest (AESI)

Preferred terms used to identify AESI will be listed before DBL and documented in the Trial Master File. Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI grouping. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

4.2.11.4 Exposure

Summaries of duration of exposure and cumulative exposure over time will be produced by treatment group. The number of patients with study drug reductions, interruptions, or discontinuation and the reasons, will be summarised by treatment group. These summaries will be repeated for the subset of patients who switch from investigators choice of NHA to olaparib.

These data will also be listed. Summary statistics (mean, standard deviation, median, quartiles, minimum, maximum) will be presented for RDI and PID.

4.2.11.5 Concomitant and other treatments

Concomitant medications will be summarized by the coded terms. The number of patients receiving a medication will be summarized for FAS by treatment group. A medication taken from the start of the screening part 2 and onwards is considered concomitant. A patient is only counted once if receiving the medication more than once.

For the purpose of inclusion in prior and/or concomitant mediation or therapy summaries, incomplete medication or radiotherapy start and stop dates will be imputed as detailed in Section 4.2.11.1.

The following summaries will be produced for all patients in the FAS by coded terms by treatment group:

- Summary of allowed concomitant medications
- Summary of disallowed medications

All concomitant and other treatment data will be listed. Missing coding terms should be listed and summarised as "Not coded".

4.2.11.6 Laboratory assessments

Laboratory data (clinical chemistry and haematology) will be summarized. Shift tables will be provided for select tests, where shift from baseline to the worst value within the study will be summarized. Laboratory data outside the reference ranges will be indicated.

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. For categorical laboratory assessments, shift from baseline will be summarised using frequency and proportion at each scheduled assessment time by actual treatment group.

For the derivation of baseline and post-baseline visit values, the definitions and rules described in Section 4.2.11.1 for visit windows and how to handle multiple records will be used.

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 on-treatment post dose value.

Shift tables for laboratory values by worst CTCAE grade will be produced, within each part of the study and overall, and for specific parameters separate shift tables indicating hyper- and hypo- directionality of change will be produced. CTCAE grades will be defined at each visit according to the CTCAE grading criteria using local ranges as required, after conversion of lab results to corresponding SI units. For parameters with no CTCAE grading, shift tables from baseline to worst value on-treatment will be provided (i.e., on-treatment is defined as data collected up until the last dose of olaparib/ investigators choice of NHA). The laboratory parameters for which CTCAE grade shift outputs will be included but not limited are:

- Hematology:
  - Hemoglobin – low
  - Leukocytes – low
  - Lymphocytes, absolute count - low and high
  - Neutrophils, absolute count – low
  - Platelets – low
- Clinical chemistry:
  - ALT - high
  - AST - high
  - ALP - high
  - Total bilirubin - high
  - Albumin - low
  - Magnesium – low and high

- Sodium – low and high
- Potassium – low and high
- Corrected calcium – low and high
- Creatinine - high
- Gamma-glutamyl transferase – high
- Amylase - high
- Lipase – high

Corrected calcium will be derived during creation of the reporting database using the following formula:

- Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 - albumin (g/L)] x 0.02)

Local reference ranges will be used throughout for reporting purposes. The denominator used in laboratory summaries of CTCAE grades will only include evaluable patients i.e., those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value
- If a CTCAE criterion does not consider changes from baseline, to be evaluable, patients would need only have 1 post dose-value recorded

A scatter plot of alanine aminotransferase (ALT) versus total bilirubin, both expressed as multiples of upper limit of normal range, will be produced. The scatter plot will be repeated for aspartate aminotransferase (AST) versus total bilirubin.

Shift tables and plots will be repeated for olaparib post switch from investigator choice, where the baseline is defined as the last observation before the first dose of olaparib (generally the measurement at the study treatment discontinuation visit).

4.2.11.7 Vital signs

Vital signs, including BP (mmHg), body temperature (°C), pulse (beats/minute) and weight(kg), will be summarized at baseline by treatment group.

4.2.12 Demographics and baseline characteristics

The following collected data will be listed.

Patient disposition (received treatment and completed the study)

Important deviations

Inclusion in analysis populations

Demographics (age, age group)

The following will be summarized for all patients in the FAS (unless otherwise specified) by treatment group:

Patient disposition (including screening failures and reason for screening failure)

Important protocol deviations

Inclusion in analysis sets

Demographics characteristics

Patient characteristics at baseline (height, weight, weight group)

Previous disease-related treatment modalities

Previous chemotherapy prior to this study

Previous/current/post treatment radiotherapy

Disease characteristics at baseline

Time from most recent disease progression to randomisation

Post-discontinuation disease-related anticancer therapy

Past/current medical history

Past medical history of opioid use

Relevant surgical history at baseline

The following will be summarized for patients who switch from investigators choice of NHA to olaparib:

Patient disposition

4.2.13 COVID-19 Impact

Depending on the extent of any impact, summaries of data relating to subjects diagnosed with coronavirus disease 2019 (COVID-19), and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued treatment, and other protocol deviations) may be generated, by treatment group, including:

- Disposition (withdrew study due to COVID-19)
- Important protocol deviations, including both COVID related and COVID unrelated IPDs
- Summary of COVID-19 disruption (visit impact, drug impacted)
- Listing for subjects affected by the COVID-19 pandemic
- Listing for subjects with reported issues in the Clinical Trial Management System due to the COVID-19 pandemic.

Additional analyses may be conducted to investigate the impact of COVID-19 on study endpoints, for example, sensitivity analyses may be performed to censor (or exclude) subjects who had a death with primary/secondary cause as COVID-19 infection or a COVID-19

infection reported as a fatal AE, whereby their COVID-19 infection death date would be used as the censor date.

5. INTERIM ANALYSES

No interim analysis for rPFS prior to the primary analysis will be performed. CCI [redacted]

Additional analyses of rPFS and/or OS may be performed to meet Regulatory Agency requests, as required.

6. CHANGES OF ANALYSIS FROM PROTOCOL

CCI [redacted] and summary analyses for DOR will not be performed due to the small sample size.

7. REFERENCES

Fleischer F, Gaschler-Markefski B, Bluhmki E. How is retrospective independent review influenced by investigator-introduced informative censoring: A quantitative approach. Stat Med. 2011; 30(29):3373-86

Gail M, Simon R. Testing for qualitative interactions between treatment effects and subject subsets. Biometrics. 1985; 41:361-72

Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, Akehurst RL, Campbell MJ. Adjusting survival time estimates to account for treatment switching in randomised controlled trials – an economic evaluation context: Methods, limitations and recommendations. Med Decis Making. 2014; 34(3):387-402

Sun X, Chen C. Comparison of Finkelstein's Method With the Conventional Approach for Interval-Censored Data Analysis. Stat Biopharm Res. 2010; 2:97-108

8. APPENDICES (NOT APPLICABLE)