Clinical Study Protocol	
Study Intervention	Olaparib
Study Code	D081LC00002
Version	3.0
Date	13 Apr 2023

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)

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s): Not applicable

This CSP has been subject to a peer review according to AstraZeneca Standard procedures. The CSP is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D081LC00002

Amendment Number: 2

Study Intervention: Olaparib

Study Phase: IV

Short Title: Clinical Study to Assess the Efficacy and Safety of Olaparib in Chinese Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have *BRCA1/2* Mutations

Acronym: PROfound-CN

Medical Monitor Name and Contact Information will be provided separately

International co-ordinating investigator Prof. Fangjian Zhou

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2 (Version 3.0)	[13-Apr -2023]
Amendment 1 (Version 2.0)	[12-Apr-2022]
Original Protocol (Version 1.0)	[01-Apr-2021]

Amendment 2 (13-Apr-2023)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.3 Schedule of Activities on Table 1 and Table 2 5.2 Exclusion Criteria 6.6.3 Management of Toxicities Related to Olaparib 8.2.4 Clinical Safety Laboratory Assessments Table 13 Laboratory Safety Variables Table 27 Definition of HBV Reactivation	Modify Exclusion Criteria 8, add new tests at screening and follow-up. Update toxicity management guidance for hepatitis B.	To broaden eligibility to allow patients with past/resolved or chronic hepatitis B to enter the study provided they meet certain pre-defined criteria, and to provide monitoring methods and toxicity management guidance for these participants. This change is based on the absence of hepatotoxicity or risk of hepatitis B reactivation for Olaparib monotherapy based on current knowledge and, therefore to permit more inclusive eligibility on this study.	Substantial
2.1.3 Olaparib	Update olaparib approval information in China.	Updated olaparib approval information in China.	Non-substantial
2.2.3 Overall Benefit:Risk Conclusion	Removal of data monitoring committee description.	Data monitoring committee is not applicable for this study.	Non-substantial
5.1 Inclusion Criteria	Inclusion Criteria 9: Correct the unit of Hemoglobin from g/L to g/dL.	Typo correction on the unit of Hemoglobin.	Non-substantial
5.2 Exclusion Criteria	Exclusion Criteria 6: Text regarding determination of participant eligibility updated.	Clarification needed to reinforce Investigator's sole accountability with determination of participant eligibility.	Non-substantial
5.2 Exclusion Criteria	Modify Exclusion Criteria 12, to clarify	To simplify description of	Non-substantial

	what kind of prior anti-cancer therapy will be prohibited.	previous treatment requirement.	
5.2 Exclusion Criteria	Updated requirement of prior palliative radiotherapy in Exclusion Criteria 13 .	According to general clinical practice.	Non-substantial
6.7 Continued Access to Study Intervention after the End of the Study 6.8 Treatment of Overdose 8.3.16 Reporting of Overdose	Update section name of 6.7. Separate "overdose" section into "6.8 Treatment of Overdose" and "8.3.16 Reporting of Overdose".	Clinical study protocol template update.	Non-substantial
8.3.15 Medication Error	Added Drug Abuse and Drug Misuse definition.	Be consistent with current AZ process.	Non-substantial
8.5.1.1 Mandatory Tumor Sample Collection	Retention period of remaining tissue samples changed from "maximally 5 years after study intervention is approved for marketing in China" to "within one year of CSR".	Be consistent with AZ requirements on sample retention in China.	Non-substantial
Appendix A1 Regulatory and Ethical Considerations	Added sub-heading "Regulatory Reporting Requirements for Serious Breaches".	Update required to comply with regulatory requirement (e.g. EU CTR) and global company requirement.	Non-substantial
Appendix A6 Dissemination of Clinical Study Data	Updated information about timelines for submission of trial results summaries to EU CTIS.	Update required to comply with EU CTR.	Non-substantial
Appendix A7 Data Quality Assurance	Updated information about retention timelines of records and documents to as required by local regulations.	Update required to comply with EU CTR and global company requirement.	Non-substantial
Appendix A7 Data Quality Assurance	Added text for Sponsor role in medical oversight and clinical reviews.	Added for completeness.	Non-substantial

Appendix B4 Medication Error	Added detailed Drug Abuse and Drug Misuse definition and examples.	Be consistent with current AZ process.	Non-substantial
Table 26 Supportive Medications/Therapies	Updated description of bone-targeted treatment.	According to general clinical practice.	Non-substantial

Amendment 1 (12-Apr-2022)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.1 Number of Participants	Add wording "approximately" before "42 participants".	For operation flexibility.	Non-substantial
Table 1 Study Schedule – Screening (Part 1 and 2)	Deleted empty line in this table.	Formatting issue in original protocol.	Non-substantial
2.2.1 Risk Assessment	Downgrade of pneumonitis from important potential risk to potential risk. And the addition of the new adverse drug reaction of venous thromboembolic events.	Changed based on Investigator Brochure Edition 21 updated information.	Non-substantial
Figure 1 Study Design	For stratification factors, clarify "measurable" as "measurable disease":	Clarify the stratification factor	Non-substantial
5.2 Exclusion Criteria	Correct the exclusion criteria number for criteria number 3 to number 6.	Formatting issues, 4-6 bullet points have been missed in original protocol.	Non-substantial
Table 6 Investigational Products	Change description "HDPE bottles with child resistant closures" to "blisters and cartons". Change "bottle" to "unit".	The Package of Olaparib changes from the bottle to carton and blister.	Non-substantial
Table 6 Investigational Products	Delete "c. Each dosing container will contain sufficient medication for at least each treatment period plus overage. Multiple bottles of study treatment will be required for dispensing in order to make up the desired dose".	Should be deleted, dispensing of drug is managed through the IRT.	Non-substantial
6.4 Study Intervention Compliance	Change "bottle" to "blisters and carton(s)" and "carton(s)".	The package of Olaparib changes from	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		the bottle to carton and blister.	
Table 13 Laboratory Safety Variables	Remove the "Total white blood cell count" in Table 13.	Both "Leukocyte count" and "Total white blood cell count" display in table 13, it is duplicate.	Non-substantial
8.3.2.3 Adverse Event Variables	Add NCI-CTCAE version number 5.0 in “Severity of AE”.	To clarify NCI-CTCAE version being used for this study.	Non-substantial
8.3.7 Disease Progression	Add section number “8.3.7” before section name.	Formatting issue, missing section information for this part.	Non-substantial
8.3.11 Adverse Events of Special Interest	Change wording “Adverse Events of Special Interest for olaparib are the Important Identified Risk of MDS/AML, and the Important Potential Risks of new primary malignancy (other than MDS/AML) and pneumonitis.” to “Adverse Events of Special Interest for olaparib are the Important Identified Risk of MDS/AML, the Important Potential Risk of new primary malignancy (other than MDS/AML) and the Potential Risk of pneumonitis.”	Changed based on Investigator Brochure Edition 21 updated information.	Non-substantial
9.2 Sample Size Determination	Add wording “approximately” before “42 randomly”.	For operation flexibility.	Non-substantial
Appendix D8 Laboratory Tests	Add wording "In this study, a local laboratory will be used for safety tests and the Hy’s Law Laboratory Kit for central laboratories is not applicable for this study. "	Central lab is not applicable for Hy’s Law test.	Non-substantial
Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation	Delete “Plain X-ray: Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.”	Bone lesions will not be included in the RECIST soft tissue assessment.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Criteria in Solid Tumors) in Soft Tissue and PCWG-3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions			
Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors) in Soft Tissue and PCWG-3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions	Delete "Bone lesions (see exception below for soft tissue component)." in "Non-measurable Lesions at Baseline"	Bone lesions will not be included in the RECIST soft tissue assessment.	Non-substantial
Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors) in Soft Tissue and PCWG-3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions	In "Special Considerations Regarding Lesion Measurability at Baseline", delete "Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions." Change wording "Blastic lesions are considered non-measurable" to "Blastic lesions are not part of the RECIST assessment and must be evaluated via PCWG3 (see page 120)."	Bone lesions will not be included in the RECIST soft tissue assessment.	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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)

Short Title: Clinical Study to Assess the Efficacy and Safety of Olaparib in Chinese Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have *BRCA1/2* Mutations

Rationale:

Olaparib (Lynparza™), originally developed by AstraZeneca, is a potent inhibitor of polyadenosine 5' diphosphoribose polymerase (PARP). PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing single-strand DNA breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to double-strand DNA breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HRR). Tumors with homologous recombination deficiencies, such as metastatic castration-resistant prostate cancer (mCRPC) in patients with *BRCA1*, *BRCA2, ATM* or other HRR gene mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available taxane-based chemotherapy regimens. In Study D081DC00007 (PROfound), 15 HRR genes were selected based on a mechanistic role in HRR and/or preclinical and clinical observations. For this study, only patients with *BRCA1* and *BRCA2* mutations will be included.

Mutations in the *BRCA* genes are the most prevalent HRR gene mutations in mCRPC (with BReast CAncer gene 2 [*BRCA2*] more prevalent than *BRCA1*). Enrichment of *BRCA1/2* mutations in advanced prostate cancer has been widely documented in the literature. *BRCA2* mutations are associated with a particular aggressive phenotype, leading to their high prevalence. A retrospective case-case analysis of *BRCA1/2* and ataxia telangiectasia mutated (*ATM*) germline mutations in advanced and low-risk localized prostate cancer patients indicated that mutation carrier status was significantly associated with a more advanced prostate cancer diagnosis and progression of the prostate cancer.

In 2018, prostate cancer was estimated to be the fifth/seventh most common cause of cancer death in men and the second/sixth most commonly newly diagnosed cancer in men, worldwide/in China, respectively. Most early-stage prostate cancer cases are amenable to curative therapy, however, advanced stages are life-threatening. Globally, for patients with metastatic disease, the 5-year survival rate is 31%. In China, nearly 54% of the disease is *de*

novo metastatic. For decades, androgen deprivation therapy has been the standard treatment for prostate cancer, achieved by surgical or medical castration. Post-castration, the development of castration-resistant prostate cancer (CRPC) is only a matter of time. Almost all patients dying from prostate cancer will have mCRPC with 90% of overall mortality in mCRPC patients due to the underlying malignant disease.

No single mCRPC standard of care (SoC) exists; the currently approved agents have not been developed for a post-new hormonal agent (NHA) setting. Upon progression on NHA therapy, the treatment effect of either a sequential NHA or taxane diminishes substantially. For patients who have progressed on an NHA who have not received taxane chemotherapy, median overall survival (OS) is approximately 8.6 to 12.5 months. Docetaxel may be administered as second-line therapy, however the efficacy of post-NHA docetaxel appears markedly reduced. Treatment with the NHA abiraterone had modest effect on efficacy (median OS 14.8 months) in mCRPC patients post-chemotherapy. Clinical practice in China is similar to that in Western countries, however, no standard second-line therapy is listed in the Chinese guidelines. Furthermore, for *BRCA*m mCRPC patients no targeted therapy is currently available in China as limited studies have been conducted in Chinese patients.

Subgroup analyses in participants with a *BRCA1* or *BRCA2* mutation from the PROfound study indicate that olaparib provides clinically meaningful and substantial benefit compared to investigator's choice of NHA: 6.8 month improvement in median rPFS (9.8 vs 3.0 months respectively; HR 0.22; 95% CI 0.15, 0.32), 5.7 month improvement in OS (median OS 20.1 vs 14.4 months respectively; HR 0.63; 95% CI 0.42, 0.95). Based on the PROfound study results, olaparib has been approved by the US FDA for adult patients with deleterious or suspected deleterious germline or somatic HRRm (including *BRCA*m) mCRPC, who have failed prior treatment with abiraterone or enzalutamide (de Bono et al 2020). In the EU and Japan, the approved indication is mCRPC patients with *BRCA1* or *BRCA2* mutation who have progressed following prior therapy that included a new hormonal agent. Given that no targeted therapy for *BRCA*m mCRPC is currently available in China due to limited studies conducted in this population and the efficacy results in the *BRCA*m population from PROfound, there is a clear rationale for evaluating the potential of olaparib for the treatment of Chinese *BRCA*m mCRPC patients who have failed prior treatment with a new hormonal agent.

Objectives and Endpoints

Objectives	Outcome measure
Primary	
To determine the efficacy (as assessed by rPFS) of olaparib in participants with mCRPC and deleterious or suspected deleterious *BRCA1*/2 mutations	rPFS by BICR assessment using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
Secondary	
To determine the efficacy (as assessed by ORR) of olaparib in participants with mCRPC and deleterious or suspected deleterious *BRCA1*/2 mutations	Confirmed ORR by BICR assessment in participants with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
To determine the efficacy (as assessed by OS) of olaparib in participants with mCRPC and deleterious or suspected deleterious *BRCA1*/2 mutations	Overall Survival (OS)
To further assess the efficacy of olaparib in participants with mCRPC and deleterious or suspected deleterious *BRCA1*/2 mutations	• Time from first dose to the first SSRE • Time from partial or complete response by BICR assessment in participants with measurable disease (RECIST 1.1) to progression (DoR) • Time from randomization to opiate use for cancer-related pain • Proportion of participants achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (PSA50 response) • Time from randomization to second progression by investigator assessment of radiological or clinical progression or death (PFS2)
Safety	
To evaluate the safety and tolerability of olaparib	Safety and tolerability will be evaluated in terms of AEs/SAEs, vital signs (including blood pressure and pulse), clinical laboratory results (including clinical chemistry/hematology parameters), and ECGs.

Overall Design

Disclosure Statement: This is a Phase IV, randomized, open-label, 2-arm, multicenter study assessing the efficacy and safety of olaparib compared with SoC (enzalutamide or abiraterone acetate) in Chinese men with mCRPC.

Participant Population:

The target population of interest in this study is participants with mCRPC who have failed prior treatment with a NHA and have *BRCA1/2* mutations.

Biomarker selection: All participants must have a documented tumor (tissue) qualifying mutation(s) in *BRCA1* or *BRCA2* (referred to as *BRCA1/2*), predicted to be deleterious or suspected deleterious. All participants must provide a formalin fixed and paraffin embedded (FFPE) tumor sample for tissue-based *BRCA1/2* mutation testing (China-based central testing lab).

Treatment setting: All participants must have mCRPC and have received and failed prior treatment with an NHA (eg, abiraterone acetate or enzalutamide). Prior receipt of other anti-prostate cancer therapies, including docetaxel, cabazitaxel, radium-223, and sipuleucel-T is permitted but not mandatory. Participants must not have received previous treatment with a DNA-damaging cytotoxic chemotherapy (eg, prior platinum-based chemotherapy and mitoxantrone are not permitted) or a PARP inhibitor, including olaparib.

Number of Participants:

Approximately 700 participants with mCRPC will be screened to achieve approximately 42 participants with *BRCA*m mCRPC randomly assigned to study intervention. Refer to Section 9.2 for further information.

Intervention Groups and Duration:

After all Part 1 eligibility criteria have been met, tissue will be submitted for *BRCA*m testing. Participants must have a confirmed qualifying *BRCA1/2* status to be eligible for the study. Following confirmation of eligibility during screening Part 2 (28-day screening period), enroled participants will be randomized in a 2:1 ratio to olaparib or to investigator's choice of NHA (enzalutamide or abiraterone acetate). Randomization will be stratified based on prior receipt of taxane chemotherapy (yes vs no) and presence of measurable disease at baseline (yes vs no).Participants in the olaparib group will receive olaparib 300 mg oral tablets, twice daily. Participants in the investigator's choice of NHA group will receive either enzalutamide 160 mg oral capsules/tablets once daily or abiraterone acetate 1000 mg oral tablets (plus prednisone 5 mg oral tablets twice daily). Participants will continue to receive study intervention until Blinded Independent Central Review (BICR)-assessed radiological progression, or after the date of data cut-off (DCO) for the primary analysis until investigator-assessed radiological progression, as long as they do not meet any of the criteria for treatment discontinuation.

Participants in the investigator's choice of NHA group will be permitted to switch to olaparib, upon objective radiological progression by BICR or, if after the date of DCO for the primary analysis, upon investigator-assessed radiological progression.

Participants may continue to receive olaparib as long as they are continuing to show clinical benefit, as judged by the investigator and in the absence of discontinuation criteria.

Follow-up of participants post discontinuation of study intervention:

After study intervention discontinuation, all participants will undergo an end-of-treatment visit (within 7 days of discontinuation) and will be followed up for safety assessments 30 (+ 7) days after their last dose of study intervention (ie, the safety follow-up visit).

Participants who have discontinued study intervention in the absence of objective radiological progression will be followed up with tumor assessments every 8 weeks (± 7 days) according to the Schedule of Activities (SoA) until radiological progression or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

In addition, after intervention discontinuation, all participants will be followed up for second progression and survival status every 12 weeks (± 14 days) from the date of randomization until death, withdrawal of consent, or the end of the study (ie, progression/survival follow-up), as per the SoA.

See Section 6.7 for a description of assessments following study DCOs.

Independent Data Monitoring Committee: No

Statistical methods

The primary analysis of radiological progression-free survival (rPFS) will be performed when approximately 21 rPFS events have occurred across both intervention groups (50% maturity). The hazard ratio (HR; olaparib vs. investigator choice) together with its corresponding 95% confidence interval (CI) and p-value (descriptive) will be presented (a HR less than 1 will favor olaparib). The HR for rPFS will be estimated using a Cox Proportional Hazards Model (with ties=Efron and the stratification variables previous taxane [yes, no] and measurable disease [yes, no] as covariates) and the 2-sided CI will be calculated using a profile likelihood approach. It is anticipated that this analysis will be performed 21 months after the first participant has been recruited. The key secondary endpoint of overall survival will be analyzed using the same methodology specified for the primary endpoint; objective response rate will be analyzed using a logistic regression model adjusting for the stratification variable.

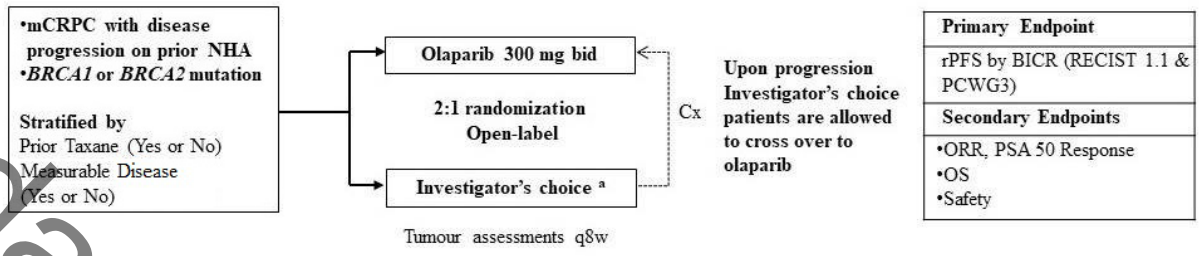
No formal testing of hypotheses will be performed as the study is designed to demonstrate the same trend of treatment effect in Chinese men as in the PROfound study, and thus no adjustment for multiplicity will be made.

Safety data will be summarized descriptively and will not be formally analyzed unless otherwise specified.

1.2 Schema

The study design diagram is provided in Figure 1.

Figure 1 Study Design

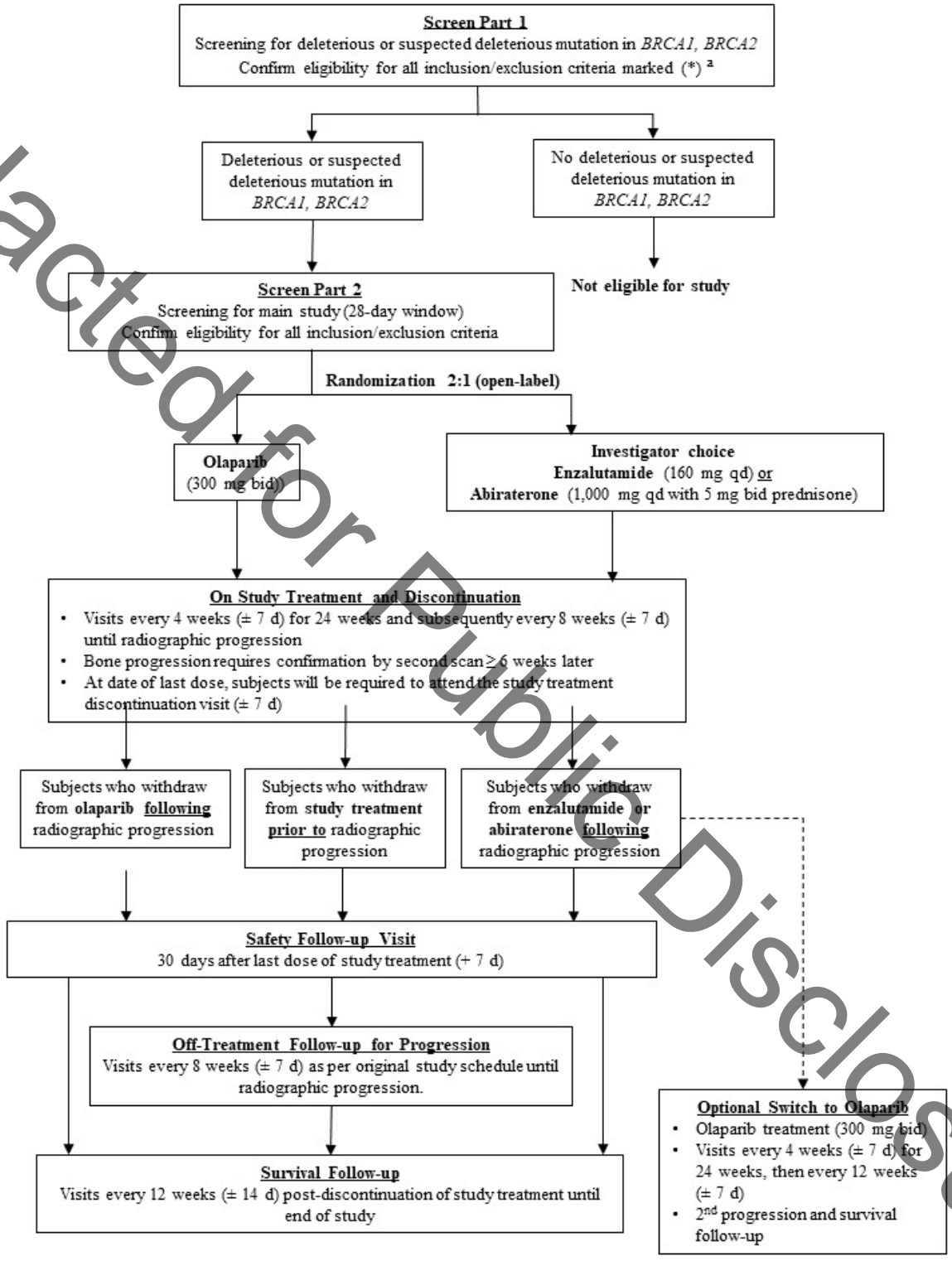


[a] Investigator's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid]).

1.3 Schedule of Activities

The study flow chart is provided in Figure 2. The procedures for this study are presented in the SoAs: screening - Part 1 and 2 (Table 1), on study treatment and discontinuation (Table 2), follow-up post discontinuation of study treatment (Table 3) and participants switching to olaparib (Table 4).

Figure 2 Study Flow Chart



[a] Sections 5.1 and 5.2.

Table 1 Study Schedule – Screening (Part 1 and 2)

	Part 1 All participants	Part 2
Day		**-28 to -1**
Informed consent	X	X
Demographics	X	
Medical and surgical history		X
Family history of cancer	X	
Prior cancer therapies including radiotherapy		X
Inclusion/exclusion criteria	X (all * criteria) [f]	X
ECOG Performance status (0-2)		X
Physical examination, body weight		X
Vital signs (includes BP, pulse, and temperature)		X
ECG		X
Hematology/clinical chemistry/coagulation [a]		X
Blood sample for testosterone		X
Urinalysis		X
Tumor tissue sample for *BRCA1/2* status [b c]	X	
HBs Ag, anti-HBc and anti-HBs		X
HBV DNA [h]		X
Tumor Assessment (Bone scan and CT/MRI) [d]		X
Adverse Events (from time of consent) [e]	X	X
Concomitant medications		X [g]

a Coagulation test should be performed at screening and if clinically indicated. For a list of all required laboratory tests please refer to Section 8.2.4.

b Participants must have a confirmed qualifying *BRCA 1/2* status based on the t*BRCA*m assay to be eligible for the study (Section 8.6.1).

c Tissue submitted for central *BRCA*m status testing with the t*BRCA*m assay only after all (*) eligibility criteria in Part 1 have been met.

d RECIST 1.1 assessments will be performed using CT scans of the chest, abdomen, and pelvis (or MRI where CT is contraindicated). Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual participants. Bone scans will be performed as detailed in Section 8.1.2, consistent with PCWG3 criteria. Baseline assessments should be performed no more than 28 days before the date of randomization, and ideally, should be performed as close as possible to the start of study treatment.

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

f See Sections 5.1 and 5.2 for marked eligibility (*) criteria.

g Includes all medication being taken from the start of screening part 2 and onwards.

h If either HBsAg or anti-HBc is positive, HBV DNA (viral load) must be tested at screening.

Table 2 Study Schedule – On Study Treatment and Discontinuation

Visit number	**2**	**3**	**4**	**5**	**6**	**7**	**Visit No. 8 onwards**	**Study treatment discontinued**	**Safety follow-up**
Week	**0 (Day 1)**	**4**	**8**	**12**	**16**	**20**	**24, and every subsequent 8 weeks**	**Last dose of study drug**	**30 days after last dose**
Visit window		**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**+ 7 d**
Randomization	X								
Physical exam, body weight [a]	X[b]								
Vital signs (includes BP, pulse and temperature) [a]	X[b]								
ECOG performance status	X	X	X	X	X	X	X	X	
ECG [a]	X[b]								
Hematology/clinical chemistry [c]	X[b]	X	X	X	X	X	X	X	X
HBV DNA, HBsAg [l]	Every 12 weeks (± 7 days) relative to the date of randomisation								X
Urinalysis [a]	X[b]								
Tumor Assessment (bone scan and CT/MRI) [d e]	Every 8 weeks (± 1 week) relative to the date of randomization until radiological progression							X[f]	
SSRE Assessment	X	X	X	X	X	X	X	X	
PSA [g]	X	X	X	X	X	X	X	X	
Adverse Events [h]	X	X	X	X	X	X	X	X	X
Concomitant medications including blood transfusions	X	X	X	X	X	X	X	X	X
Opioid use [i]	X	X	X	X	X	X	X	X	X
Study treatment dispensed/returned	X	X	X	X	X	X	X[j]	X	

Table 2 Study Schedule – On Study Treatment and Discontinuation

Visit number	**2**	**3**	**4**	**5**	**6**	**7**	**Visit No. 8 onwards**	**Study treatment discontinued**	**Safety follow-up**
Week	**0 (Day 1)**	**4**	**8**	**12**	**16**	**20**	**24, and every subsequent 8 weeks**	**Last dose of study drug**	**30 days after last dose**
Visit window		**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**± 7 d**	**+ 7 d**
Subsequent cancer therapy following discontinuation of study treatment [k]									X

a To be additionally performed if clinically indicated at any other time.
b If assessed within 7 days before randomization and meets the stated eligibility criteria (if applicable), it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.
c Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly. Coagulation test should be performed at screening and if clinically indicated. For a list of all required laboratory tests please refer to Section 8.2.4.
d Follow-up assessments will be performed every 8 weeks (± 7 days) relative to the date of randomization until radiological progression as assessed by BICR, and post primary analysis, as assessed by investigator. Whole body bone scan and CT/MRI of the chest, abdomen and pelvis should be conducted, and any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the participant has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.
e Bone progression observed by bone scan requires confirmation by bone scan at least 6 weeks later (see Section 8.1.2). Soft tissue progression observed by CT or MRI, according to RECIST 1.1 criteria, does not require a confirmatory scan.
f Patients who discontinue study treatment before disease progression should continue follow-up tumor assessments until objective disease progression as defined by RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), regardless of initiation of subsequent anticancer therapy.
g PSA values while on the study will not be reported to the site prior to final analysis.
h All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30 calendar days follow-up period after last dose of study medication must be followed to resolution .
i Opioid use will be captured by the site in the eCRF.
j Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to participants to last longer in accordance with local practice.
k All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigator's opinion of response to them, post discontinuation of study treatment need to be recorded.
l If either HBsAg or anti-HBc is positive at screening, HBV DNA and HBsAg must be tested every 12 weeks (± 7 days) relative to the date of randomisation during the interventional period and at 30-day safety follow-up. Refer to sections 5.2 and 8.2.4 for more detail.

Table 3 Study Schedule – Follow-up Post Discontinuation of Study Treatment

Visit number	**Off-treatment follow-up for progression** **For participants who discontinue therapy prior to radiological progression** [a]	**2nd Progression and survival follow-up** **Follow-up after radiological progression**
Visit frequency	**Every 8 weeks per original schedule until radiological progression**	**Every 12 weeks**
Visit window	**± 7 d**[a]	**± 14 d**
Adverse Events	X [b]	X [b]
Tumor Assessment (bone scan and CT/MRI)	X [c]	
Opioid use [d]	X [d]	X [d]
Secondary malignancies including MDS/AML [e]	X	X
Subsequent cancer therapy following discontinuation of study treatment [f]	X	X
Time to second progression [g]		X [g]
Survival [h]		X

a Visit schedule for participants who discontinue study treatment prior to radiological progression determined by BICR. This includes participants with ≥ 2 new lesions on a bone scan that has not been confirmed by a second scan ≥6 weeks later (see Section 8.1.2). Visits continue every 8 weeks (± 7 days) per original study schedule until documentation of radiological progression as assessed by BICR. Following radiological progression participants move to follow-up for 2nd progression and survival with visits every 12 weeks (± 14 days) relative to the randomization date. Until the primary rPFS analysis all imaging assessment and study treatment should continue until objective disease progression as assessed by BICR. 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 radiological progression will prevail.

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

c Imaging assessments (CT/MRI and bone scan) will be performed as per the original schedule every 8 weeks (± 7 days) relative to date of randomization until radiological progression as assessed by BICR and post primary analysis, by investigator. Bone progression observed by bone scan requires confirmation by bone scan at least 6 weeks later (see Section 8.1.2). Soft tissue progression observed by CT or MRI, according to RECIST 1.1 criteria, does not require confirmation.

d Opioid use will be captured by the site in the eCRF. After treatment discontinuation, only participants with no on-treatment opioid use need to be followed until first opioid use. Continued use does not need to be recorded.

e Since some cases of MDS/AML or new primary malignancies develop after discontinuing treatment with olaparib, investigators will be asked during the regular follow-up if the participant has developed MDS/AML or a new primary malignancy and prompted to report any cases as a SAE (or AE if at least one of the criteria for SAE is not met, such as for non-melanoma skin cancers, see Appendix B 2) even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm (see Sections 8.3.11 and 8.3.2.1).

f All anti-cancer treatments post discontinuation of study treatment (including, but not limited to, chemotherapy and targeted agents), and the investigator's opinion of response need to be recorded.

g Second progression is based on investigator assessment according to local standard clinical practice and includes both radiological and clinical progression. Second progression status will be reviewed every 12 weeks following the progression event used for the primary variable PFS (ie, first progression).

h The status of ongoing, withdrawn (from the study) and "lost to follow-up" participants at the time of an overall survival analysis should be obtained by the site personnel by checking the participants notes, hospital records, contacting the participants general practitioner and checking publicly available death registries, if allowable per local regulations. In the event that the participant has actively withdrawn consent to the processing of their personal data the vital status of the participant can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 7.1.1). In addition to their regular 12 weekly contact, participants will be contacted in the 7 days following a specified date (data cut-off date) for the survival analysis.

Table 4 Study Schedule – Participants Switching to Olaparib Following Radiological Progression

Visit number	**Switch to olaparib treatment visits**	**Treatment discontinued**	**Safety follow-up**	**2nd Progression and survival follow-up**
Visit Frequency	**Every 4 weeks for 24 weeks, then every 12 weeks [a]**	**Date last dose of olaparib**	**30 days after last dose of olaparib**	**Every 12 weeks after last dose of olaparib**
Visit window	**± 7 d**	**± 7 d**	**+ 7 d**	**± 14 d**
Switch to olaparib ICF	X			
Physical exam, body weight [b]	X [b]			
Vital signs (includes BP, pulse and temperature) [b]	X [b]			
ECG [b]	X [b]			
Hematology/clinical chemistry	X	X	X	
Urinalysis [b]	X [b]			
HBV DNA, HBsAg	X every 12 weeks (if either HBsAg or anti-HBc is positive)		X	
Adverse Events [c]	X	X	X	
Concomitant medications including blood transfusions	X	X	X	
Opioid use [d]	X [d]	X [d]	X [d]	X [d]
Study treatment dispensed/returned	X			
Subsequent cancer therapy following discontinuation of randomized treatment [e]	X	X	X	X
Secondary malignancies including MDS/AML [f]	X	X	X	X
Second Progression [g]	X	X		X
Survival [h]	X	X	X	X

a Visit schedule for participants who switch to olaparib post BICR-assessed radiological progression or post primary analysis by investigator-assessed radiological progression. Visits every 4 weeks (± 7 days) for 24 weeks following initiation of olaparib, then visits every 12 weeks (± 14 days).

b Only required at initiation of olaparib treatment. To be additionally performed if clinically indicated at any other time.

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

d Opioid use will be captured by the site in the eCRF. After treatment discontinuation, only participants with no on-treatment opioid use need to be followed until first opioid use. Continued use does not need to be recorded.

e All anti-cancer treatments post discontinuation of study treatment (including, but not limited to, chemotherapy and targeted agents), and the investigator's opinion of response need to be recorded.

f Since some cases of MDS/AML or new primary malignancies develop after discontinuing treatment with olaparib, investigators will be asked during the regular follow-up if the participant has developed MDS/AML or a new primary malignancy and prompted to report any cases as a SAE (or AE if at least one of the criteria for SAE is not met, such as for non-melanoma skin cancers, see Appendix B 2) even after discontinuation of therapy and regardless of investigator's assessment of causality or knowledge of the treatment arm (see Sections 8.3.11 and 8.3.2.1).

g Second progression is based on investigator assessment according to local standard clinical practice and includes both radiological and clinical progression. Second progression status will be reviewed every 12 weeks following the progression event used for the primary variable PFS (ie, first progression).

h The status of ongoing, withdrawn (from the study) and "lost to follow-up" participants at the time of an overall survival analysis should be obtained by the site personnel by checking the participants notes, hospital records, contacting the participants general practitioner and checking publicly available death registries, if allowable per local regulations. In the event that the participant has actively withdrawn consent to the processing of their personal data the vital status of the participant can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 7.1.1). In addition to their regular 12 weekly contact, participants will be contacted in the 7 days following a specified date (data cut-off date) for the survival analysis.

2 INTRODUCTION

Olaparib (Lynparza™, AZD2281, KU-0059436) is a potent polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

2.1 Study Rationale

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing single-strand DNA breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to double-strand DNA breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HRR). Tumors with homologous recombination deficiencies (HRD), such as metastatic castration-resistant prostate cancer (mCRPC) in patients with BReast CAncer gene 1 (*BRCA1*), *BRCA2*, ataxia telangiectasia mutated (*ATM*) or other HRR gene mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available taxane-based chemotherapy regimens.

BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo (Hay et al 2009, Rottenberg et al 2008) and in the clinic (Fong et al 2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011, Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HRR. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

In the Study D081DC00007 (PROfound), the following 15 HRR genes were selected based on a mechanistic role in HRR and/or pre-clinical and clinical observations: *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L*. For PROfound-CN (this study), only patients with *BRCA1* and *BRCA2* mutations will be included, as justified below.

Mutations in the *BRCA* genes (*BRCA1* and/or *BRCA2*) are the most prevalent HRR gene mutations in mCRPC (with *BRCA2* more prevalent than *BRCA1*) (Armenia et al 2018, Chung et al 2019, Mateo et al 2015, Robinson et al 2015). Enrichment of *BRCA1/2* mutations in advanced prostate cancer has been documented in the literature by several studies (Abida et al 2017, Armenia et al 2018, Chung et al 2019, Mateo et al 2018). The high representation of

BRCA2 mutations in advanced/metastatic prostate cancer is considered to be a consequence of *BRCA2* mutations being associated with a particular aggressive phenotype (Castro et al 2015, Cheng et al 2015, Mateo et al 2018, Pritchard et al 2016) rather than these mutations being acquired under treatment with standard therapies (eg, androgen receptor mutations and amplifications [Mateo et al 2018]). Moreover, when *BRCA1/2* and *ATM* germline mutations were analyzed in a retrospective case-case study of advanced and low-risk localized prostate cancer patients, the mutation carrier status was significantly associated with both a more advanced prostate cancer diagnosis and progression of the prostate cancer itself (Na et al 2017).

In summary, there is a high unmet medical need for treatment for mCRPC patients with *BRCA* mutations in China.

AstraZeneca considers that the advanced castration-resistant prostate cancer patient population involved in this study falls under the advanced cancer limited life expectancy definition outlined in ICH S9 guideline "Nonclinical Evaluation For Anticancer Pharmaceuticals" and meets the requirements outlined in the guideline.

2.1.1 *BRCA*m Metastatic Castration-resistant Prostate Cancer

Worldwide in 2018, prostate cancer was estimated to be the fifth most common cause of cancer death in men (358,989 deaths) and the second most commonly newly diagnosed cancer in men (1,276,106 new cases) (Globocan 2018). While the majority of prostate cancer cases are amenable to curative therapy if detected early, advanced stages constitute life-threatening disease. For patients diagnosed with metastatic disease, the 5-year survival rate is 31% (American Cancer Society 2020, Siegel et al 2020). Nearly 54% of the disease is de novo metastatic in China (Ma et al 2008). For decades, androgen deprivation therapy has been the standard treatment for prostate cancer, which can be achieved either by surgical or medical castration. However, post castration, the development of CRPC is only a matter of time. Almost all patients dying from prostate cancer will have mCRPC, and 90% of overall mortality in mCRPC patients is attributable to the underlying malignant disease (Scher et al 2015).

In China, prostate cancer is the seventh most common cause of cancer death in men (51,895 deaths) and the sixth most commonly newly diagnosed cancer in men (99,322 new cases) (Globocan 2018). There are very limited data on the prevalence of *BRCA* mutations in Chinese patients with mCRPC. According to reports from Wei Y et al and Na R et al, the germline mutation prevalence of *BRCA1/2* and *ATM* ranged from 7.55% to 18.18%. It should be noted that both studies had a limited sample size (53 and 22 patients, respectively). (Na et al 2017, Wei et al 2018).

2.1.2 Current Treatment Options

Currently, no clear single standard of care (SoC) for mCRPC exists as none of the currently approved agents have been developed for a post-new hormonal agent (NHA) setting. Once the disease progresses on NHA therapy, the treatment effect of either another sequential NHA or taxane diminished substantially. The median overall survival (OS) of patients who have progressed on an NHA but who have not previously received taxane chemotherapy appears to be between 8.6 months and 12.5 months (Azad et al 2015, Mezynski et al 2012), reflecting a high unmet medical need from CRPC patients for whom NHA has failed. Docetaxel may be administered as secondline therapy. The efficacy of docetaxel appears markedly reduced when given after NHA as compared to first-line use (Mezynski et al 2012, Schweizer et al 2014), likely attributable to at least partial cross-resistance between taxanes and NHA (van Soest et al 2013). Similarly, NHA treatment with abiraterone had modest effect on efficacy (median OS of 14.8 months) in mCRPC patients post chemotherapy (de Bono et al 2011). Based on the results of Study D081DC00007 (PROfound), olaparib has been approved by the US FDA for adult patients with deleterious or suspected deleterious germline or somatic HRRm (including *BRCA*m) mCRPC, who have failed prior treatment with abiraterone or enzalutamide (de Bono et al 2020). In the EU and Japan, the approved indication is mCRPC patients with *BRCA1* or *BRCA2* mutation who have progressed following prior therapy that included a new hormonal agent.

Clinical practice in China is similar to that in Western countries. In China, both chemotherapy with docetaxel and NHA (eg, abiraterone) are widely used in the first line treatment of mCRPC.

Based on a subgroup analysis of the D081DC00007 (PROfound) study, which showed that olaparib demonstrated a substantial improvement in radiographic progression-free survival (rPFS) and overall survival (OS) versus abiraterone or enzalutamide in men with BRCA1/2 mutations, olaparib has been granted conditional approval in China to treat adult patients with germline or somatic BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following treatment that included a new hormonal agent (abiraterone, enzalutamide).PROfound-CN (this study) is a planned bridging trial with Chinese patients for continued approval.

2.1.3 Olaparib

Olaparib (Lynparza™), originally developed by AstraZeneca, is a potent inhibitor of PARP, which, compared to normal cells, kills cancer cells with DNA repair pathway deficiencies by using these defects. Olaparib traps PARP at the sites of DNA SSBs damage and prevents its repair (Murai et al 2012). During replication, the SSBs trapped with PARP are converted to DNA DSBs. DSBs are normally repaired by HRR, which is a high-fidelity process. In cancer cells with homologous recombination deficiency (HRD), DSBs cannot be effectively repaired resulting in preferential killing of cancer cells over normal cells. Defects in *BRCA1* or *BRCA2*

(key HRR proteins) lead to the increase of sensitivity to PARP inhibitors (Farmer et al 2005). Several clinical trials are evaluating the efficacy of olaparib (monotherapy or combination therapy) in cancers with HRD including *BRCA1 or BRCA2* mutations (germline and somatic).

Olaparib capsules were approved in December 2014 by the US FDA and the European Commission. The majority of completed studies were performed with olaparib capsules; however most new olaparib studies, including Phase III registration studies and all studies in China, are being performed with olaparib tablets.

In China, olaparib monotherapy is approved for the maintenance treatment of platinum-sensitive relapsed (PSR) ovarian cancer (August 2018; SOLO2) and first-line maintenance treatment of *BRCA*m ovarian cancer (November 2019; SOLO1). Olaparib in combination with bevacizumab is approved as first-line maintenance treatment for adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status (September 2022; PAOLA-1).

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of olaparib is provided in the IB/prescribing information.

2.2 Benefit:Risk Assessment

2.2.1 Risk Assessment

Data from the available pre-clinical studies and subsequent clinical development programme demonstrate that olaparib appears to be active and generally well tolerated in patients with solid tumors including those with *BRCA*m cancers. In ovarian cancer, responses have been seen in all patient groups, including platinum resistant and refractory cancer.

From the available data to date in patients with advanced cancer, there is no evidence of any unexpected toxicity following long-term olaparib monotherapy exposure.

Adverse laboratory findings and/or clinical diagnoses considered to be causally associated with administration of olaparib monotherapy include hematological effects (anemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean corpuscular volume [MCV] elevation), nausea and vomiting, decreased appetite, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash, dermatitis, cough, dyspnea, angioedema, myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML), erythema nodosum and venous thromboembolic events.

MDS/AML is an important identified risk for olaparib that occurs uncommonly in patients on treatment and during the 30-day safety follow-up, and < 1.5% at any time after starting

olaparib, including cases actively solicited during the long-term follow-up for OS. In the majority of cases, the event is fatal. The risk of MDS/AML is greatest in patients with PSR ovarian cancer and a higher chemotherapy burden at baseline. Considering the benefits of olaparib, this risk is not considered to impact the positive benefit risk profile of olaparib across the indications.

In a relatively small number of patients, pneumonitis (potential risk) and new primary malignancies (important potential risk) have been observed. Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These events remain adverse events of special interest (AESI) for olaparib and are being kept under close surveillance. Similarly, MDS/AML remains an AESI, despite being considered an adverse drug reaction, and is still subject to additional reporting requirements.

Furthermore, the safety and tolerability profile of olaparib in the Study D081DC00007 (PROfound), was consistent with the known safety and tolerability profile of olaparib and considered to be acceptable in men with mCRPC who had failed prior treatment with a NHA and had HRR gene mutations.

2.2.2 Benefit Assessment

In Study D081DC00007 (PROfound), subgroup analyses indicated the greatest efficacy benefit of olaparib in the *BRCA*m subgroup compared to other subgroups. Subgroup analyses in participants with a *BRCA1* or *BRCA2* mutation indicated that olaparib provides clinically meaningful and substantial benefit compared to investigator's choice of NHA: 78% reduction in risk of progression of disease (PD) or death with median radiological progression-free survival (rPFS) of 9.8 months for the olaparib group compared with median rPFS of 3.0 months for the investigator's choice of NHA group (hazard ratio [HR] 0.22; 95% confidence interval [CI] 0.15, 0.32); substantial improvement in confirmed objective response rate (ORR; 43.9% with olaparib vs 0% with NHA), 37% reduction in risk of death and 5.7 month improvement in OS (median OS 20.1 vs 14.4 months respectively; HR 0.63; 95% CI 0.42, 0.95). Considering that 69% of participants in the NHA arm received olaparib as a subsequent treatment following PD, the analysis of OS adjusting for investigator's choice of NHA-treated participants receiving subsequent olaparib further supports the clinical benefit of olaparib observed (HR 0.29; 95% CI 0.10, 0.86). These results suggest that the true effect of olaparib is likely to be greater than observed in the unadjusted final OS analysis.

Furthermore, subgroup analysis in the Asian population indicated a consistent treatment effect compared with global population in terms of rPFS, OS and ORR. In addition, a trend of substantial improvement of ORR, rPFS and OS for Asian participants with a *BRCA1* or *BRCA2* mutation was maintained with more than 1 year median OS improvement with olaparib treatment compared to NHA.

2.2.3 Overall Benefit:Risk Conclusion

Results of subgroup analyses from the PROfound study indicate that the *BRCA*m subgroup of mCRPC participants are considered sensitive to olaparib, that olaparib is anticipated to be effective for Chinese *BRCA*m mCRPC participants and a similar olaparib safety profile in Global and Asian *BRCA*m participants. Therefore, as olaparib has been found to be well tolerated across various cancer entities including the PROfound study, a positive benefit/risk profile is expected and no ethical issues are identified from exposing participants to olaparib within the planned registration trial.

More detailed information about the known and expected benefits and risks of olaparib may be found in the current version of the olaparib IB/prescribing information.

The emergence of the novel coronavirus disease 2019 (COVID-19) could present a potential risk for participants. Risk mitigation factors have been implemented related to study conduct during the COVID-19 pandemic (see Appendix H) and for patient management in an event of COVID-19 infection and actions to be taken on study treatment administration (see Appendix I).

3 OBJECTIVES AND ENDPOINTS

Table 5 Objectives and Endpoints

Objectives	Outcome measure
Primary	
To determine the efficacy (as assessed by rPFS) of olaparib in participants with mCRPC and deleterious or suspected deleterious *BRCA1*/2 mutations	rPFS by BICR assessment using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
Secondary	
To determine the efficacy (as assessed by ORR) of olaparib in participants with mCRPC and deleterious or suspected deleterious *BRCA1*/2 mutations	Confirmed ORR by BICR assessment in participants with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria
To determine the efficacy (as assessed by OS) of olaparib in participants with mCRPC and deleterious or suspected deleterious *BRCA1*/2 mutations	Overall Survival (OS)
To further assess the efficacy of olaparib in participants with mCRPC and deleterious or suspected deleterious *BRCA1*/2 mutations	• Time from first dose to the first SSRE • Time from partial or complete response by BICR assessment in participants with measurable disease (RECIST 1.1) to progression (DoR) • Time from randomization to opiate use for cancer-related pain • Proportion of participants achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline 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)
Safety	
To evaluate the safety and tolerability of olaparib	Safety and tolerability will be evaluated in terms of AEs/SAEs, vital signs (including blood pressure and pulse), clinical laboratory results (including clinical chemistry/hematology parameters), and ECGs.

4 STUDY DESIGN

4.1 Overall Design

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

Eligible participants will have histologically confirmed mCRPC; *BRCA*m status will be confirmed by central testing of tumor tissue.

Approximately 42 participants 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).

All participants must have mCRPC and have received and failed prior treatment with an NHA (eg, abiraterone acetate or enzalutamide). Prior receipt of other anti-prostate cancer therapies, including docetaxel, cabazitaxel, radium-223, and sipuleucel-T is permitted but not mandatory. Participants must not have received previous treatment with a DNA-damaging cytotoxic chemotherapy (eg, prior platinum-based chemotherapy and mitoxantrone are not permitted) or a PARP inhibitor, including olaparib.

All participants must have a documented tumor (tissue) qualifying mutation(s) in *BRCA1* or *BRCA2* (referred to as *BRCA1/2*), predicted to be deleterious or suspected deleterious. All participants must provide a formalin fixed and paraffin embedded (FFPE) tumor sample for tissue-based *BRCA1/2* mutation testing (China-based central testing lab).

Participants will receive study intervention until BICR-assessed radiographic progression or, if after the date of DCO for the primary analysis, until investigator-assessed radiological progression.

Subjects Who Switch to Olaparib

Once participants receiving investigator's choice of NHA are determined to have objective radiological progression by Blinded Independent Central Review (BICR) or, if after the date of DCO for the primary analysis, participants are determined to have radiological progression by the investigator, they will be eligible to receive olaparib (300 mg bid), see Section 6.1 for further details.

4.2 Scientific Rationale for Study Design

Based on data from the TOPARP A study (Mateo et al 2015) a decision was made for Study D081DC00007 (PROfound) to require the presence of a qualifying tissue HRR gene mutation as an inclusion criterion for participants with mCRPC who have failed prior therapy with an NHA. Subjects in Cohort A had gene mutations in either *BRCA1, BRCA2,* or *ATM* whereas subjects in Cohort B had mutations in *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* or *RAD54L.*

The rationale for only using *BRCA1* and *BRCA2* in this study in Chinese men, is based upon the prevalence of these mutations and/or how well mutations in these genes are characterized to date. It is expected that qualifying mutations will be detectable in the tissue of about one out of 10 mCRPC participants. Additionally, based on results from Study D081DC00007 (PROfound) it is anticipated that olaparib will be effective in Chinese *BRCA*m mCRPC participants (Section 2.2).

The other main design elements of this study will be consistent with Study D081DC00007 (PROfound). While the TOPARP A trial was limited to participants who had failed both NHA and a taxane, this study (like Study D081DC00007 [PROfound]) will also enroll patients not yet having received taxane chemotherapy for mCRPC as there is a medical need for participants failing NHA both pre- and post-taxane (see Section 2.1.2) and as the biological activity of olaparib is expected to be independent of prior taxane therapy. In Study D081DC00007 (PROfound), both participants with previous taxane use (72/106 [67.9%]) and no previous taxane use (34/56 [60.7%]) experienced clinical benefit with olaparib treatment.

The randomization will be 2:1 (olaparib vs. enzalutamide or abiraterone acetate). Enzalutamide and abiraterone acetate were chosen as comparators for the following reasons:

- Enzalutamide and abiraterone acetate are broadly approved for the treatment of mCRPC. Switch to the alternate NHA mirrors a relevant real-world scenario for a situation in which no single standard of care exists (Vogelzang et al 2016).
- Similar efficacy compared to docetaxel in post-NHA setting (Sun and Chen 2010 and Suzman et al 2014), but oral availability and superior tolerability compared to taxanes make them the preferred treatment of choice.
- Documented effectiveness both pre and post docetaxel (Beer et al 2014, de Bono et al 2011, Ryan et al 2013 and Scher et al 2012).

Due to the open-label design of the study, rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with the primary analysis of rPFS based on BICR of all scans. Also, acknowledging the bone predominance of mCRPC and the particular challenges of determining bone progression in participants with high skeletal tumor burden

(Kluetz et al 2013), progression in bone will require confirmation by a repeat scan at least 6 weeks later as outlined in detail by Prostate Cancer Working Group 3 (PCWG3) criteria (Scher et al 2016).

4.2.1 Rationale for the t*BRCA*m Assay in China

In Study D081DC00007 (PROfound), the molecular analysis was performed by a designated central diagnostic provider (Foundation Medicine, Inc.) using a next-generation sequencing (NGS) assay, the investigational Lynparza HRR Assay.

In this study, *BRCA1/2* mutation testing will be performed using an investigational tumor tissue-based NGS assay (t*BRCA*m assay - formal name to be confirmed in the clinical study report [CSR]) at a central testing laboratory. The assay has been evaluated and shown high concordance with the assay used in Study D081DC00007 (PROfound).

4.3 Justification for Dose

The dose used in TOPARP A (400 mg tablets bid) was chosen at a time when information on the relative clinical activity with the tablet formulation was not fully complete; as a 300 mg bid tablet dose is now considered maximally effective, is used across the ongoing olaparib development program, and is currently approved, this dose was chosen for Study D081DC00007 (PROfound) and subsequently for this study.

4.4 End of Study Definition

A participant is considered to have completed the study if he has completed all phases of the study including the last visit.

The study may be stopped if, in the judgment of AstraZeneca, study participants are placed at undue risk because of clinically significant findings.

The end of the study is defined as the date of the last visit of the last participant in the study.

See Section 6.7 for details on participant management following the final DCO as well as following study completion.

5 STUDY POPULATION

The target population of interest in this study is Chinese men with mCRPC who have failed prior treatment with a NHA and have a qualified *BRCA1/2* mutation in their tumor sample.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Participants who do not meet the eligibility criteria requirements are screen failures; refer to

Section 5.4.

5.1 Inclusion Criteria

Patients that already know they have a mutation in *BRCA1* or *BRCA2* gene that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) must fulfil all of the criteria below. Patients that do not know their mutation status, and who are being considered for this trial should be identified early so that the appropriate *BRCA* mutation screening procedures can be put in place in a timely manner. Patients that do not know their *BRCA* mutation status must fulfil all of the criteria marked with an asterisk (*) below prior to *BRCA* mutation testing being carried out. Prior to performing the *BRCA* testing, an investigator judgement of a patient's potential eligibility for the study should be made according to details within Table 1 and by reviewing the inclusion/exclusion criteria. All inclusion criteria will then be assessed following confirmation that they harbor an appropriate *BRCA* mutation.

Any patients that fulfil the eligibility criteria for the *BRCA* test, are required to have their eligibility assessed again prior to randomization.

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 *Participant must be ≥18 years at the time of screening.

Type of Participant and Disease Characteristics

2 *Histologically confirmed diagnosis of prostate cancer.

3 *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 computed tomography (CT)/magnetic resonance imaging (MRI) scan. Participants whose disease spread is limited to regional pelvic lymph nodes or local recurrence (eg, bladder, rectum) are not eligible.

4 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.

5 Serum testosterone levels ≤ 50 ng/dL (≤ 1.75 nmol/L) within (≤) 28 days before randomization.

6 *Participants without prior surgical castration must be currently taking and willing to continue luteinizing hormone-releasing hormone (LHRH) analog (agonist or antagonist) therapy throughout the duration of study treatment.

7 Radiological progression at study entry while on androgen deprivation therapy (or after bilateral orchiectomy). Determination of progression is done per local investigator.

8 Deleterious or suspected deleterious *BRCA1/2* mutation in tumor tissue (see Section 8.6.1).

9 Participants must have normal organ and bone marrow function measured within (≤) 28 days prior to administration of study treatment as defined below

- Hemoglobin ≥ 10.0 g/dL with no blood transfusions in the past 28 days.
- Absolute neutrophil count (ANC) ≥ 1.5×10^9/L.
- Platelet count ≥ 100×10^9/L.
- Total bilirubin (TBL) ≤ 1.5 × upper limit of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN; for participants with hepatic metastases, ALT and AST ≤ 5 × ULN.
- Calculated creatinine clearance (CrCL) of ≥51 mL/min, as determined by Cockcroft-Gault (using actual body weight) or based upon a 24-hour urine test or another validated test as per local practice

$$\text{Estimated CrCL} = \frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$$

10 *Eastern Cooperative Oncology Group (ECOG) performance status 0-2 with no deterioration over the previous 2 weeks prior to baseline or day of first dosing. (Section 8.2.5.1).

11 *Minimum life expectancy of ≥ 16 weeks.

Sex

12 *Male

Reproduction

13 Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

14 Non-sterilized male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Appendix F) from Cycle 1 Day 1 throughout the total duration of the study and for 3 months after the last dose of study intervention to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Female partners of male participants should also use a highly effective form of contraception (see Appendix F) if they are of childbearing potential.

Informed Consent

15 *Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled (any asterisked* are also applicable as an exclusion criteria for patients that are being screened to determine their BRCA mutation status via central testing); to perform the BRCA testing, investigator judgement of patient's potential eligibility to the study should be assessed as per the SoA and by reviewing the exclusion criteria.

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 *As judged by the investigator, any evidence of a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection (examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent [within 3 months] myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high resolution CT scan or any psychiatric disorder) which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the protocol.

2 *Refractory nausea and vomiting, chronic gastrointestinal disease or inability to swallow the formulated product that would preclude adequate absorption, distribution, metabolism, or excretion of olaparib.

3 *History of another primary malignancy except for malignancy treated with curative intent with no known active disease for ≥5 years before the first dose of study intervention and of low potential risk for recurrence. Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy and ductal carcinoma in situ.

4 *Participants with MDS/AML or with features suggestive of MDS/AML.

5 Resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.

6 *Persistent toxicities (Common Terminology Criteria for Adverse Events [CTCAE] Grade >2) caused by previous anticancer therapy, excluding alopecia or toxicities related to the use of LHRH agonist or antagonist. Participants with irreversible toxicity that is not reasonably expected to be exacerbated by study intervention in the opinion of the Investigator may be included (eg, hearing loss).

7 *Spinal cord compression or brain metastases unless asymptomatic, stable, and not requiring steroids for at least 4 weeks prior to start of study intervention.

8 *Participants with known active hepatis (ie, heptaitis B or C), participants are eligible if they

a. Are negative for HBsAg (HBV surface antigen) and anti-HBc (hepatitis B core antibody) or

b. Are anti-HBc positive, HBs-Ag negative (past, resolved hepatitis B), and have undetectable HBV DNA viral load or

c. Are HBsAg positive(chronic hepatitis B), and meet all of the conditions below:

i. HBV DNA viral load < 2000 IU/mL

ii. Have normal aminotransferase values, or, if liver metastases are present, abnormal aminotransferase, with a result of AST/ALT < 3 × ULN, which are not attributable to HBV infection.

Note: any participants with chronic hepatitis should be under the care of a hepatologist as per local standard practice.

Participants positive for hepatitis C virus (HCV) antibody are eligible only if PCR negative for HCV RNA.

9 *Immunocompromized participants, eg, those who are known to have tested positive for human immunodeficiency virus (HIV) or active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiological findings, or tuberculosis testing in line with local practice).

Prior/Concomitant Therapy

10 *Any previous treatment with PARP inhibitor, including Olaparib.

11 *Any previous treatment with DNA-damaging cytotoxic chemotherapy, except if for non-prostate cancer indication and last dose > 5 years prior to randomization. For example, participants who have received prior mitoxantrone or platinum-based chemotherapy for prostate cancer are excluded.

- Prior estramustine is allowed

12 Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment. (Bone-targeted therapy with denosumab or zoledronic acid is allowed.)

13 Patients who receive palliative radiotherapy need to stop radiotherapy 1 week before randomisation.

14 Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 3 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

15 *Concomitant use of known strong cytochrome P450 (CYP)3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks (see Appendix G).

16 *Concomitant use of known strong (eg, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's wort) or moderate CYP3A inducers (eg, bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents (see Appendix G).

17 *Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

Prior/Concurrent Clinical Study Experience

18 *Previous randomization in the present study.

19 Exposure to an investigational product within 30 days or five half-lives (whichever is the longer) prior to randomization.

20 *Participants with a known hypersensitivity to any of the agents included in the study intervention, including olaparib, any of the excipients of olaparib or the comparator agent.

Diagnostic assessments

21 Subjects inevaluable for both bone and soft tissue progression as defined by meeting both of the following criteria:

- A bone scan referred to as a superscan showing an intense symmetric activity in the bones.
- No soft tissue lesion (measurable or non-measurable) that can be assessed by Response Evaluation Criteria in Solid Tumors (RECIST).

Other Exclusions

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

23 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

5.3 Lifestyle Considerations

Restrictions relating to concomitant therapies are described in Appendix G.

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after.

5.3.1 Meals and Dietary Restrictions

It is prohibited to consume grapefruit juice while on olaparib therapy.

5.3.2 Contraception

Non-sterilized male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Appendix F) from the time of screening throughout the total duration of the study and the drug washout period (3 months after the last dose of study intervention) to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Female partners of male participants should also use a highly effective form of contraception (see Appendix F) if they are of childbearing potential.

For details of acceptable methods of contraception refer to Appendix F.

5.3.3 Blood Donation

Participants should not donate blood or blood components while participating in this study and for 3 months after the last dose of study intervention.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants who are ineligible for the study based on *BRCA1/2* status will be screen failed in the interactive voice response system (IVRS)/interactive web response system (IWRS) and electronic case report form (eCRF), should not continue with any remaining screening evaluations and are not permitted to enter the main study phase or be re-screened for study.

In exceptional cases, where a participant has met *BRCA1/2* status and has screen failed eligibility for other criteria, the participant may be re-evaluated for study eligibility, as determined by the AstraZeneca physician, provided that they have not previously been randomized, assigned or received treatment.

Where a participant is permitted to re-screen (by the AstraZeneca study physician), the same E-code initially assigned by the IVRS/IWRS should be used. The rationale and approval will be documented in the investigator site file.

Participant enrolment and randomization is described in Section 6.3.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the clinical study protocol (CSP).

6.1 Study Intervention(s) Administered

AstraZeneca will supply olaparib.

Investigator's choice of NHA agents (abiraterone acetate and enzalutamide) will be sourced locally or centrally and should be administered according to local prescribing information, including any treatment restrictions. Abiraterone acetate must be dosed with prednisone in accordance with the approved label (prednisolone is permitted for use instead of prednisone if necessary).

Dose modifications are described in Section 6.6.

Table 6 Investigational Products

ARM Name	Olaparib	Investigator's choice of NHA	Investigator's choice of NHA
Intervention Name	Olaparib [a]	Abiraterone acetate [b]	Enzalutamide
Type	drug	drug	drug
Dose Formulation	tablet	tablet	capsule/tablet
Unit Dose Strength(s)	150 mg; 100 mg available if dose reductions are required	250 mg and/or 500 mg	40 mg
Dosage Level(s)	300 mg (2 x 150 mg tablets) bid	1,000 mg qd	160 mg qd
Route of Administration	oral	oral	oral
Use	experimental	active comparator	active comparator
IMP and NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca or locally by the study site, subsidiary, or designee.	Provided centrally by AstraZeneca or locally by the study site, subsidiary, or designee.
Packaging and Labeling	Study intervention will be provided in blisters and cartons. Each unit will be labelled per GMP	If provided by AstraZeneca, study treatment will be labeled in accordance with	If provided by AstraZeneca, study treatment will be labeled in accordance with

	Annex 13 and local regulatory guidelines.	GMP Annex 13 and per country requirements	GMP Annex 13 and per country requirements

[a] Descriptive information for olaparib can be found in the olaparib IB/prescribing information. Manufacturer will be included in the quality section of the IMPD.
[b] With prednisone.

Olaparib

Olaparib is available as film-coated tablet containing 150 mg or 100 mg of olaparib.

Participants will be administered olaparib orally twice daily at 300 mg bid continually. Two × 150 mg olaparib tablets should be taken at the same times each day, approximately 12 hours apart with one glass of water. If required, dose reductions to 250 mg bid and a further dose reduction to 200 mg bid are permitted, however once dose is reduced, no return to the higher dose will be allowed.

The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

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

Abiraterone acetate

Abiraterone acetate will be administered orally at 1,000 mg once daily. Four × 250 mg or two × 500 mg tablets should be taken at a similar time each day in combination with prednisone 5 mg administered orally twice daily (each prednisone dose approximately 12 hours apart). Participants should take abiraterone acetate doses at a similar time each day. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate and one hour after the dose of abiraterone acetate. The tablets should be swallowed whole with water and not crushed or chewed, in full accordance with local prescribing information.

Enzalutamide

Enzalutamide will be administered orally at 160 mg once daily. Four × 40 mg capsules/tablets should be taken at a similar time each day. Capsules/tablets should be swallowed whole and can be taken with or without food, in full accordance with local prescribing information.

Duration of Treatment

Participants will continue to receive study intervention until BICR-assessed radiographic progression, or after the date of DCO for the primary analysis until investigator-assessed radiological progression, as long as they do not meet any of the criteria for treatment discontinuation.

Participants Who Switch to Olaparib

Once participants receiving investigator's choice of NHA, are determined to have objective radiological progression by BICR or, if after the date of DCO for the primary analysis, upon investigator-assessed radiological progression, they will be eligible to receive olaparib (300 mg bid).

If a participant 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. Participants should continue to receive randomized study treatment until progression determined by BICR.

The following criteria must be met in order for a participant to switch to olaparib:

- No intervening anti-cancer therapy following discontinuation of randomized treatment
- Any unresolved toxicities from prior therapy should be controlled, and be no greater than CTCAE grade 1 at the time of starting olaparib treatment

If subjects are not eligible to switch to olaparib, or choose not to switch, they will enter into the follow-up phase of the study (see Table 4), and should discuss other treatment options with the investigator.

Participants may continue to receive olaparib as long as they are continuing to show clinical benefit, as judged by the investigator and in the absence of discontinuation criteria (Section 7.1).

Dose Reductions

For guidance on dose reductions refer to Section 6.6.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee (eg, unblinded pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enroled in the study may receive study intervention and only authorized site staff may dispense study intervention. At site, all study intervention must be stored in

a secure, environmentally controlled, and monitored (manual or automated) area at the site in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

The investigator's choice of NHA agent(s) will either be locally sourced by the study site or centrally supplied by AstraZeneca and will be administered according to Prescribing Information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing by the study site is not feasible, AstraZeneca will centrally supply the drug, which will be labeled with local language translated text in accordance with regulatory guidelines.

6.3 Measures to Minimise Bias: Randomization and Blinding

Participant Enrolment and Randomization

Study using IVRS/IWRS	All participants will be centrally assigned to randomized study intervention using an IVRS/IWRS. Before the study is initiated, the call/log-in directions and user guides for the IVRS/IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in SoA or per investigator's choice of NHA after DCO. Returned study intervention should not be re-dispensed to the participants.

If a participant withdraws from the study, then his enrolment/randomization code cannot be reused. Withdrawn participants will not be replaced.

Investigators should keep a record (ie, the participant screening log) of participants who entered screening.

At screening/baseline (Days -28 to -1), the investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.
- Participants will be identified to the IVRS/IWRS per country regulations. Obtain a unique 7-digit enrolment number (E-code), through the IVRS/IWRS in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being

the participant enrolment code at the centre). This number is the participant's unique identifier and is used to identify the participant on the eCRFs.

- Obtain sample and send for centralized *BRCA1/2* testing. Obtaining the sample should be given the highest priority and, as such, the sample may be obtained and sent for central testing prior to the 28-day screening window (after obtaining signed informed consent) in order to permit analysis prior to randomization. Screening procedures may be performed while *BRCA1/2* status is being assessed.
- Determine participant eligibility (see Sections 5.1 and 5.2).

At randomization, once the participant is confirmed to be eligible, the investigator or suitably trained delegate will:

- Select the NHA treatment (abiraterone acetate or enzalutamide, based on the most appropriate option for the participant) that the participant would receive if randomized to the investigator's choice of NHA group, prior to randomization of the participant. This must be completed for all participants. The information will be recorded in the IVRS/IWRS system.
- Assign a randomized treatment group via the IVRS/IWRS. Randomization codes will be assigned strictly sequentially within each stratum as participants become eligible for randomization. The system will randomize the eligible participant to 1 of the 2 treatment groups.

If the participant is ineligible, the IVRS/IWRS should be accessed to terminate the participant in the system.

Participants will begin treatment on Day 1. Participants must not be randomized and treated unless all eligibility criteria have been met.

Procedures for Handling Incorrectly Enroled or Randomized Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enroled or receive study medication. There can be no exceptions to this rule. Participants who are enroled but subsequently found not to meet all the eligibility criteria must not be randomized or started on study intervention and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

Methods for Assigning Treatment Groups

The actual treatment given to participants will be determined by the randomization scheme in the IVRS/IWRS. The randomization scheme will be produced by a computer software programme that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated and randomization will be balanced within the IVRS/IWRS at the central level. Participants will be randomized in a 2:1 ratio to olaparib or investigator's choice of NHA (enzalutamide or abiraterone acetate). The randomization will be stratified by previous taxane use (yes, no) and whether subject had measurable disease (yes, no).

Randomization codes will be assigned strictly sequentially, within each stratum and country, as participants become eligible for randomization. The IVRS/IWRS will provide the kit identification number to be allocated to the participant at the randomization visit and subsequent treatment visits.

Methods for Ensuring Blinding

Not applicable.

6.4 Study Intervention Compliance

When participants self-administer study intervention(s) at home, patients should be given clear instructions on how and when to take their study treatment and compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets/capsules during the site visits and documented in the source documents and eCRF.

A record of the number of tablets/capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their blisters and carton(s) of study treatment at the appropriate scheduled visit, when new carton(s) will be dispensed. Patients will be instructed to notify study site personnel of missed doses.

Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

The Investigational Product Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention. The investigator(s) is responsible for ensuring that the participant has returned all unused study intervention.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, or other medication considered necessary by the investigator for the participant's safety and wellbeing, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving from the time of screening or receives during the study including the 30-day follow-up period following the last dose of study intervention must be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix G 2.

For agents in the investigator's choice of NHA (abiraterone acetate or enzalutamide) group, refer to the local Prescribing Information with regard to warnings, precautions, and contraindications.

Drug-drug Interactions

Guidance regarding potential interactions with concomitant medications is provided in Appendix G 1.

Strong or moderate CYP3A inhibitors are restricted (see Appendix G 2). If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration (see Appendix G 2). Strong or moderate CYP3A inducers are restricted (see Appendix G 2). Co-administration of enzalutamide with strong CYP2C8 inhibitors may increase exposure to enzalutamide and thus should be avoided if possible; for enzalutamide dose modification guidance if participants must be co-administered a strong CYP2C8 inhibitor, see Appendix G 2.

Anti-emetics/Anti-diarrheals

From screening Part 2 onwards, should a patient develop nausea, vomiting and/or diarrhea, then these symptoms should be reported as AEs (Section 8.3) and appropriate treatment of the event given.

Subsequent Therapies for Cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. CCI [redacted]

6.5.1 Other Concomitant Medication

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

6.6 Dose Modification

6.6.1 Dose Reductions for Olaparib

In case a dose reduction is necessary, olaparib will be administered as described in Table 7, Table 8 and Table 9.

Table 7 Dose Reductions for Olaparib to Manage Adverse Events

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

Table 8 Dose Reduction for Olaparib if Patient Develops Moderate Renal Impairment

Initial dose	Moderate renal impairment dose reduction [a]
300 mg twice daily	200 mg twice daily

[a] Calculated CrCL by Cockcroft-Gault equation or based on a 24 hour urine test between 31 and 50 mL/min)

Table 9 Dose Reductions for Olaparib if Patient Has to Start Taking a Strong or Moderate CYP3A Inhibitor

Initial dose	Strong CYP3A inhibitor	Moderate CYP3A inhibitor
300 mg twice daily	100 mg twice daily	150 mg twice daily

For guidance on dose reductions for management of adverse events (AEs; including renal impairment) refer to Table 7, Table 8 and Section 6.6.3.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Table 9 and Appendix G.

6.6.2 Dose Reductions for Abiraterone Acetate and Enzalutamide

For agents in the investigator's choice of NHA (abiraterone acetate or enzalutamide) group, refer to the local Prescribing Information with regard to dose reductions.

6.6.3 Management of Toxicities Related to Olaparib

Dose modification guidelines for olaparib-related toxicities are shown below. Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. Prior to discontinuation of study intervention due to toxicities, please consult with the study physician.

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

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors, see Appendix G 2).

6.6.3.1 Management of Hematological Toxicity

6.6.3.1.1 Management of Anemia

Table 10 Management of Anemia

Hemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dL (CTCAE Grade 2)	Give appropriate supportive treatment, continue to monitor and investigate causality. • For *first* incidence: investigator judgement to continue olaparib with supportive treatment (eg, transfusion) or interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb HAS recovered to > 9g/dL. • For *repeat* incidence (after recovery of first event) ° If Hb < **10** but ≥ 9 g/dL investigator judgement to continue olaparib with supportive treatment (eg, transfusion) or dose interrupt (for maximum of 4 weeks) and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). ° If Hb < **9** but ≥ **8 g/dL**, dose interrupt (for maximum of 4 weeks) until Hb ≥ 9 g/dL and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).
Hb < 8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (eg, transfusion), continue to monitor and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dL. Upon recovery dose reduce olaparib to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where participants develop prolonged hematological toxicity (≥ 2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 6.6.3.1.3 for the management of this.

6.6.3.1.2 Management of Neutropenia, Leukopenia and Thrombocytopenia

Table 11 Management of Neutropenia, Leukopenia and Thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue study treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption for a maximum of 4 weeks until recovered to CTCAE grade 1 or better. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to 250 mg twice daily as a first step and 200 mg twice daily as a second step.

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a subject develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

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

For cases where participants develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 6.6.3.1.3.

6.6.3.1.3 Management of Prolonged Hematological Toxicities While on Study Treatment

If a subject develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the subject should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as a SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if subject's diagnosis of MDS and/or AML is confirmed.

6.6.3.2 Management of Non-hematological Toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose

interruptions are considered inadequate for management of toxicity, then the subject should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step. Treatment must be interrupted if any National Cancer Institute (NCI)-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

6.6.3.2.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

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

6.6.3.2.2 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, participants should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer participants (European Society for Medical Oncology, National Comprehensive Cancer Network), generally a single agent antiemetic should be considered eg, dopamine receptor antagonist, antihistamines or dexamethasone.

6.6.3.2.3 Interruptions for Intercurrent Non-toxicity Related Events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a subject cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the AstraZeneca study physician. See Table 7 for dose reductions for olaparib

to manage AEs.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a subject undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, participants should be advised to use caution while driving or using machinery if these symptoms occur.

6.6.3.2.4 Hepatitis B

For participants with past/resolved or chronic hepatitis B: In case of HBV reactivation* during the interventional period, study treatment should be interrupted and the participant should be referred to a hepatologist. Following proper care, study treatment can be restarted when exceptions of exclusion criteria #8 are met and after discussion with AZ study physician.

Participants with chronic hepatitis B should be under the care of a hepatologist as per local standard practice.

* For HBV reactivation, please refer to table 27 for detailed definitions.

Table 27 Definition of HBV Reactivation

Baseline serologies			Definition for HBV reactivation
HBsAg	**HbcAb**	**DNA**	
+	+	Undetectable	HBV DNA >100 IU/ml
+	+	Detectable	HBV DNA > 100 fold, 2 log compared to baseline value
-	+	Undetectable	Detection of any DNA (even if not quantifiable) -or- HBs Ag (+) (ie, reverse seroconversion)

6.6.3.3 Renal Impairment

If subsequent to study entry and while still on study therapy, a subject's estimated CrCL falls below the threshold for study inclusion (≥ 51 mL/min), retesting should be performed promptly.

A dose reduction is recommended for subjects who develop moderate renal impairment

(calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 mL/min) for any reason during the course of the study; the dose of olaparib should be reduced to 200 mg bid (Table 8).

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in subjects with severe renal impairment (creatinine clearance ≤ 30 mL/min) or end-stage renal disease; if subjects develop severe impairment or end-stage disease it is recommended that olaparib be discontinued.

6.6.4 Management of Toxicities related to Enzalutamide and Abiraterone Acetate

For management of toxicities due to investigator's choice of NHA (enzalutamide and abiraterone acetate) refer to the locally approved Prescribing Information or manage in accordance with institutional guidelines.

6.7 Continued Access to Study Intervention after the End of the Study

As described in Section 4.4, the study will remain open until all participants have discontinued study intervention and completed their last expected visit/contact.

After the final DCO for this study, AstraZeneca will continue to supply olaparib to participants who were randomized to receive olaparib until PD occurs as judged by the investigator or until meeting any other discontinuation criteria as defined in Section 7.1. Participants should be followed according to the institution's standard of care assessments. No further data collection is required, except for reporting of SAEs.

Participants receiving investigator's choice of NHA at progression (Section 4.1) will be given the option of switching to olaparib 300 mg bid and AstraZeneca will continue to supply this treatment as described above.

Participants who were randomized to receive investigator's choice of NHA who are not eligible to switch to olaparib, or choose not to switch, or participants who discontinue from the study, should continue appropriate treatment at the discretion of the investigator.

6.8 Treatment of Overdose

Study treatment must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg bid (tablet). There is currently no recommended specific treatment in the event of overdose of

olaparib and possible symptoms of overdose are not established. For participants receiving SoC (Investigator's choice of either enzalutamide or abiraterone), refer to the local Prescribing Information for treatment of cases of overdose.

In the event of an overdose, the investigator/treating physician should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to section 8.3.16 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for PD (if discontinuation in the absence of PD) and OS, per the SoA (Table 3). Any subject discontinuing investigational product should be seen at 30 days post discontinuation for the evaluations outlined in the SoA (Table 2). The investigator should instruct the participant to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IVRS/IWRS. All study intervention should be returned by the participant at their next on-site study visit or unscheduled visit.

Any patient discontinuing investigational product should be seen at 30 days post discontinuation for the evaluations and sample collections outlined in the study schedule. The patient's tumor status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow-up

(see Section 7.3). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 8.3.13) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study medication to collect and/or complete AE information. For guidance on reporting adverse events after the 30 day follow-up period see Section 8.3.2.1.

Participants may be discontinued from study intervention in the following situations.

- Subject decision: The subject is at any time free to discontinue treatment, without prejudice to future treatment.
- Any AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of olaparib-related toxicities (see Section 6.6) or as defined in the local Prescribing Information for the investigator's choice of NHA agents (abiraterone acetate and enzalutamide).
- Severe non-compliance with the study protocol
- Bone marrow findings consistent with MDS/AML
- Objective radiological progression by BICR as defined in Section 8.1.2.
- Unequivocal clinical progression:
  - Cancer pain requiring initiation of chronic administration of opioids, or
  - Immediate need to initiate cytotoxic chemotherapy, radiation therapy, or surgical intervention for complications due to tumor progression, or
  - Deterioration in ECOG performance status to ≥ Grade 3.
- Initiation of restricted anticancer therapy (see Section 6.5).

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. Switching to olaparib will be permitted once participants receiving investigator's choice of NHA are determined to have objective radiological progression by BICR or, if after the date of DCO for the primary analysis, upon investigator-assessed radiological progression (Section 6.1).

Participants who have discontinued study intervention prior to objective radiological progression, regardless of whether or not they have commenced subsequent anticancer therapy, will be followed up with tumor assessments as indicated in the SoA until radiological PD or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

See the SoA for data to be collected at the time of intervention discontinuation (ie, the end-of-treatment visit) and follow-up and for any further evaluations that need to be completed.

7.1.1 Follow-up of Participants Post Discontinuation of Study Intervention

All participants who discontinue the study intervention will be followed up for safety assessments 30 days after their last dose of study intervention. Additional assessments to be performed at the time of the 30-day safety follow-up are detailed in the SoA.

Participants who have discontinued study intervention prior to objective radiological progression, regardless of whether or not they have commenced subsequent anticancer therapy, will be followed up with tumor assessments as indicated in the SoA until radiological progression or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

7.1.2 Follow-up of Participants to PFS2

Following objective progression that is confirmed by BICR assessment, participants will have their subsequent progression status recorded every 12 weeks per local standard clinical practice to assess time from randomization to second progression by investigator assessment of radiological or clinical progression or death (PFS2). Assessments will be performed according to the local practice, and formal Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) measurements will not be collected for assessment of PFS2. See Section 8.1.4 for additional information.

7.1.3 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA (Section 1.3) until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, by contact with the participant's current physician or by checking publicly available death registries, if allowable per local regulations. Additional assessments to be performed at the time of survival follow-up are detailed in the SoA (Section 1.3).

7.2 Participant Withdrawal from the Study

Reasons for withdrawal from the study:

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

  - Death

- A participant may withdraw from the study at any time at his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 30 days [+7 days] after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he still agrees for existing samples to be used in line with the original consent. If he requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time.

Participants who decline to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered to have been lost to follow-up from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant during survival follow-up within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.In order to support key efficacy endpoints of PFS and OS analyses, the survival status of all participants in the Full Analysis and the Safety Analysis Sets should be re-checked; this includes those participants who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up – Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the participants' current physician, to obtain a current survival status (the applicable eCRF modules will be updated).
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Data collection following study analysis until the end of the study is described below.

- Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

Data Collection Following Study Analysis until the End of the Study

Following the DCO for the primary efficacy endpoint, central review of scans will be discontinued. Participants will continue with all other assessments as indicated in the SoA.

For SAE and AE reporting and laboratory assessment collection after final analysis, see Section 8.3.12.After the final DCO and database closure, only SAEs will be reported for the purposes of this study (see Section 8.3.12).

Following the DCO for the final analysis, all participants who remain in the study will continue the scheduled "progression/survival follow-up" site visits indicated in the SoA.

8.1 Efficacy Assessments

8.1.1 Imaging Tumor Assessments

All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to an AstraZeneca appointed CRO to enable independent central review. Upon investigator-assessed objective disease progression as defined in Section 8.1.2, review of all scans will be conducted by BICR. The results will be reported back to the sites. All imaging assessments and study treatment should continue until objective disease progression as assessed by BICR (see Figure 3).

The baseline assessments of all imaging modalities should be performed as close as possible to the start of study treatment and no more than 4 weeks (-28 days) before randomization. Following the baseline assessment, subsequent assessments should be performed every 8 weeks (± 7 days), relative to the date of randomization, until objective radiological disease progression by BICR, even after investigator has deemed objective disease progression,

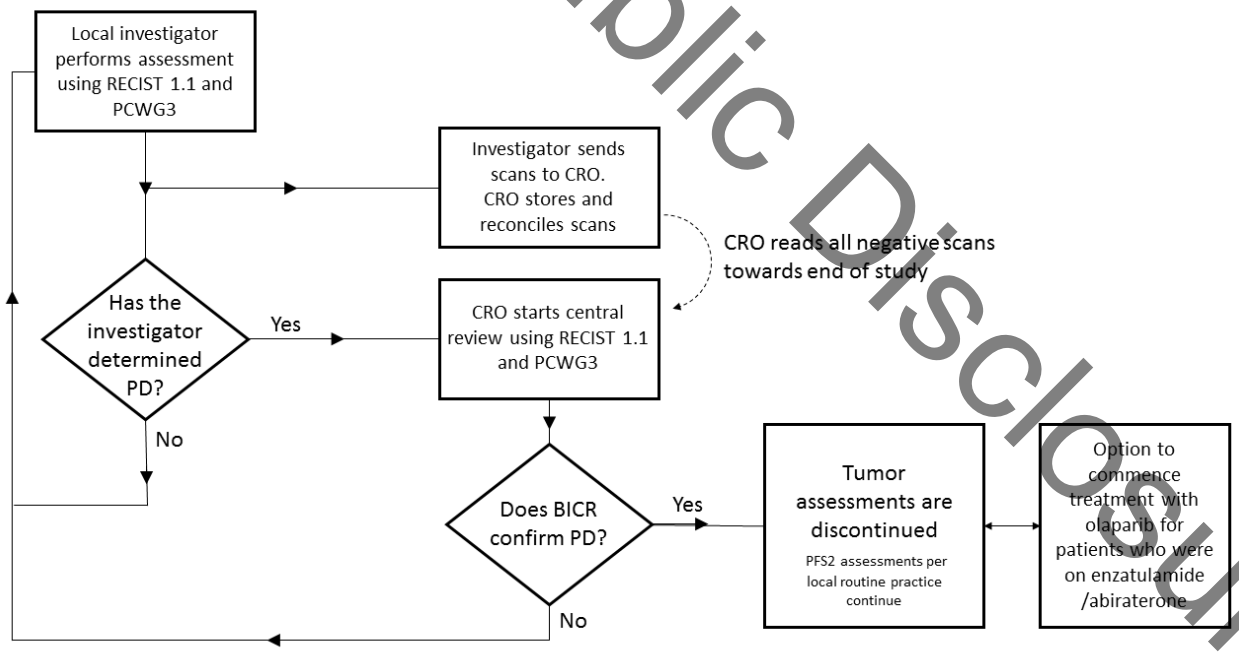
irrespective of treatment decisions or dose interruptions. The assessments by different imaging modalities can be done on different days but should all be performed within assessment schedule. It is important to follow the imaging assessment schedule as closely as possible (see Table 2). If scans are performed outside of scheduled visit window interval, and the subject has not progressed, every attempt should be made to perform the subsequent scans at their originally scheduled time points.

In order for participants randomized to investigator choice arm to be eligible to switch to olaparib, scheduled tumor assessments must continue until objective radiological disease progression as assessed by BICR, without any intervening systemic anti-cancer therapy following discontinuation of randomized study treatment (see Section 6.1).

Until the primary rPFS analysis all imaging assessment and study treatment should continue until objective disease progression as assessed by BICR (see Figure 3). 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.

Radiological examinations performed during the study should be retained at site as source data.

Figure 3 Assessment of Progression by BICR (prior to primary rPFS analysis)



8.1.1.1 CT and MRI Scans Tumor Assessments (RECIST 1.1)

The imaging modalities used for RECIST assessment will be CT or MRI scans of the chest, abdomen and pelvis. Any other areas of disease involvement should be additionally investigated based on the signs and symptoms of individual participants. At assessments subsequent to baseline, any other sites at which new disease is suspected should also be appropriately imaged. The methods of assessment of tumor burden used at baseline must be used at each subsequent assessment. In this study, bone lesions will not be included in the RECIST soft tissue assessment.

8.1.1.2 Bone Scans Tumor Assessment (Based on PCWG3 Criteria)

Bone lesions will be assessed by bone scintigraphy commonly performed with Technetium-99 (bone scans). Bone lesions will be assessed by bone scan and will not be part of the RECIST 1.1 malignant soft tissue assessment. Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions.

8.1.2 Tumor Evaluation

Disease progression will be deemed to have occurred if one or more of the following criteria is met:

- Soft tissue disease progression as defined by RECIST 1.1
- Bone lesion progression by bone scan (see Table 12)
- Death.

RECIST 1.1 criteria will be used to assess subject response to treatment by determining PFS, objective response rates (ORR), and DoR. Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, and SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment. If the investigator is in doubt as to whether progression has occurred, particularly with regard to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the tumor burden at the next scheduled assessment or sooner if clinically indicated. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumor response criteria are presented in Appendix E. For ORR, a visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed.

Bone lesions will be assessed by bone scan and will not be part of the RECIST 1.1 malignant soft tissue assessment. The definition for bone progression is based on PCWG3 criteria.

Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions.

Progression on a bone scan is defined as:

At the 8 week scan:

If **2 or more** new metastatic bone lesions are observed on the first 8-week scan, the confirmatory scan performed (at least 6 weeks later), must show **2 or more additional new** metastatic bone lesions (for a total of **4 or more new** metastatic bone lesions since the baseline assessment).

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

After the 8 week scan:

For participants **without progression** at the 8 week scan, this scan now serves as new baseline for all subsequent scans, ie, all bone scans after week 8 are compared to the week 8 scan. If **2 or more** new metastatic bone lesions are observed on scans obtained after the first 8-week assessment (compared to week 8 scan), a confirmatory scan performed **at least 6 weeks later** and preferably no later than the next scheduled visit must show the persistence of, or an increase in, the number of metastatic bone lesions compared to the prior scan.

The date of progression is the date of the first scan documenting the 2 new lesions. If the investigator is in doubt as to whether progression has occurred, it is advisable to continue study treatment and reassess the bone lesion status at the next scheduled assessment, or sooner if clinically indicated.

The requirements for determination and confirmation of radiological progression by either bone scan (bone progression) or CT/MRI (soft tissue progression) are summarized in Table 12:

Table 12 Requirements for Documentation of Progression

Visit date	Criteria for bone progression	Criteria for soft tissue progression
Week 8	2 or more new lesions compared to baseline bone scan. Requires confirmation scan at least 6 weeks later with ≥2 additional lesions compared to week 8 scan	Progressive disease on CT or MRI by RECIST 1.1 No confirmation scan required.

Table 12 Requirements for Documentation of Progression

Visit date	Criteria for bone progression	Criteria for soft tissue progression
Week 16 or later	2 or more new lesions compared to week 8 bone scan. Requires confirmation scan at least 6 weeks later for persistence or increase in number of lesions	Progressive disease on CT or MRI by RECIST 1.1 No confirmation scan required.

It is important to follow the assessment schedule as closely as possible. Please refer to the study schedule in Section 1.3.

8.1.3 Central Reading of Scans

All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to an AstraZeneca appointed Clinical Research Organization (CRO) to enable BICR. Upon documentation of radiological progression by the investigator, all imaging assessments for the given subject, including unscheduled visit scans, will be reviewed by BICR. Results of this independent review will be communicated to investigators. Participants should continue imaging assessments until BICR-assessed progression (see Section 8.1.1).

An independent review of all scans used in the assessment of tumors will be conducted prior to the primary analysis of rPFS, including for participants without investigator-assessed progression.

The primary analysis for this study will be based on the BICR of all radiological scans (CT/MRI and bone scans).

After the primary rPFS analysis, central review of scans will no longer be required, and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. After rPFS analysis, all treatment decisions will be based on site assessment of scans. Ongoing collection of site review tumor assessment is required and must be recorded in the eCRF.

Further details of the BICR will be documented in an Independent Review Charter.

8.1.4 Time to Second Progression or Death

Following objective progression by BICR, participants will have their subsequent progression status recorded every 12 weeks per local standard clinical practice to assess PFS2. A participant's PFS2 status is defined according to the local practice and may involve any of: objective radiological progression (preferred), symptomatic progression (but not PSA progression), or death. Scans will be performed according to the local practice and formal RECIST 1.1 and PCWG3 measurements will not be collected for assessment of PFS2. The

second progression event must have occurred during or after treatment with a subsequent therapy after the progression event used for the primary variable PFS or death. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the source documents and the eCRF.

8.1.5 Symptomatic Skeletal-related Events

Symptomatic skeletal-related events (SSREs) will be assessed at each visit during the treatment phase, up to and including the study treatment discontinued visit (see Table 2). An SSRE is defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of spinal cord compression, or a tumor related orthopedic surgical intervention.

The occurrence of a SSRE alone, in the absence of disease progression, is discouraged as a reason to discontinue treatment or to initiate new systemic anti-cancer therapy.

8.1.6 PSA Assessments

Blood samples will be collected for PSA assessment at baseline and at each visit during the treatment phase, up to and including the study treatment discontinued visit (Section 1.3). The samples will be analyzed by central laboratory. In order to prevent early withdrawal from treatment phase, PSA results will not be sent back to sites prior to final analysis.

Samples will be collected, labeled, stored and shipped as detailed in the Laboratory manual.

8.1.7 Overall Survival

Assessments for survival will be conducted every 12 weeks following objective PD or treatment discontinuation. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries as described in Section 7.1.3.

8.1.8 Clinical Outcome Assessments

Clinical Outcome Assessments are not evaluated in this study.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

A complete physical examination will be performed as specified in the SoA (Section 1.3) and if clinically indicated at any other time. A complete physical examination will include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin,

head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

Physical examination, as well as assessment of height and weight, will be performed at timelines as specified in the SoA; investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.5 for details.

Weight measurements will not be recorded in the eCRF after Cycle 1 Day 1 (C1D1). If a patient's weight change is clinically significant, it should be entered as an AE in the Adverse Events eCRF.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Section 1.3).

Body temperature, pulse rate and blood pressure will be assessed.

The date of collection and measurement of vital sign will be recorded on the appropriate eCRF. Vital signs will not be recorded in the eCRF after C1D1. If a participant's vital signs are clinically significant, the medical term for the abnormality should be entered as an AE in the Adverse Events eCRF.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be performed at timelines as specified in the SoA after the participant has been resting semi-supine for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT interval corrected by Fridericia's formula (QTcF) intervals.

All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal. Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, hematology and urinalysis will be performed locally. Instructions for sample collection, labeling, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following laboratory variables will be measured.

Table 13 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical chemistry (serum or plasma)
Hemoglobin	Creatinine
Leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count)	ALP
Platelet count	AST
Absolute neutrophil count	ALT
Absolute lymphocyte count	Albumin
B-Mean Cell volume (MCV)	Potassium
Total red blood cell count	Calcium, total
Hematocrit	Sodium
	Urea nitrogen/blood urea nitrogen
	Protein, total
Urinalysis	Lactate dehydrogenase
Hemoglobin/Erythrocytes/Blood	Amylase

Hematology/Hemostasis (whole blood)	Clinical chemistry (serum or plasma)
Protein/Albumin	Gamma-glutamyl transferase
Glucose	Glucose (fasting)
	Coagulation variables (aPTT, PTT, and INR)
	HBs Ag
	Anti-HBc
	Anti-HBs
	HBV DNA

ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; INR, international normalized ratio; PTT, partial thromboplastin time. HBsAg, hepatitis B surface antigen; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody;

The investigator should assess the available results with regard to clinically relevant abnormalities in the documentation. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All participants with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study intervention must be followed and have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

NB. In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix D "Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law (HL)", for further instructions.

8.2.4.1 Coagulation

Activated partial thromboplastin time (aPTT) will be performed at screening and if clinically indicated.

International normalized ratio (INR) will be performed at screening and if clinically indicated. Participants taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Each coagulation test result will be recorded in eCRF.

8.2.4.2 Bone Marrow or Blood Cytogenetic Samples

Bone marrow or blood cytogenetic samples may be collected for participants with prolonged hematological toxicities as defined in Section 6.6.3.1.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not

possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patients Safety database. These data are not required to be entered into eCRF.

The investigator should assess the available results for clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.5.

8.2.4.3 Hepatitis B Blood Test

HBsAg, anti-HBc and anti-HBs blood tests will be performed at screening. And if either HBsAg or anti-HBc is positive, HBV DNA (viral load) and HBsAg should also be tested at screening, every 12 weeks (± 7 days) relative to the date of randomisation during the interventional period and at 30-day safety follow-up.

8.2.5 Other Safety Assessments

8.2.5.1 ECOG Performance Status

ECOG performance status will be assessed at the times specified in the SoA (Section 1.3) based on the following:

0 Fully active; able to carry out all usual activities without restrictions.

1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).

2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair.

5 Dead.

Any significant change from baseline or screening must be reported as an AE.

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, recording, and reporting events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from the time of signature of the ICF, throughout the treatment period and until the 30-day follow-up period is completed*. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.12.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

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

8.3.2 Follow-up of AEs and SAEs

8.3.2.1 Adverse Events After the 30-day Follow-up Period

For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30-day follow-up period should be reported to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow-up for overall survival if the subject has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

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

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

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

8.3.2.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.2.3 Adverse Event Variables

The following variables will be collected for each AE;

- AE (verbatim).
- The date when the AE started and stopped.
- CTCAE grade and changes in CTCAE grade.
- Whether the AE is serious or not (Appendix B).
- Investigator causality rating against the study intervention(s) (yes or no).
- Action taken with regard to study intervention(s).
- Outcome.

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

- Date AE met criteria for SAE.
- Date investigator became aware of SAE.
- Seriousness criteria.
- Date of hospitalization.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment to other medication.
- Description of AE.

Severity of AE

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

The grading scales found in the NCI-CTCAE (Version 5.0) will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?".

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether treatment or non-planned visits were required or other

action was taken with the study intervention, eg, dose adjustment or study intervention interruption).

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the study intervention is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study.

8.3.8 New Cancers

The development of a new cancer should be regarded as an AE (see Section 8.3.11) and will generally meet at least one of the serious criteria (with the exception of some non-melanoma skin cancers). New primary cancers are those that are not the primary reason for the administration of study intervention and are identified after the participant's inclusion in this study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

8.3.9 Lack of Efficacy

When there is deterioration in the cancer, for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

8.3.10 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of the last dose of study intervention, must be reported as follows:

- Death clearly resulting from PD should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.3.11 Adverse Events of Special Interest

Adverse Events of Special Interest 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 can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.13.

Adverse Events of Special Interest for olaparib are the Important Identified Risk of MDS/AML, the Important Potential Risk of new primary malignancy (other than MDS/AML)

and the Potential Risk of pneumonitis.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

8.3.12 Safety Data to be Collected Following the Final Data Cutoff of the Study

For participants continuing to receive study treatment after the final DCO, AEs and SAEs will be collected, but only SAEs will be reported. In addition, it is recommended that investigators monitor the participant's safety laboratory results periodically during treatment with study treatment in order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6). All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving study treatment (or within the 30 days following the last dose of study treatment) after the final DCO must be reported as detailed in Section 8.3.13.

8.3.13 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s)*. All SAEs will be recorded in the eCRF.

*Exception: In screening part 1, only SAEs related to study procedures must be reported.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** from when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an

automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB/prescribing information for olaparib and the prescribing information for the active comparator product.

8.3.14 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca.

8.3.14.1 Paternal Exposure

Non-sterilized male participants who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for the duration of the study (from the time of screening) and for 3 months after the last dose of study intervention.

Participants in the investigator's choice of NHA (enzalutamide or abiraterone acetate) group should follow the local Prescribing Information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the investigator's choice of NHA (enzalutamide or abiraterone acetate) group.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose of study intervention until 3 months after the last dose of study intervention should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant Regulatory Authority/IRBs/IECs prior to use.

8.3.15 Medication Error, Drug Abuse and Drug Misuse

8.3.15.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.13) and **within 30 days** for all other events.

8.3.15.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.3.15.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.15.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.3.16 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives

immediately, but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.13) and **within 30 days** for all other overdoses.

For participants receiving investigator's choice of NHA (enzalutamide or abiraterone acetate) refer to the local Prescribing Information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.4 Human Biological Samples

8.4.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.4.2 Immunogenicity Assessments

Immunogenicity parameters are not evaluated in this study.

8.4.3 Pharmacodynamics

Pharmacodynamics parameters are not evaluated in this study.

8.5 Human Biological Sample Biomarkers

8.5.1 Collection of Mandatory Samples for Biomarker Analysis

Participant consent to the study includes participation in the mandatory biomarker assessment components of the study.

Samples for biomarker assessment are required and will be collected from all participants in this study as specified in the SoA (Section 1.3).

8.5.1.1 Mandatory Tumor Sample Collection

The provision of a FFPE tumor tissue sample during screening for central testing is mandatory in this study. Samples will be tested for *BRCA1/2* gene mutation to evaluate their association with the observed clinical responses to olaparib. If the test results indicate that the participant has a qualifying mutation in the *BRCA1* or *BRCA2* genes, the participant is eligible for the study.

Tumor tissue samples can be from either primary tumor (eg, transrectal biopsies or radical prostatectomy specimen) or metastatic biopsy.

All samples will be tested for *BRCA1/2* mutations in a China based central laboratory for

patient eligibility. No other local testing results, other commercially offered NGS analyses or other pre-existing molecular test results are accepted.

FFPE tumor samples submitted to establish eligibility should be of sufficient quantity and quality to allow for t*BRCA* testing. The detailed sample requirements are described in the Laboratory Manual. Residual samples will be retained at the central testing laboratory to support potential Chinese regulatory filing or the development of companion diagnostic assays (CDx). Consent for use of the FFPE samples for *BRCA* testing, future diagnostic development and regulatory filing is mandatory.

No future research and exploratory biomarker analysis will be conducted. Remaining tissue samples will be destroyed or repatriated within one year of CSR.

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to Appendix C and the Laboratory Manual.

8.5.1.2 *BRCA* Mutation Testing of Tumor Biopsy Sample

The *BRCA* results must be available prior to randomization. Therefore, a FFPE tumor sample (meets the tissue requirements outlined in the Laboratory Manual) will be submitted to a China based central laboratory for *BRCA1/2* testing. The tumor testing will be conducted using a NGS assay based on DNA extracted from the provided FFPE tumor tissue. Only participants with positive *BRCA1/2* mutations (deleterious or suspected deleterious) are eligible for this study.

8.5.1.3 Collection, Analysis and Reporting of Tumor Samples

Tumor samples will be collected as detailed in the Laboratory Manual. Participants must consent to provide either archived FFPE samples, or a de novo tumor biopsy sample for analysis. Consideration should be given to the potential benefit to the subject (should he be eligible for study) in the context of the risk posed by the biopsy procedure. Tissue biopsy sampling should be conducted in accordance with expert guidelines, only by investigators experienced in performing these sampling methods in appropriate clinical settings. Samples that meet the minimal requirement as specified in the Laboratory Manual will be shipped to a central testing laboratory to determine *BRCA1/2* status.

If the initial testing is inconclusive due to technical test failure, a repeat may be carried out if additional sample is available and Human Genetics Resources approval has been obtained for use of the additional samples.

Upon successful testing, a report will be issued to sites including information of the *BRCA* mutation status for subject eligibility assessment.

8.6 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.7 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be prepared prior to first subject randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

All personnel involved with the analysis of the study will remain blinded at aggregate level until database lock and protocol violations identified. Prior to the database lock, any analysis tasks being performed will use a dummy random scheme (Section 6.3).

9.1 Statistical Hypotheses

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.

9.2 Sample Size Determination

Approximately 700 participants will be screened to achieve approximately 42 randomly assigned to study intervention. The primary rPFS analysis will be performed when approximately 21 rPFS events have occurred (50% maturity). Assuming a true underlying rPFS 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. With 42 patients, the study 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 participant has been randomized, taking into account study dropout.

9.3 Populations for Analyses

The following populations are defined:

Table 14 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the ICF.
Full analysis set (FAS)	All participants who are randomized in the study. The FAS will be used for all the efficacy analyses, except for ORR, DoR and BoR. Treatment groups will be compared on the basis of randomized study intervention, regardless of the treatment actually received. Participants who were randomized but did not subsequently receive study intervention are included in the analysis in the treatment group to which they were randomized.
Evaluable for response (EFR) analysis set	All participants in the FAS, who have measurable disease at baseline per 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 participants who have received at least 1 dose of study intervention.

9.4 Statistical Analyses

The SAP will be finalized prior to first participant in and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

- For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values. Where appropriate, assessments will be summarized by visit.
- The number of participants who were screened, randomized to treatment, received treatment and completed the study will be produced for each treatment group using the full analysis set. A summary table of analysis sets will be produced. Demographic and baseline characteristics will be summarized using the full analysis set.

- In general, missing data will not be imputed. For the date variables of historical data (ie, 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.
- The treatment comparison is olaparib versus investigator choice. Results of statistical analyses will be presented using corresponding 2-sided confidence intervals and 2-sided p-values, where appropriate.

9.4.2 Efficacy

9.4.2.1 Calculation or Derivation of Tumor Response Variables

BICR RECIST 1.1 and PCWG3-based assessments

A BICR of radiological scans will be performed on all participants.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and PCWG3, and will be adjudicated, if required. For each participant, the BICR will define the overall visit response data (complete response [CR], partial response [PR], stable disease [SD], PD, Non-PD or not evaluable [NE]) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). Endpoints (rPFS, ORR, BoR, and DoR) will then be derived from the scan dates and overall visit responses.

Further details of the BICR will be documented in an Independent Review Charter.

Investigator RECIST 1.1 and PCWG3-based assessments

All RECIST 1.1 and PCWG3 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a participant discontinues study intervention or receives another anticancer therapy.

At each visit, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD, or NE depending on the status of their disease compared with baseline and previous assessments. Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment. Progression on a bone scan is identified using PCWG3. At each visit an overall assessment (Non-PD, PD or NE) of the bone lesion progression should be recorded by the investigator. Baseline will be assessed within 28 days prior to randomization.

The visit responses for soft tissue (according to RECIST 1.1 criteria) and bone progression status (according to PCWG3 criteria) will be combined to give an overall radiological objective visit response.

The tumor response endpoints by investigator (rPFS, ORR, best observed response and DoR) will then be derived from the scan dates and overall visit responses.

9.4.2.2 Primary Endpoint

9.4.2.2.1 Radiological Progression-Free Survival (rPFS)

Radiological progression-free survival is defined as the time from randomization to radiological progression (see Section 3), as assessed by BICR per RECIST version 1.1 (soft tissue) and PCWG3 criteria (bone), or, death due to any cause (ie, date of event or censoring – date of randomization + 1). The comparison will include all randomized participants, as randomized, regardless of whether the participant withdraws from randomized therapy, or receives another anti-cancer therapy prior to progression. Participants who have not progressed (defined as CR, PR or SD by RECIST 1.1 for soft tissue disease, or non-PD for bone disease (see Section 8.1.2 and Appendix E) or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 or bone scan assessment. However, if the participant progresses or dies after 2 or more consecutive missed radiologic assessments, the participant will be censored at the time of the latest evaluable RECIST 1.1 or bone scan assessment prior to the 2 missed visits.

If the participant 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).

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

CT/MRI and bone scans contributing toward a particular visit may be performed on different dates. For BICR (RECIST 1.1 and PCWG3) assessments, the following rules will be applied:

1 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 who read baseline first if there is no adjudication for ICR data.
2 When censoring a participant for rPFS, the participant will be censored at the latest of the dates contributing to a particular overall visit assessment.

The primary analysis will be based on the BICR of the radiological scans. A charter for the BICR will be developed in advance of the start of study. 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.

Investigator-assessed radiographic progression

CT/MRI and bone scans contributing toward a particular visit may be performed on different

dates. For investigator assessments, the following rules will be applied:

1 The date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
2 When censoring a participant for rPFS, the participant will be censored at the latest of the dates contributing to a particular overall visit assessment.

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

Analysis Methods

The HR for rPFS will be estimated using a Cox Proportional Hazards Model (with ties=Efron and the stratification variables previous taxane [yes, no] and measurable disease [yes, no] as covariates) and the 2-sided CI will be calculated using a profile likelihood approach. rPFS will also be analyzed using a stratified log rank test and a corresponding (descriptive) p-value will be generated. If there are less than 5 rPFS events within each stratum, then the levels of strata will be collapsed until the minimum 5 event criterion is achieved for the primary rPFS endpoint. All analyses (secondary analyses) will be conducted in accordance with the corresponding final pooling strategy. Further details of the pre-defined pooling strategy indicating the order in which the levels of stratum will be collapsed will be documented in the SAP. Stratification variables will be defined according to data from the IVRS/IWRS.

The HR (olaparib vs. investigator choice) together with its corresponding 95% CI and p-value (from the log-rank test) will be presented (a HR less than 1 will favor olaparib).

Any participants mis-stratified in the IVRS/IWRS will be included in the stratified log-rank test using the baseline data collected in the IVRS/IWRS.

A Kaplan-Meier (KM) plot of rPFS will be presented by treatment group. Summaries of the number and percentage of participants experiencing a progression or death event, and the type of event (RECIST 1.1 or bone progression or death) will be provided along with median rPFS for each treatment arm.

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

The primary analysis will be based on the BICR assessment of rPFS using all scans regardless of whether they were scheduled or not.

The estimated rPFS rates at 6-monthly intervals from randomization will be summarized (using the KM curve) and presented by treatment group.

A sensitivity analysis based on the programmatically derived rPFS based on investigator recorded assessments will be performed. Further sensitivity analyses to explore the robustness of the primary rPFS endpoint will be documented in the SAP.

CCI

[redacted]

9.4.2.3 Secondary Endpoint(s)

9.4.2.3.1 Confirmed Objective Response Rate (ORR)

For the secondary endpoint ORR assessed by BICR (RECIST 1.1 and PCWG3), analysis will be based on the EFR analysis set. A responder will be any subject with a confirmed best overall response of PR or CR in their soft tissue disease assessed by RECIST 1.1, in the

absence of progression on bone scan assessed by PCWG3. A subject will be classified as a responder if the RECIST 1.1 criteria for a CR or PR are satisfied (as well as the absence of confirmed progression on bone scan assessed by PCWG3) at any time up to and including the defined analysis cut-off point. For each treatment group, the ORR is the number of participants with a CR or PR divided by the number of participants in the treatment group in the EFR analysis set.

Additionally, analyses will also be performed on ORR assessed by investigator.

Analysis Methods

ORR will be assessed based on BICR assessed RECIST and bone scan data (using all scans regardless of whether they were scheduled or not) using the EFR analysis set. ORR will be compared between olaparib and investigator choice using a logistic regression model adjusting for the stratification variable, previous taxane (yes, no). The results of the analysis will be presented in terms of an odds ratio (an odds ratio greater than 1 will favor olaparib) together with its associated profile likelihood 95% CI (eg, 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 enough responses for a meaningful analysis using logistic regression then a Fisher's exact test using mid p-values will be presented. The mid-p-value modification of the Fisher's exact test amounts to subtracting half of the probability of the observed table from Fisher's p-value.

$$\text{Fisher's exact test mid p-value} = \text{Two sided p-value} - \frac{\text{Table probability}}{2}$$

Summaries will be produced that present the number and percentage of participants with a tumor response (CR/PR) per BICR and investigator assessment.

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

9.4.2.3.2 Overall Survival

OS is defined as the time from the date of randomization until death due to any cause. The comparison will include all randomized participants, as randomized, regardless of whether the participant withdraws from randomized therapy or receives another anti-cancer therapy. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive. Note: Survival calls will be made in the week following the date of DCO for the analysis. If participants are confirmed to be alive or if the death date is after the DCO date, then these participants will be censored at

the date of DCO. See Section 7.2 and Section 7.3 for methods that can be used to determine status of participants who withdraw consent or are lost to follow-up.

Analysis Methods

OS will be analyzed at the time of the primary analysis of rPFS with approximately 29% maturity expected at this point, and an OS analysis will also be performed with approximately 25 events (60% maturity) estimated to occur at approximately 37 months after first subject randomized in the study. OS will be analyzed using the same methodology specified for rPFS, in accordance with the pooling strategy. The p-value will be based on the stratified log-rank test and HR and 95% CI will be based on the Cox model.

Kaplan-Meier plots 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.

CCI [redacted]

9.4.2.3.3 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 non-vertebral). Radiologic documentation is required.
- Occurrence of spinal cord compression. Radiologic documentation required.
- Orthopedic surgical intervention for bone metastasis.

Participants who have not experienced any of the above conditions will be censored at time of death, or time of analysis if the subject is living.

Analysis Methods

Time to SSRE will be analyzed using the same methods as in the analysis of the primary endpoint rPFS, in accordance with the pooling strategy. The p-value will be based on the stratified log-rank test using previous taxane use and measurable disease as strata and HR and 95% CI will be based on the Cox model.

A KM plot of time to SSRE will be presented by treatment group. Summaries of the number and percentage of participants 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.

9.4.2.3.4 Duration of Response

Duration of response (DoR) will be defined as the time from the date of first documented confirmed response (by BICR using RECIST 1.1 and PCWG3) until date of documented progression (by BICR) or death in the absence of disease progression.

The end of response should coincide with the date of progression or death from any cause used for the rPFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a subject does not progress following a response, then their duration of response will use the rPFS censoring date as the date at which that subject is censored for DoR. The time to response is the time from randomization to the first onset of an objective tumor response.

Analysis Methods

Descriptive data will be provided for the duration of response in responding participants, including the associated KM curves (without any formal comparison of or p-value attached).

9.4.2.3.5 Time to Opiate Use for Cancer Pain

Time to opiate use is defined as the time from randomization to the date of opiate use for cancer-related pain on participants who have not received any opiates at baseline. Participants who have not received opiates during the study or died prior to receiving opiates will be considered censored at the last known on study date of no opiate use.

Analysis Methods

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, in accordance with the pooling strategy. The p-value will be based on the stratified log-rank test and 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 participants using opiates will be provided along with median time to opiate use for each treatment arm.

9.4.2.3.6 Prostate Specific Antigen Response

Prostate Specific Antigen (PSA) response is defined as the proportion of participants achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later.

- A subject 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 subject 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 (ie, decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 3 weeks apart).

Analysis Methods

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

9.4.2.3.7 Time from Randomization to Second Progression or Death (PFS2)

Defined as the time from randomization to investigator-assessed objective radiological progression on next-line treatment or death from any cause.

Analysis Methods

Time from randomization to second progression or death will be analyzed using the same methods as in the analysis of rPFS, in accordance with the pooling strategy. The p-value will be based on the stratified log rank test and HR and 95% CI will be based on the Cox model.

A KM plot of time to second progression or death will be presented by treatment group. Summaries of the number and percentage of participants with second progression or death and those who are censored will be provided along with median time to second progression or death for each treatment arm.

9.4.3 Safety

Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified.

Safety profiles will be assessed in terms of AEs, vital signs (including BP and pulse rate), laboratory data (clinical chemistry and hematology), and physical examination.

Summaries will be presented for scheduled visits only. Any unscheduled assessments will be listed.

Baseline

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of study intervention. Details will be described in the SAP.

Additional tables, figures, or listings may be produced to aid interpretation. Further details of summaries of the safety data will be provided in the SAP.

9.4.3.1 Adverse Events

An AE is the appearance of or worsening of any pre-existing condition, undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent. AEs will be grouped separately as AE onset before and after first dose of study drug.

Any AE commencing (or worsening) on the same day as the first dose of study treatment, will be assumed to occur after study treatment has been administered. A treatment emergent AE (TEAE) will therefore be defined as an AE with the start date on or after the first dose date, and up to and including the 30-day (± 7 days) follow-up visit after discontinuation of study treatment.

Analysis Methods

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AZ/designee.

AEs will be presented for each treatment group by System Organ Class (SOC) and/or preferred term (PT) covering number and percentage of participants reporting at least one event and number of events where appropriate.

AEs occurring prior to start of study intervention and treatment emergent AEs will be presented separately.

An overview of AEs will present for each treatment group the number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of study intervention, as well as AEs leading to study intervention dose interruptions and AEs leading to study intervention dose reduction as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taking into consideration relationship as assessed by the investigator, intensity by CTC grading, seriousness, death and events leading to discontinuation of study intervention as well as other action taken related to study treatment and other significant AEs (OAEs).

An additional table will present number and percentage of participants with most common AEs. Most common (eg, frequency of >x%, ≥x%) will be defined in the SAP.

Key subject information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of study intervention.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

9.4.3.2 Other Significant Adverse Events (OAE)

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

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

Analysis Methods

Refer to Section 9.4.3.1.

9.4.3.3 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 (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.

Analysis Methods

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

Disallowed medications will be listed.

9.4.3.4 Compliance and Exposure

Study drug exposure (days) will be defined as time from first dose of olaparib to last dose. Exposure to investigator choice will be calculated in the same way.

Exposure will be defined as:

Last dose date – first dose date + 1.

If the last dose date is unknown, the soonest available date afterwards where it is confirmed that no drug is being taken will be used instead.

Percentage compliance will be defined as:

{(No. tablets dispensed in period – no. tablets returned from period)/ (no. days of study drug exposure in period * expected tablets per day)} * 100%

Where expected tablets per day will take into account once daily or bid dosing.

Overall compliance may be calculated over various periods if the dose has been modified, to take into account the differing expected tablets per day or the protocol-specified dose interruptions. Missed doses will not be adjusted for; the overall compliance will be reduced.

Analysis Methods

Listings and summaries of exposure and compliance will be produced for olaparib and investigator's choice.

The number of participants who discontinued study drug, and the reasons, will be summarized by treatment.

9.4.3.5 Other Safety Data

Laboratory data

Laboratory data (clinical chemistry and hematology) 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.

Vital signs

Vital signs, including BP (mmHg), body temperature (°C) and weight (kg), will be summarized at baseline. The baseline value is the last pre-dose assessment.

The remaining safety variables will be presented using summary statistics for quantitative data and frequency counts for qualitative parameters.

9.5 Interim Analyses

No interim analysis for rPFS prior to the primary analysis will be performed. An OS analysis will be performed at the time of the primary rPFS analysis and at a later OS DCO when it is expected that 25 OS events have occurred (60% maturity), it is anticipated that this OS analysis could be performed at approximately 37 months after the first participant has been randomized.

Additional analyses of rPFS and/or OS may be performed to meet Regulatory Agency

requests, as required.

9.6 Independent Data Monitoring Committee

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organization but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal

Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enroled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.The ICF will contain a separate section that addresses and documents the collection and use of any mandatory human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The participant's samples will not be used for any purpose other than those described in the study protocol.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.
Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.
A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Study Level Medical Oversight Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorized site

personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Clinical Study Agreement. All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are

not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a participant or clinical study participant administered a study intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the study intervention.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definitions of Serious Adverse Event

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

- Results in death.
- Is immediately life-threatening.
- Requires in-participant hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is *not* the tumor for which entry into the study is a criterion and that is being treated by the study intervention under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

Life-threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

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

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

Intensity Rating Scale

The grading scales found in the revised NCI-CTCAE latest version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as "not related".

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration

- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refridgerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The investigator *at each site* keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

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

AstraZeneca or delegated representatives will keep oversight of the entire lifecycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of or repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per protocol.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

IATA (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are, for example, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, for example, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name: UN 3373 – Biological Substance, Category B. They are to be packed in accordance with UN 3373 and IATA 650.

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

PHL

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study intervention irrespective of an increase in alkaline phosphatase.

HL

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN.
- AST ≥ 3 × ULN.
- TBL ≥ 2 × ULN.

Local laboratories being used

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Determine whether the participant meets PHL criteria (see Section D 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

D 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, report the case as an SAE of PHL; serious criterion "Important medical event" and causality assessment "yes/related" according to CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.
  - Complete the 3 Liver eCRF Modules as information becomes available.

#A "significant" change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study intervention:

- Send updated SAE (report term "Hy's Law") according to AstraZeneca standard processes.
  - The "Medically Important" serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of PHL, (report term now "Hy's Law case") ensuring causality assessment is related to study intervention and seriousness criterion is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants with liver metastases who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the participant's condition compared with the last visit where PHL criteria were met.

- If there is no significant change no action is required.

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section D 4.2.

D 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study intervention and at their first on-study intervention visit as described in Section D 6 of this Appendix?

If **No**: follow the process described in Section D 4.2 for reporting PHL as an SAE.

If **Yes**: determine if there has been a significant change in the participant's condition compared with when PHL criteria were previously met.

- If there is no significant change no action is required.
- If there is a significant change follow the process described in Section D 4.2 for reporting PHL as an SAE.

D 8 Laboratory Tests

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HCV DNA [a] IgG anti-HCV HCV RNA [a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear antibody Anti-liver/kidney microsomal antibody Anti-smooth muscle antibody
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin saturation

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; EBV=Epstein-Barr virus; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HBc=hepatitis B core antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; HSV=herpes simplex virus; IgG=immuno-globulin G; IgM=immuno-globulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; RNA=ribonucleic acid.

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive.

In this study, a local laboratory will be used for safety tests and the Hy's Law Laboratory Kit for central laboratories is not applicable for this study.

D 9 References

Aithal et al 2011

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-15.

FDA Guidance 2009

Food and Drug Administration. Guidance for industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009. Available from: URL: https://www.fda.gov/downloads/guidances/UCM174090.pdf. Accessed 08 October 2019.

Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors) in Soft Tissue and PCWG-3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions

Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009) and PCWG-3 guidelines (Scher et al 2016) for the D081LC00002 study with regards to assessment of tumor burden including protocol-specific requirements for this study. Investigator assessments will be based on the guidelines described in this appendix.

Imaging Modalities and Acquisition Specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs and NLs is provided in Table 15.

Table 12 Summary of Imaging Modalities for Tumor Assessment

Target Lesions	Non-target lesions	New lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray ^{18}F-fluoro-deoxyglucose-PET/CT

CT=computed tomography; MRI=magnetic resonance imaging; PET/CT=positron emission tomography/CT.

Computed Tomography and Magnetic Resonance Imaging

CT with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the SoA), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of

the chest is recommended over MRI due to significant motion artefacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumor evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen (-pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a NL representing PD, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these time points are specified in the SoA. Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis).
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis).
- IV contrast-enhanced CT or MRI of the head and neck.
- IV contrast-enhanced MRI (preferred) or CT of the brain.

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when participants have sensitivity to IV contrast or have compromised renal function:

1. Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred).
2. Chest CT without IV-contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study.

3. Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the participant has compromised renal function.
4. Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study.

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. Oral contrast is recommended to help visualise and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤5 mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Isotopic bone scan

Isotopic bone scan will not be used for the RECIST assessment. Bone lesions will be evaluated with the PCWG-3 criteria. Lytic or mixed bone lesions with a soft tissue component which is observed on CT/MRI can have the soft tissue component evaluated by RECIST 1.1.

^{18}F-fluoro-deoxyglucose-PET/CT

^{18}F-fluoro-deoxyglucose positron emission tomography (PET)/CT scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is

positive ^{18}F-Fluoro-deoxyglucose uptake[1] not present on baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the ^{18}F-fluoro-deoxyglucose-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined ^{18}F-fluoro-deoxyglucose-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other Tumor Assessments

Clinical Examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Histology and Cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor

1 A positive ^{18}F-fluoro-deoxyglucose-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Furthermore, an overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

Measurability of Tumor Lesions at Baseline

RECIST 1.1 Measurable Lesions at Baseline

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable Lesions at Baseline

- Truly non-measurable lesions include the following:
  - Leptomeningeal disease.
  - Ascites, pleural effusion, or pericardial effusion.
  - Inflammatory breast disease.
  - Lymphangitic involvement of skin or lung.
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline).[3]
- Previously irradiated lesions.[4]
- Brain metastasis.

Special Considerations Regarding Lesion Measurability at Baseline

- Bone lesions:
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.

2 The short axis is defined as the longest in-plane axis perpendicular to the long axis.
3 Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.
4 Localized post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

  - Blastic lesions are not part of the RECIST assessment and must be evaluated via PCWG3 (see page 120).
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same participant, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL Selection at Baseline

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special Cases for TL Assessment at Baseline

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumor lesions selected for newly acquired screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.

- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

RECIST 1.1 NTL Selection at Baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of Tumor Response and Progression

RECIST 1.1 TL Assessment at Follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special Cases for TL Assessment at Follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of "Too large to measure" in the eCRF will trigger an overall visit response of PD.

- When a TL has had any intervention (eg, definitive radiotherapy, embolization, surgery, transarterial chemoembolization, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 eCRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 13 RECIST 1.1 Evaluation of Target Lesions

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir). This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	Only relevant if no TLs present at baseline.

CR=complete response; NE=not evaluable; PD=progression of disease; PR=partial response; SD=stable disease; TL=target lesion.

RECIST 1.1 NTL Assessment at Follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Table 14 RECIST 1.1 Evaluation of Non-Target Lesions

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of 1 or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when 1 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 participants 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	Only relevant if no NTLs present at baseline.

CR=complete response; NE=not evaluable; NTL=non-target lesion; PD=progression of disease; TL=target lesion.

RECIST 1.1 NL Identification at Follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the eCRF. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If a NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

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

RECIST 1.1 Evaluation of Overall Visit Response at Follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 18.

Table 15 RECIST 1.1 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR

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

Non-CR/Non-PD for overall response if only NTL (no TLs) are present at baseline.
Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR=complete response; NA=not applicable (only relevant if there were no TLs at baseline or NTLs at baseline); NE=not evaluable; NED=no evidence of diseases (only relevant if there were neither target lesions nor non-target lesions at baseline); NTL=non-target lesion; PD=progression of disease; PR=partial response; SD=stable disease; TL=target lesion.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE.
- For participants with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE.
- For participants with no disease at baseline: no evidence of disease (available as an option in the eCRF), PD, or NE.

ASSESSMENT OF BONE LESION PROGRESSION USING PCWG-3 CRITERIA

Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment.

Method of Assessment

Bone lesions identified on a whole-body isotopic bone scan at baseline should be recorded and followed by the same method as per baseline assessment.

In the D081LC00002 study isotopic bone scans will be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive and unequivocal hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion.

Tumor Progression Evaluation

Schedule of the Evaluation

Baseline assessments should be performed no more than 28 days before the start of study treatment. Follow-up assessments will be performed every 8 weeks (± 7 days) after randomization until objective disease progression assessed by investigator as defined by RECIST 1.1 (soft tissue) or PCWG-3 (bone).

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

Documentation of Lesions

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. This section provides the definitions of the criteria used to determine and record bone progression at the investigational site at each visit.

Progression on a bone scan is identified using PCWG-3 as follows:

- At the first visit after baseline:
  If **2 or more** new metastatic bone lesions are observed on the bone scan from the first visit after baseline, a confirmatory scan performed at the next schedule visit (and a minimum of 6 weeks later), must show **2 or more additional new** metastatic bone lesions (for a total of **4 or more new** metastatic bone lesions since the baseline assessment).
- All others visits from the second visit after baseline:
  For patients **without progression** at the first visit after baseline, the scan from this first visit after baseline now serves as new reference for all subsequent scans, ie, assuming all visits are acquired according to schedule all bone scans after week 8 are compared to the week 8 scan. If **2 or more** new metastatic bone lesions are observed on scans obtained after the first visit after baseline assessment compared to the new reference, a confirmatory scan performed preferably no later than the next scheduled visit and **at least 6 weeks later**, must show the persistence of, or an increase in, the 2 or more metastatic bone lesions.

The date of progression is the date of the first scan documenting the 2 new lesions. If the investigator is in doubt as to whether progression has occurred, it is advisable to continue study treatment and reassess the bone lesion status at the next scheduled assessment, or sooner if clinically indicated.

The requirements for determination and confirmation of radiological progression by either bone scan (bone progression) or CT/MRI (soft tissue progression) are summarized in Table 19.

Table 16 Requirements for Documentation of Progression

Visit date	Criteria for bone progression	Criteria for soft tissue progression
First visit after baseline (expected week 8)	• 2 or more new lesions compared to baseline bone scan. • Requires confirmation at least 6 weeks later with ≥2 additional lesions compared to the first scan after baseline	• Progressive disease on CT or MRI by RECIST 1.1 • No confirmation required.
From the 2nd visit after baseline	• 2 or more new lesions compared to the first bone scan after baseline. • Requires confirmation at least 6 weeks later for persistence or increase in number of lesions	• Progressive disease on CT or MRI by RECIST 1.1 • No confirmation required.

CT, computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid tumors.

Evaluation of bone progression status

Table 20 provides the definitions for the visit bone progression status for bone lesions.

Table 17 Bone Progression Status

Bone progression status	
Non Progressive Disease (Non-PD)	No evidence of progression, or appearance of 1 new bone lesion, or non-fulfillment 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 a follow-up bone scan is not performed

Central Imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (iCRO) for quality control, storage, and for BICR. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. A BICR of images will be performed at the discretion of AstraZeneca.

The management of participants will be based in part upon the results of the tumor assessments conducted by the investigator. Further details of the BICR will be documented in an Independent Review Charter.

References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Scher et al 2016
Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.

Appendix F Contraception Requirements

Olaparib is regarded as a compound with medium/high fetal risk.

Contraception requirements for this study are as follows.

F 1 Male Participants with a Female Partner of Childbearing Potential

Non-sterilized male participants (including males sterilized by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception such as male condom plus spermicide (condom alone in countries where spermicides are not approved) from Cycle 1 Day 1 throughout the total duration of the study and the drug washout period (3 months after the last dose of olaparib) to prevent pregnancy in a partner.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation or banking throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

Vasectomized (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing fetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 21).

F 2 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table 21. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Participants in the investigator's choice of NHA (abiraterone acetate or enzalutamide) group: Follow the local Prescribing Information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the investigator's choice of NHA

(abiraterone acetate or enzalutamide) group.

Table 18 Highly Effective Methods of Contraception (<1% Failure Rate)

Non-hormonal methods	Hormonal methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomized sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) PLUS male condom • Tubal occlusion PLUS male condom • Intrauterine device (provided coils are copper-banded) PLUS male condom	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®)[a] PLUS male condom • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a] PLUS male condom • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) PLUS male condom • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) PLUS male condom • Combined pill: Normal and low dose combined oral contraceptive pill PLUS male condom • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) PLUS male condom • Mini pill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill PLUS male condom

[a] Hormonal methods not prone to drug-drug interactions.

Appendix G Concomitant Medications

G 1 Guidance Regarding Potential Interactions with Concomitant Medications

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

DRUGS INDUCING OR INHIBITING CYTOCHROME P450 (CYP) 3A4/5 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMENDS ARE NOT COMBINED WITH OLAPARIB

Olaparib is metabolized by CYP3A4 and CYP3A5 enzymes. Therefore, inhibitors or inducers of CYP3A4/5 may increase or decrease exposure, respectively, to olaparib.

A drug-drug interaction study of olaparib evaluated in participants showed that there is potential for olaparib to be a victim when co-administered with strong inducers of CYP3A4/5 (olaparib concentrations are decreased when co-dosed with phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, and St John's wort).

A drug-drug interaction study of olaparib evaluated in participants showed that there is potential for olaparib to be a victim when co-administered with strong inhibitors of CYP3A4/5 (olaparib concentrations are increased when co-dosed with itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir).

Strong or moderate inducers of CYP3A should not be combined with olaparib and should be stopped at least 3 weeks (5 weeks for phenobarbital) before the first dose of olaparib.

Strong or moderate inhibitors of CYP3A should not be combined with olaparib and should be stopped at least 2 weeks before the first dose of olaparib.

The following are drugs known to be inducers of CYP3A4/5 (Table 22).

Table 19 Drugs Known to be Inducers of CYP3A4/5

Strong CYP3A4/5 inducers	Moderate CYP3A4/5 inducers
avasimibe	semagacestat[a]
carbamazepine	talviraline[a]
mitotane	bosentan
nevirapine	efavirenz
phenobarbital	etravirine
phenytoin	genistein
rifabutin	lersivirine
rifampin	lopinavir
rifapentine	modafinil
St John's wort	nafcillin
	thioridazine
	tipranavir and ritonavir[b]

[a] Not available on the United States market.
[b] Ritonavir has dual effects of simultaneous CYP3A inhibition and induction; the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.

The following are drugs known to be inhibitors of CYP3A4/5 (Table 23).

Table 20 Drugs Known to be Inhibitors of CYP3A4/5

Strong CYP3A4/5 inhibitors	Moderate CYP3A4/5 inhibitors
boceprevir	amprenavir
clarithromycin	aprepitant
conivaptan	atazanavir
elvitegravir/ritonavir	casopitant
fluconazole	cimetidine
grapefruit juice [a,b]	ciprofloxacin
indinavir	crizotinib
itraconazole	cyclosporine
ketoconazole	darunavir
lopinavir/RIT	diltiazem
mibefradil	dronedarone
nefazodone	erythromycin
nelfinavir	grapefruit juice [b]
posaconazole	imatinib
ritonavir	schisandra sphenanthera
saquinavir	tofisopam

Table 20 Drugs Known to be Inhibitors of CYP3A4/5

Strong CYP3A4/5 inhibitors	Moderate CYP3A4/5 inhibitors
telaprevir telithromycin tipranavir/ritonavir troleandomycin voriconazole	verapamil

[a] Double-strength grapefruit juice

[b] It is prohibited to consume grapefruit juice while on olaparib therapy. Participants should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, marmalade) during the study (eg, no more than half a grapefruit or 1 to 2 teaspoons [15 g] of Seville orange marmalade daily).

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

If the investigator feels that concomitant administration of medications or herbal supplements that strongly modulate CYP3A4/5 is essential (eg, to treat AEs) olaparib treatment should be discontinued.

G 2 Prohibited, Restricted and Permitted Concomitant Medications/Therapies

Prohibited, restricted and permitted concomitant medications/therapies are described in Table 24, Table 25 and Table 26. Refer also to the dose modification guidelines for management of study intervention-related toxicities in Section 6.6.

Table 21 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Anticancer therapy: • Chemotherapy • Immunotherapy • Hormonal therapy [a, b] • Radiotherapy (except palliative) • Biological therapy • Other novel agents	Not permitted while the patient is receiving study medication

Table 21 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Live virus vaccines Live bacterial vaccines	Not permitted while the patient is receiving study medication and during the 30-day follow-up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

[a] Hormone Replacement Therapy (HRT) is acceptable.
[b] Except LHRH agonist/antagonist which is required during treatment phase.

Table 22 Restricted Medications/Therapies

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it's allowed)
Strong CYP3A inhibitors Moderate CYP3A inhibitors See Appendix G 1	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib or study treatment should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. • Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards. • After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.
Strong CYP3A inducers Moderate CYP3A inducers See Appendix G 1	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of olaparib. Refer to local prescribing information for guidance on dose modification for abiraterone acetate and enzalutamide in situations where co-administration with strong CYP3A4 inducers cannot be avoided.

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it's allowed)
Strong CYP2C8 inhibitors	Co-administration of enzalutamide with strong CYP2C8 inhibitors may increase exposure to enzalutamide and thus should be avoided if possible. If subjects must be co-administered a strong CYP2C8 inhibitor, reduce the enzalutamide dose to 80 mg once daily (or per local prescribing information if different). If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • CYP2C9 substrates: warfarin • CYP2C19 substrates: lansoprazole, omeprazole, S-mephenytoin • P-gp substrates: simvastatin, pravastatin, digoxin, dabigatran, colchicine • OATP1B1 substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs: Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates CYP3A4, 2B6, 2C9, 2C19 and P-gp. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
• P-gp inhibitors: amiodarone, azithromycin	Co-administration of P-gp inhibitors may increase exposure to olaparib. Caution should therefore be observed.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

CYP3A4/5 = Cytochrome P450 3A4/5; CYP2C8 = Cytochrome P450 2C8; P-gp = P glycoprotein

Table 23 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
LHRH agonist/antagonist	Continuous ADT with an LHRH agonist/antagonist (unless bilateral orchiectomy) must be continued during the trial. Since LHRH is standard of care, it will not be provided nor reimbursed.
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate AE management, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table 24
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc]) except for those medications identified as "prohibited," as listed above	Should be used, when necessary, for all participants except for those medications identified as "prohibited," as listed in Table 24 Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Olaparib should be discontinued for a minimum of 3 days before a subject undergoes therapeutic palliative radiation treatment. Olaparib should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Corticosteroids and/or bisphosphonates for the treatment of bone metastases	Patients may receive bisphosphonates or denosumab at any point before or during the study for the prevention of skeletal related events in patients with bone metastases as clinically indicated and in line with local prescribing information.
Inactivated viruses, such as those in the influenza vaccine	Permitted
Required for management of other medical conditions	As required except for those identified as "prohibited," as listed in Table 24.

Appendix H Changes Related to the COVID-19 Pandemic

Note: Changes below should be implemented only during study disruptions due to the COVID-19 pandemic (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the Sponsor.

Remote Visit to Replace On-site Visit (where applicable)

A qualified health care professional from the study site or third-party vendor service may visit a remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified health care professional will be expected to collect information per the CSP.

Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During the COVID-19 pandemic, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication data to be collected according to study requirements to be reported and documented.

Data Capture During Telemedicine or Remote Visits

Data collected during telemedicine or remote visits will be captured in the source documents by the qualified health care professional from the study site or third-party vendor service, or from the participants themselves.

Appendix I Olaparib/Investigator's Choice of NHA Product-specific Guidance in Relation to the COVID-19 Pandemic

Every effort should be made to follow the CSP. For clarity, the Sponsor has provided in this Appendix a dose modification and management plan for study participants with confirmed or suspected COVID-19 who are being treated with olaparib/investigator's choice of NHA.

I 1 Study Participant Risks during COVID-19

The risk-benefit balance should be carefully assessed for each patient enroling in the study based on the known safety risks related to COVID-19 infections, individual needs, and local guidelines and restrictions. Treating investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

I 2 Study Treatment Administration Impacted by COVID-19

If an AE or SAE is associated with COVID-19, the investigator should determine whether the patient's treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the clinical study protocol.

Treatment interruptions associated with COVID-19 (AE or logistical issues) should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the Treatment Discontinuation Form(s) completed.

I 2.1 Olaparib/Investigator's Choice of NHA: Product-specific Guidance in Relation to the COVID-19 Pandemic

- Participants must continue to have safety assessments as per protocol schedule. Alternative methods for safety assessments include using local laboratories; follow-up by phone contact or virtual visits can be used.
- If it becomes unfeasible to perform the required safety assessments for a patient, then study treatment should be interrupted until this can be resumed and the reason clearly documented, with reference to COVID-19.
- If a patient tests positive for the COVID-19 virus, interrupting olaparib/investigator's choice of NHA treatment for 14 days or until symptoms resolve should be considered. Factors that should be taken into consideration might include:
  - Severity of COVID-19 symptoms
  - Status of safety blood results, particularly hemoglobin, neutrophils and lymphocytes
  - Benefit risk for the individual participants including curative vs palliative intent of treatment and response to olaparib/investigator's choice of NHA

- If participants present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib/investigator's choice of NHA treatment should be interrupted and prompt investigation initiated to determine whether symptoms are due to COVID-19 or potentially drug-induced pneumonitis.
- Olaparib is cleared by metabolism, predominantly by the CYP3A4/5 isozymes. Therefore, the use of olaparib/investigator's choice of NHA with the concomitant use of strong inhibitors of these isoenzymes including some antibiotics and antivirals (eg telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir and telaprevir) is not recommended.

Alternative secure delivery methods for drug supply may be permitted if the patient is unable to attend the site, but only provided the critical safety assessments have been performed and the delivery methods are in line with local regulatory requirements.

If a site is impacted by the COVID-19 pandemic so that study activities are unable to be performed, the AstraZeneca representative should be informed as soon as possible. Described measures taken due to the COVID-19 pandemic are temporary measures and will be repealed back to the previous state as soon as the situation allows.

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Appendix J Abbreviations

Abbreviation or Special Term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase;
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
Anti-HBc	Hepatitis B Core Antibody
Anti-HBs	Hepatitis B Surface Antibody
aPTT	activated partial thromboplastin time
AQA	Analgesic Quantification Algorithm
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
BICR	Blinded Independent Central Review
bid	twice daily
BoR	best objective response
BP	blood pressure
BRCA1/2	BReast CAncer gene 1/2
*BRCA*m	BReast CAncer gene mutation
CI	confidence interval
CR	complete response
CrCL	creatinine clearance
CRO	Clinical Research Organization
CRPC	castration-resistant prostate cancer
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cx	crossover
CYP	cytochrome P450
DAE	adverse event leading to discontinuation
DCO	data cutoff
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid

Abbreviation or Special Term	Explanation
DoR	duration of response
DSB	double-strand DNA break
dUCBT	double umbilical cord blood transplantation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFR	Evaluable for response
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	formalin fixed and paraffin embedded
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HL	Hy's Law
HR	hazard ratio
HRD	homologous recombination deficiency
HRR	homologous recombination repair
HRRm	homologous recombination repair gene mutations
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
iCRO	imaging Contract Research Organization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
INR	international normalized ratio

Abbreviation or Special Term	Explanation
International co-ordinating investigator	If a study is conducted in several countries the international co-ordinating investigator is the investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
KM	Kaplan-Meier
LHRH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
NGS	next-generation sequencing
NHA	new hormonal agent
NIMP	non-investigational medicinal product
NL	new lesion
NTL	non-target lesion
OAE	other significant AE
ORR	objective response rate
OS	overall survival
PARP	polyadenosine 5'diphosphoribose polymerase
PCWG3	Prostate Cancer Working Group 3
PD	progression of disease
PET	positron emission tomography
PFS	progression-free survival
PFS2	time from randomization to second progression by investigator assessment of radiological or clinical progression or death
PHL	Potential Hy's Law
PR	partial response
PSA	prostate specific antigen
PSR	Platinum-sensitive relapsed
PT	preferred term

Abbreviation or Special Term	Explanation
PTT	partial thromboplastin time
q8w	every 8 weeks
qd	once daily
QTcF	QT interval corrected by Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	ribonucleic acid
rPFS	radiological progression-free survival
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SoA	Schedule of Activities
SoC	Standard of care
SOC	System Organ Class
SSB	single-strand DNA break
SSRE	symptomatic skeletal related events
TBL	total bilirubin
t*BRCA*	BReast CAncer gene tissue
t*BRCA*m	BReast CAncer gene mutation tissue
TEAE	treatment emergent adverse event
TL	target lesion
ULN	upper limit of normal
US	United States
WHO	World Health Organization

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