China Local Clinical Study Protocol

Drug Substance	Olaparib (AZD2281, KU 0059436)
Study Code	D081SC00001
Version	China Version 2.0
Date	30 Jan 2024

A Randomised, Double-blind, Placebo-controlled, Multicentre Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men with Metastatic Castration-resistant Prostate Cancer

Sponsor: AstraZeneca AB, 151 85 CCI , Sweden

Regulatory Agency Identifying Number(s):

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IND number: IND 121413.

VERSION HISTORY

China Version 2.0 30 Jan 2024

The main changes in this amendment include:

- This China version is developed based on global CSP version 3, dated 14 May 2021.
- **Title Page:** Addition of EU CT number
- **1.2 Synopsis,** and CCI [redacted]
- **Section 4.4 End of study definition** - Update of text to include both EU and FDA definition, in line with the document template.
- **Section 6.7 Treatment after final DCO before the end of the study** - Addition of text related to continued access phase of the study, in line with the document template.
- **Section 8.1.3.2 Analgesic log** - Deletion of text related to opioid medication reconciliation.
- **Section 8.3.13 Olaparib adverse events of special interest** - Update of safety risk for pneumonitis from Important Potential Risk to Potential Risk, in line with Olaparib IB v.21.
- **Section 8.3.14 Safety data to be collected following the final DCO of the study** – Addition of new section to describe safety data collection following final DCO.
- **Section 8.4.2 Medication Error, Drug Abuse and Drug Misuse** - Update and addition of text, in line with the document template.
- **Section 8.7.1.1 Determination of HRR gene mutation** - CCI [redacted]
- **Section 8.7.3 Storage and destruction of genetic samples and Section 8.8.1 Storage, re-use and destruction of biomarker samples** – Update sample retention timeline to within one year of final CSR publication.
- **Section 9.4.5 China cohort –** Keep consistent with China cohort analysis plan
- **Appendix C** - Addition of text related to Regulatory reporting requirements for serious breaches, dissemination of clinical study data and document retention period, in line with the document template.
- **Appendix D** - Update and addition of text related to medication error, drug abuse and drug misuse, in line with the document template.

Version 3.0, 14 May 2021

The main changes in this amendment include:

- Key secondary efficacy objective of OS to additionally be formally tested at DCO1 and therefore, the alpha spend for the now 3 analyses of OS is adjusted to control the overall 1-sided type I error rate at 2.5%.
- Primary efficacy objective of rPFS assessed by investigator: Alpha spend at DCO1 corrected.
- Supply of olaparib after final DCO has been clarified in Section 6.7 Treatment after final DCO before the end of the study.
- Minor administrative changes, correction of typographical errors, and text clarifications were also made.

Version 2.0, 05 January 2021

The main changes in this amendment include:

- Key secondary objective amended to be solely OS (all comers).
- Multiplicity strategy amended to remove TFST and TTPP.
- Subgroup analyses and sensitivity analyses added/clarified for primary endpoint (rPFS); subgroup analysis added for key secondary objective (OS).
- Sample size determination, populations for analyses and statistical analyses (including multiplicity strategy) updated in line with changes to endpoints.
- A China cohort with 108 patients was added to the study. The analysis plan for the China cohort will be detailed in a separate SAP and data from patients enrolled in this cohort will not be included in the analysis for the global part (Section 9.4.5). A new schedule of assessments was included for the China cohort (Section 1.1, Table 2) and clarification of relevant assessments added to Section 8, as Chinese patients in this cohort will not participate in optional studies/analyses.
- Estimated dates for the global study period were updated and dates included for the China cohort. The current protocol will replace China local protocol version 1.0, dated 29 September 2018.
- Secondary objectives and exploratory objectives amended to clarify which objectives are not applicable for the China cohort.
- CCI [redacted] (Section 3.2 Secondary Objectives and Section 3.4. Section 9.4.3.3 CCI [redacted]).

- Definition of secondary objective PFS2 amended to state that the second progression can only be judged in patients who have moved on to next-line anticancer therapy (after the original randomised treatment has ended) and added investigator assessment methods of radiological progression, clinical symptomatic progression, PSA progression and death (Section 3.2 Secondary objectives, Section 8.1.4.3 Time to second progression or death [PFS2], and Section 9.4.3.5 Secondary endpoint: Time to second progression or death [PFS2]).
- Pain palliation removed from secondary objectives (Section 3.2 Secondary objectives) and from statistical analyses (Section 9.4.3.7 Secondary objective: Pain palliation removed).
- CCI [redacted]
- Inclusion of study mitigation language to provide sites with measures that may be implemented if a patient is unable to visit a study site to ensure that the clinical trial can continue whilst minimising risk to the patient, maintaining compliance with GCP, and minimising risk to study integrity (Section 2.3 and Section 9 updated, and Appendix K and Appendix L added).

Additionally, the following changes have been made in version 2.0 of the protocol:

Section 1.1 Schedule of Activities
Table 1 (Schedule of activities):

- Routine clinical procedures updated to include family history of cancer
- SSRE assessments added (also Section 8.1.4.4)
- ePRO assessment (BPI-SF, EQ-5D-5L, and FACT-P) timepoints clarified
- Healthcare resource use assessment (HOSPAD) timepoints clarified
- Collection timepoints for CTC blood samples clarified
- Collection timepoints for blood samples for longitudinal assessment of biomarkers (eg, ctDNA) clarified
- Collection timepoints for urinalysis clarified
- CCI [redacted]
- New footnote added clarifying that all screening procedures must be completed at least 1 day before randomisation day

- ECG footnote updated to clarify ECG schedule
- CCI
- Tumour imaging CT/MRI bone scan footnote updated to clarify confirmatory bone scan requirements

Section 1.2 Synopsis: Updated to align with changes made in the body of the protocol.

Section 2.2 Background: Subsection added to provide further detail regarding homologous recombination repair genes in prostate cancer.

Section 2.3 Benefit/risk assessment: Updated in line with current safety information to include adverse events of special interest of pneumonitis, MDS/AML, and new primary malignancies.

Section 3.2 Secondary objectives: Clarification added in a footnote that patient visits that are not evaluable for pain progression are 'consecutive' visits.

Section 4.4 End of study definition: Additional detail included to describe individual centre termination or termination of the study for safety concerns.

Section 5.4 Screen failures: IXRS replaced with randomisation and trial supply management system (interactive response technology). Also updated as necessary throughout the document.

Section 6.3.2 Methods for unblinding the study: Updated to remove reference to 'pharmacist' from unblinding process.

Section 6.5 Concomitant therapy: Table 8 updated to reflect current clinical practice in managing and preventing bone events for patients with prostate cancer. Table 9 updated to remove restrictions for palliative radiotherapy to allow for optimal pain management for the patient.

Section 6.7 Treatment after the end of the study: Updated to more clearly describe supply of olaparib after completion of the study.

Section 8.1.3.6 Administration of PRO questionnaires: Clarification added that PRO questionnaires must be completed prior to treatment administration and, if feasible, prior to other study procedures to avoid biasing patients' responses. Clarification added that patients should not receive help to answer PRO questionnaires.

Section 8.1.4.3 Time to second progression or death (PFS2): Clarification added that patients will be assessed every 12 weeks for second progression on next-line anticancer therapy by investigator assessment of clinical progression or death. The definition has been

updated to include 'next-line anticancer therapy' in line with the EMA guidance on the definition of PFS2 as 'PFS on next-line therapy' (in 'Guideline on the evaluation of anticancer medicinal products in man', EMA/CHMP/205/95 Rev.5, 22 September 2017).

Section 8.2.1 Clinical safety laboratory assessments: Updates, corrections, and clarifications to Table 14. Clarification added that carbon dioxide or bicarbonate may be measured. Fasting glucose removed from clinical chemistry and added to its own subheading. CCI [redacted] Removal of 'with differential' from B-platelet count. Column headings renamed from 'Clinical chemistry: electrolytes' and 'Clinical chemistry: general' to 'Chemistry: electrolytes' and 'Chemistry: liver function'.

Section 8.2.1.1 Coagulation: Clarification added that 'Tests' for coagulation factors will be performed.

Section 8.2.4 Electrocardiogram: Clarification added that ECGs reviewed by the investigator or designated physician will be 12-lead resting ECGs on each of the study days when they are collected, and that no paper copies will be reviewed.

Section 8.4.3 Medication error: Redundant text removed for clarity.

Section 8.4.4 Management of adverse events related to olaparib: 'Study treatment' replaced by 'olaparib' for clarity.

Section 8.5 Pharmacokinetics: Clarification added for what PK sampling information should be captured and where this should be recorded. Clarification added that IP dosing confirmation should be recorded. Removal of statement that non-linear mixed effect modelling will be performed if appropriate. Clarification that residual back-up PK samples may be used for future diagnostic development.

Section 8.7.1 Collection of mandatory genetic samples: Clarification added that in the event of a tumour tissue test failure, additional consent for replacement sample is not required, and that the patient can continue in the study if a replacement sample is not available. Addition of statement that data and samples collected as part of the study may be used for development of current or future diagnostic tests.

Section 8.7.2 Optional exploratory genetic sample: CCI [redacted]

Section 8.7.3 Storage and destruction of genetic samples: Details added for the China cohort.

Section 8.8 CCI [redacted] Clarification that samples will be collected at **radiological** progression. Details added for storage, re-use, and destruction of biomarker samples in the China cohort.

Section 9.2 Sample size determination: The statistical model was re-estimated based on an updated size of study population and actual recruitment rate.

Section 9.3 Populations for analyses: Table 18 updated to add clarification that the safety analysis set will be used for safety analyses. Table 19 added to define the China cohort populations.

Section 9.4.2.4 Exposure: Further detail included regarding analysis of exposure data.

Section 9.4.3.2 Secondary endpoint: Time to pain progression (TTPP): Clarification added in a footnote that patient visits that are not evaluable for pain progression are 'consecutive' visits.

Section 9.4.3.5 Secondary endpoint: Time to second progression or death (PFS2): Clarification added for the definition of time to second progression or death. The definition has been updated to include 'next-line anticancer therapy' in line with the EMA guidance on the definition of PFS2 as 'PFS on next-line therapy' (in 'Guideline on the evaluation of anticancer medicinal products in man', EMA/CHMP/205/95 Rev.5, 22 September 2017).

Section 9.4.3.6 Secondary endpoint: Pain severity, **Section 9.4.3.7 Secondary endpoint: Pain interference**, and **Section 9.4.3.8 Secondary endpoint: FACT-P**: Analysis methods updated to include MMRM analysis.

Section 9.4.3.8 Secondary endpoint: FACT-P: Analysis methods updated to clarify analysis of patients who died or discontinued.

Section 9.4.5 China cohort: New section included to provide details of statistical analyses for the China cohort.

Section 9.5 Interim analyses: Change in number of events related to the planned interim analyses. Detail on interim analyses for each DCO is provided in Table 22. This has been moved from Section 9.2 to Section 9.5, and updated in line with statistical analysis amendments.

Appendix D6: CTCAE version updated. **Appendix E:** IATA link updated. **Appendix G:** Updated instructions for investigators in cases of increases in liver biochemistry and evaluation of Potential Hy's Law. **Appendix I:** Updated in line with current guidelines and IB edition 19. Additionally, changes were made throughout the protocol for consistency. Text was clarified, and administrative (typographical and formatting) changes were implemented where necessary.

Version 1.0, 02 July 2018
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol 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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADT	Androgen deprivation therapy
AE	Adverse event
AESI	Adverse event of special interest
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AQA	Analgesic quantification algorithm
AR	Androgen receptor
AST	Aspartate aminotransferase
AUC_{0-8}	Area under the plasma concentration-time curve from time zero to 8 hours post-dose
AUC_{ss}	Area under the plasma concentration-time curve across the dosing interval at steady state
BICR	Blinded independent central review
BP	Blood pressure
BPI-SF	Brief Pain Inventory-Short Form
BRCA	Breast cancer susceptibility gene
BRCA1, BRCA2	Breast Cancer 1 gene or Breast Cancer 2 gene
BUN	Blood urea nitrogen
cfDNA	Cell-free DNA
CI	Confidence interval
CL_{ss} /F	Apparent total body clearance of drug from plasma after extravascular administration at steady state
$C_{max\ ss}$	Maximum observed plasma (peak) drug concentration at steady state
$C_{min\ ss}$	Minimum observed plasma (peak) drug concentration at steady state
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organisation
CSP	Clinical study protocol
CT	Computed tomography
CTC	Circulating tumour cells

Abbreviation or special term	Explanation
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour DNA
CYP	Cytochrome P450
DAE	Discontinuation of investigational product due to adverse event
DCO	Data cut-off
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSB	Double strand break
dUCBT	Double umbilical cord blood transplantation
E-code	Enrolment code
EC	Ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQol 5-dimension, 5-level health state utility index
ESMO	European Society for Medical Oncology
EuroQoL	European Quality of Life
EWB	Emotional well-being
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy - Prostate Cancer
FA DCO	Final formal analysis data cut-off
FAPSI-6	Functional Assessment of Prostate Cancer Symptoms Index-6
FDA	Food and Drug Administration
FFPE	Formalin fixed, paraffin embedded
FWB	Functional well-being
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
Hb	Haemoglobin
Hct	Haematocrit

Abbreviation or special term	Explanation
HOSPAD	Hospital Admission. An AstraZeneca module used to record resource use during unscheduled hospital visits and admissions
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HRRm	Homologous recombination repair gene mutation
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
INR	International normalised ratio
IP	Investigational medicinal product
IRB	Institutional review board
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
ITT	Intention-to-treat
KM	Kaplan–Meier
LHRH	Luteinising hormone-releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer
MDS	Myelodysplastic syndrome
mHSPC	Metastatic hormone-sensitive prostate cancer
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan Cardiology A
NCA	Non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Non-evaluable
NED	No evidence of disease
NHA	New hormonal agent (eg, abiraterone, enzalutamide)
NL	New lesion
NRS	Numeric rating scale
NT-proBNP	N-terminal pro B-type natriuretic peptide
OAE	Other significant adverse event

Abbreviation or special term	Explanation
OME	Oral morphine equivalents
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase
PCS	Prostate cancer subscale
PCWG-2	Prostate Cancer Working Group-2
PCWG-3	Prostate Cancer Working Group-3
PD	Progression of disease
PFS	Progression-free survival
PFS2	Time to second progression or death
PK	Pharmacokinetics
PR	Partial response
PRO	Patient-reported outcome
PSA	Prostate Specific Antigen
PT	Prothrombin
PTT	Partial thromboplastin time
PWB	Physical well-being
RECIST	Response Evaluation Criteria in Solid tumours. This study will use RECIST version 1.1.
rPFS	Radiological progression-free survival
RTSM (IRT)	Randomisation and Trial Supply Management System (Interactive Response Technology)
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SmPC	Summary of Product Characteristics
SoA	Schedule of activities
SOP	Standard operating procedure
SRC	Safety review committee
SSB	Single strand breaks
SSRE	Symptomatic skeletal-related event (symptomatic fracture, need for radiation to bone metastasis, need for surgery for bone metastasis, or spinal cord compression)
SWB	Social well-being
TEAE	Treatment-emergent adverse event
TFST	Time to start of first subsequent anticancer therapy or death
TL	Target lesion

Abbreviation or special term	Explanation
t_{last}	Time of last observed (quantifiable) concentration
$t_{max,ss}$	Time to reach peak or maximum observed plasma concentration at steady state
TOI	Trial outcome index
TTPP	Time to pain progression
ULN	Upper limit of normal

1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The schedule of study assessments is provided in Table 1 for the global study and Table 2 for the China cohort.

Table 1 Schedule of assessments – Global study

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
Week (visit window ± 3 days except visit 2)	**Week -4 to day 0 (28 days)**	**1 (day 1)**	**3 (day 15)**	**5 (day 29)**	**7 (day 43)**	**9 (day 57)**	**11 (day 71)**	**13+ Every 4 weeks (starting week 13)**				
Informed consent	X											Section **5.1** & **Appendix C**
Inclusion/exclusion criteria	X											Section **5.1** and **5.2**
Routine clinical procedures												
Demography	X											
Family history of cancer	X											
Medical and surgical history	X											Section **5.1**
Prior cancer therapies (includes radiotherapy, surgery, ADT and chemotherapy)	X											Section **5.1**
History of blood transfusions[a]	X											Section **5.1**

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
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ECOG performance status[b]	X	X[c]						X	X	X		**Appendix B**
Physical examination[d]	X	X[c]		X[e]		X[e]		X[e+]				Section **8.2.2**
Vital signs (includes BP, pulse rate and body temperature)[d]	X	X[c]		X		X		X	X	X		Section **8.2.3**
Weight	X	X		X		X		X	X	X		Section **8.2.3**
Electrocardiogram[d,f]	X	Every 12 weeks							X	X		Section **8.2.4**
Cardiac function (by ECHO or MUGA)[g]	X	As clinically indicated[g]										Section **8.2.5**
Concomitant medication (including blood transfusions)	X	At every visit and may be conducted by phone if not tied to a scheduled visit							X	X		Section **6.5**
SSRE assessment[h]		At every visit from randomisation up to and including treatment discontinuation visit (patients who discontinue study treatment and continue in the study should be followed for SSREs at every visit until disease progression)[i]										Section 8.1.4.4

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
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Routine safety measurements												
Adverse events[j]	X	At every visit and may be conducted by phone if not tied to a scheduled visit							X	X		Section **8.3**
Haematology	X	X[e]	X	X	X	X	X	X	X	X		Section **8.2.1**
Coagulation factors	X[d]											Section **8.2.1.1**
Clinical chemistry, electrolytes	X	X[e]		X		X		X	X	X		Section **8.2.1**
Fasting glucose	X	X[e]	Every 12 weeks						X	X		Section **8.2.1**
Serum lipids	X	X[e]	Every 12 weeks						X	X		Section **8.2.1**
Chemistry: liver function	X	X[e]	X	X	X	X	X	X	X	X		Section **8.2.1**
Serum testosterone	X											Section **8.2.1**
Urinalysis[d]	X	X[e]	As clinically indicated									Section **8.2.1**

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
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Secondary malignancies (including MDS/AML)[k]	X	X										Section **8.3.10**
Biomarker analyses												
Local HRR gene mutation status[l]	X											Section **8.7**
Bone marrow aspirate or blood cytogenetic sample for prolonged haematological toxicities		As clinically indicated										Section **8.2.1.2**
Archival or newly collected FFPE tumour sample[m]	X											Section **8.7.1**
Blood sample for central germline HRR gene testing		X[n]										Section **8.7.1**
Blood sample for central ctDNA analysis of HRR genes		X[o]										Section **8.7.1**

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
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CCI		CCI						CCI	CCI			CCI 8.8
CCI	CCI	CCI		CCI		CCI			CCI			CCI
Tumour biopsy (optional)		X (radiological progression)										Section 8.8
CCI	CCI	CCI										CCI CCI
Pharmacogenetic sampling (optional)[s]												
Blood sample for pharmacogenomics (optional)		X										Section 8.7.2

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
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Pharmacokinetic measurements												
Blood sample for pharmacokinetic analysis (subset of patients)		At visit 4, samples will be collected at the following times: Pre-dose (- 30 min ± 15 min), and post-dose at 30 min ± 15 min, 2 ± 0.5 h, 3 ± 0.5 h, 5 ± 0.5 h and 8 ± 1h[t]										Section **8.5**
Efficacy measurements												
BPI-SF, analgesic log (captured on ePRO device)	X[u]	To be completed by patient daily for 7 consecutive days every 4 weeks (not required to be at site), with Day 1 as the baseline visit date[v]										Section **8.1.3.1**
EQ-5D-5L		Every 8 weeks from Day 1, at Week 52, then every 8 weeks; and at treatment discontinuation visit[v]										Section **8.1.3.5**
FACT-P		Every 4 weeks from Day 1 until Week 52, at Week 52, then every 8 weeks; and at treatment discontinuation visit[v]										Section **8.1.3.4**
Healthcare resource use (HOSPAD)		From Visit 2 onwards, to be completed by site staff at each hospitalisation and unscheduled visit										Section **8.9.1**
Opiate use	X	X		X		X		X	X	X		Section **8.1.3.3**
Prostate-specific antigen	X	X		X		X		X	X			Section **8.2.1**

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
Week (visit window ± 3 days except visit 2)	**Week -4 to day 0 (28 days)**	**1 (day 1)**	**3 (day 15)**	**5 (day 29)**	**7 (day 43)**	**9 (day 57)**	**11 (day 71)**	**13+ Every 4 weeks (starting week 13)**				
Tumour imaging CT/MRI and bone scan[w]	X	Every 8 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) relative to the date of randomisation[x]										Section **8.1.1**
Subsequent cancer therapy following discontinuation of study treatment[y]										X	X	Section **6.5**
Survival[z] and second progression (PFS2) follow-up[aa]											X	Section **8.1.4.2** and Section **8.1.4.3**
Study treatment administration												
Randomisation		X										Section **6.3**
Study drug dispensed/returned (daily dosing)		X		X		X		X	X	X		Sections **6.1, 6.2**

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

[b] To be assessed a maximum of 14 days prior to randomisation.

[c] If assessed within 7 days before randomisation, does not need to be repeated on Day 1 of study treatment unless the investigator or designee believes that it is likely to have changed significantly.

[d] To be additionally performed if clinically indicated at any other time for all patients. Patients with hypertension at baseline need to be monitored closely, and BP must be recorded at all visits.

[e] The investigator or qualified designee will perform a symptom directed physical examination, as clinically indicated, prior to dosing on the day of each visit.

[f] The electrocardiogram should be performed within 7 days prior to randomisation. The 12-weekly assessments should be counted from the date of randomisation.

[g] Patient must have a left ventricular ejection fraction measurement of at least 50% by ECHO (preferable) or MUGA, a maximum of 14 days prior to randomisation. The method used for individual patients pre-randomisation should preferably be used for any clinically indicated future assessments.

[h] An SSRE is defined by any of the following or a combination thereof: use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral, resulting from minimal or no trauma), occurrence of radiologically confirmed spinal cord compression, or a tumour-related orthopaedic surgical intervention.

[i] For patients who discontinue study treatment for reasons other than objective disease progression, and who continue in the study, any SSREs determined at an imaging visit should be recorded under an unscheduled visit in eCRF.

[j] All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-calendar-day follow-up period after the last dose of study treatment must be followed to resolution.

[k] Because some cases of MDS/AML or new primary malignancies may develop on or after discontinuing treatment with study treatment, investigators will be asked during the regular follow-up if the patient has developed MDS/AML or a new primary malignancy and will be prompted to report any case as an SAE (or an AE if at least 1 of the criteria for an SAE is not met, such as for non-melanoma skin cancers) even after discontinuation of therapy and regardless of the investigator's assessment of causality or knowledge of the treatment assignment.

[l] Collect any locally available HRR gene mutation data from analysis of, eg, blood, tumour tissue, and/or plasma.

[m] For randomised patients only. Archival or newly collected FFPE biopsies must be submitted. Confirmation is required in clinical notes regarding availability of a sample that meets the specimen guidelines outlined in the Laboratory Manual during the screening period; however, the sample will only be submitted to AstraZeneca once the patient has been randomised. This sample may also be used to develop current or future diagnostic tests.

[n] If the sample is not collected for any reason during visit 2, it should be collected at any visit thereafter. This sample may also be used to develop current or future diagnostic tests.

[o] If the sample is not collected for any reason during visit 2, it should be collected at visit 3. This sample may also be used to develop current or future diagnostic tests.

[p] If the sample is not collected at visit 8, it should be collected at visit 9.

[q] Progression sample may be collected at either a scheduled visit or an unscheduled visit per site preference.

[r] Central testing.

[s] Blood sample for pharmacogenomics reflects Genomic Initiative Sample.

[t] Approximately 50 patients assigned to each treatment arm at pre-agreed sites will have pharmacokinetic assessment samples taken. Sampling times: Pre-dose (- 30 min ± 15 min); post-dose, 30 min ± 15 min, 2 ± 0.5 h, 3 ± 0.5 h, 5 ± 0.5 h, 8 ± 1 h.

[u] To be completed by the patient daily for any 7 consecutive days during screening (not required to be at site).

[v] Patient-reported outcomes assessments will continue until 12 weeks after confirmed progressive disease.

[w] Tumour assessment will be performed using a CT or MRI scan for soft tissue of chest, abdomen, and pelvis and a bone scan for whole body. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Follow-up assessments will be performed every 8 weeks (±7 days) for the first 24 weeks and then every 12 weeks (±7 days) relative to the date of randomisation until objective disease progression as defined by RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), regardless of discontinuation of study treatment or initiation of subsequent anticancer therapy. A confirmatory bone scan is required to confirm progression due to new bone lesions, preferably at the next scheduled visit for a bone scan and at least 6 weeks later. The date of progression is the date of the first bone scan documenting the 2 new lesions. If there is no confirmatory scan this is not PD. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the patient's scheduled visits.

[x] Patients who discontinue study treatment before disease progression should continue follow-up tumour 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. After the initial assessment of progression, whether the patient receives a subsequent therapy or not, the patient should have 1 follow-up scan collected preferably at the next (and no later than the next) scheduled imaging visit, and no less than 6 weeks after the prior assessment of PD.

[y] All anticancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigator's opinion of response to these treatments plus the date of progression, following discontinuation of study treatment, must be recorded.

[z] The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients' notes, hospital records, contacting the patients' general practitioner, and checking publicly available death registries, if allowable per local regulations. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 7.3). In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut-off date) for the survival analysis.

[aa] Second progression is based on investigator assessment according to local standard clinical practice and includes radiological, PSA progression 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) and the start of the next-line anticancer therapy.

ADT, Androgen-deprivation therapy; AE, Adverse event; AML, Acute myeloid leukaemia; BP, Blood pressure; BPI-SF, Brief Pain Inventory-Short Form; CT, Computed tomography; CCI [redacted] ECHO, Echocardiography; ECOG, Eastern Cooperative Oncology Group; ePRO, Electronic patient-reported outcomes; EQ-5D-5L, EuroQol 5-dimension, 5-level, health state utility index; FACT-P, Functional Assessment of Cancer Therapy - Prostate Cancer; FFPE, Formalin-fixed, paraffin-embedded CCI [redacted] HRR, Homologous recombination repair; INR, International normalized ratio; MDS, Myelodysplastic syndrome; MRI, Magnetic resonance imaging; MUGA, Multigated acquisition scan; CCI [redacted] PCWG-3, Prostate Cancer Working Group 3; PD, Progressive disease; PFS2, Time to second progression or death; PT, Prothrombin time; PTT, Partial thromboplastin time; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, Serious AE; SSRE, Symptomatic skeletal-related event.

Table 2 Schedule of assessments – China cohort

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
Week (visit window ± 3 days except visit 2)	**Week -4 to day 0 (28 days)**	**1 (day 1)**	**3 (day 15)**	**5 (day 29)**	**7 (day 43)**	**9 (day 57)**	**11 (day 71)**	**13+ Every 4 weeks (starting week 13)**				
Informed consent	X											Section 5.1 & Appendix C
Inclusion/exclusion criteria	X											Section 5.1 and 5.2
Routine clinical procedures												
Demography	X											
Family history of cancer	X											

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
Week (visit window ± 3 days except visit 2)	**Week -4 to day 0 (28 days)**	**1 (day 1)**	**3 (day 15)**	**5 (day 29)**	**7 (day 43)**	**9 (day 57)**	**11 (day 71)**	**13+ Every 4 weeks (starting week 13)**				
Medical and surgical history	X											Section **5.1**
Prior cancer therapies (includes radiotherapy, surgery, ADT and chemotherapy)	X											Section **5.1**
History of blood transfusions[a]	X											Section **5.1**
ECOG performance status[b]	X	X[c]						X	X	X		**Appendix B**
Physical examination[d]	X	X[c]		X[e]		X[e]		X[e+]				Section **8.2.2**
Vital signs (includes BP, pulse rate and body temperature)[d]	X	X[c]		X		X		X	X	X		Section **8.2.3**
Weight	X	X		X		X		X	X	X		Section **8.2.3**
Electrocardiogram[d,f]	X	Every 12 weeks							X	X		Section **8.2.4**

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
Week (visit window ± 3 days except visit 2)	**Week -4 to day 0 (28 days)**	**1 (day 1)**	**3 (day 15)**	**5 (day 29)**	**7 (day 43)**	**9 (day 57)**	**11 (day 71)**	**13+ Every 4 weeks (starting week 13)**				
Cardiac function (by ECHO or MUGA)[g]	X	As clinically indicated[g]										Section **8.2.5**
Concomitant medication (including blood transfusions)	X	At every visit and may be conducted by phone if not tied to a scheduled visit							X	X		Section **6.5**
SSRE assessment[h]		At every visit from randomisation up to and including treatment discontinuation visit (patients who discontinue study treatment and continue in the study should be followed for SSREs at every visit until disease progression)[i]										Section 8.1.4.4
Routine safety measurements												
Adverse events[j]	X	At every visit and may be conducted by phone if not tied to a scheduled visit							X	X		Section **8.3**
Haematology	X	X[c]	X	X	X	X	X	X	X	X		Section **8.2.1**
Coagulation factors	X[d]											Section **8.2.1.1**
Clinical chemistry, electrolytes	X	X[c]		X		X		X	X	X		Section **8.2.1**
Fasting glucose	X	X[c]	Every 12 weeks						X	X		Section **8.2.1**

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
Week (visit window ± 3 days except visit 2)	**Week -4 to day 0 (28 days)**	**1 (day 1)**	**3 (day 15)**	**5 (day 29)**	**7 (day 43)**	**9 (day 57)**	**11 (day 71)**	**13+ Every 4 weeks (starting week 13)**				
Serum lipids	X	X[c]	Every 12 weeks						X	X		Section **8.2.1**
Chemistry: liver function	X	X[c]	X	X	X	X	X	X	X	X		Section **8.2.1**
Serum testosterone	X											Section **8.2.1**
Urinalysis[d]	X	X[c]	As clinically indicated									Section **8.2.1**
Secondary malignancies (including MDS/AML)[k]	X	X										Section **8.3.10**
Biomarker analyses												
Bone marrow aspirate or blood cytogenetic sample for prolonged haematological toxicities		As clinically indicated										Section **8.2.1.2**
Archival or newly collected FFPE tumour sample[l]	X											Section **8.7.1**

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
Week (visit window ± 3 days except visit 2)	**Week -4 to day 0 (28 days)**	**1 (day 1)**	**3 (day 15)**	**5 (day 29)**	**7 (day 43)**	**9 (day 57)**	**11 (day 71)**	**13+ Every 4 weeks (starting week 13)**				
CCI	CCI	CCI										CCI
Efficacy measurements												
BPI-SF, analgesic log (captured on ePRO device)	X[n]	To be completed by patient daily for 7 consecutive days every 4 weeks (not required to be at site), with Day 1 as the baseline visit date[o]										Section 8.1.3.1
EQ-5D-5L		Every 8 weeks from Day 1, at Week 52, then every 8 weeks; and at treatment discontinuation visit[o]										Section 8.1.3.5
FACT-P		Every 4 weeks from Day 1 until Week 52, at Week 52, then every 8 weeks; and at treatment discontinuation visit[o]										Section 8.1.3.4
Healthcare resource use (HOSPAD)		From Visit 2 onwards, to be completed by site staff at each hospitalisation and unscheduled visit										Section 8.9.1
Opiate use	X	X		X		X		X	X	X		Section 8.1.3.3
Prostate-specific antigen	X	X		X		X		X	X			Section 8.2.1
Tumour imaging CT/MRI and bone scan[p]	X	Every 8 weeks (±7 days) for the first 24 weeks, then every 12 weeks (±7 days) relative to the date of randomisation[q]										Section 8.1.1

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**Study treatment discontinuation (+7 days of last study drug dose)**	**30-day follow-up after last dose of study medication (+7 days)**	**Survival follow-up (±14 days every 12 weeks)**	**Details in CSP Section or Appendix**
Week (visit window ± 3 days except visit 2)	**Week -4 to day 0 (28 days)**	**1 (day 1)**	**3 (day 15)**	**5 (day 29)**	**7 (day 43)**	**9 (day 57)**	**11 (day 71)**	**13+ Every 4 weeks (starting week 13)**				
Subsequent cancer therapy following discontinuation of study treatment[r]										X	X	Section **6.5**
Survival[s] and second progression (PFS2) follow-up[t]											X	Section **8.1.4.2** and Section **8.1.4.3**
Study treatment administration												
Randomisation		X										Section **6.3**
Study drug dispensed/returned (daily dosing)		X		X		X		X	X	X		Sections **6.1, 6.2**

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

[b] To be assessed a maximum of 14 days prior to randomisation.

[c] If assessed within 7 days before randomisation, does not need to be repeated on Day 1 of study treatment unless the investigator or designee believes that it is likely to have changed significantly.

[d] To be additionally performed if clinically indicated at any other time for all patients. Patients with hypertension at baseline need to be monitored closely, and BP must be recorded at all visits.

[e] The investigator or qualified designee will perform a symptom directed physical examination, as clinically indicated, prior to dosing on the day of each visit.

[f] The electrocardiogram should be performed within 7 days prior to randomisation. The 12-weekly assessments should be counted from the date of randomisation.

[g] Patient must have a left ventricular ejection fraction measurement of at least 50% by ECHO (preferable) or MUGA, a maximum of 14 days prior to randomisation. The method used for individual patients pre-randomisation should preferably be used for any clinically indicated future assessments.

[h] An SSRE is defined by any of the following or a combination thereof: use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral, resulting from minimal or no trauma), occurrence of radiologically confirmed spinal cord compression, or a tumour-related orthopaedic surgical intervention.

[i] For patients who discontinue study treatment for reasons other than objective disease progression, and who continue in the study, any SSREs determined at an imaging visit should be recorded under an unscheduled visit in eCRF.

[j] All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30-calendar-day follow-up period after the last dose of study treatment must be followed to resolution.

[k] Because some cases of MDS/AML or new primary malignancies may develop on or after discontinuing treatment with study treatment, investigators will be asked during the regular follow-up if the patient has developed MDS/AML or a new primary malignancy and will be prompted to report any case as an SAE (or an AE if at least 1 of the criteria for an SAE is not met, such as for non-melanoma skin cancers) even after discontinuation of therapy and regardless of the investigator's assessment of causality or knowledge of the treatment assignment.

[l] For randomised patients only. Archival or newly collected FFPE biopsies must be submitted. Confirmation is required in clinical notes regarding availability of a sample that meets the specimen guidelines outlined in the Laboratory Manual during the screening period; however, the sample will only be submitted to AstraZeneca once the patient has been randomised. This sample may also be used to develop current or future diagnostic tests.

[m] Central testing.

[n] To be completed by the patient daily for any 7 consecutive days during screening (not required to be at site).

[o] Patient-reported outcomes assessments will continue until 12 weeks after confirmed progressive disease.

[p] Tumour assessment will be performed using a CT or MRI scan for soft tissue of chest, abdomen, and pelvis and a bone scan for whole body. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Follow-up assessments will be performed every 8 weeks (±7 days) for the first 24 weeks and then every 12 weeks (±7 days) relative to the date of randomisation until objective disease progression as defined by RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), regardless of discontinuation of study treatment or initiation of subsequent anticancer therapy. A confirmatory bone scan is required to confirm progression due to new bone lesions, preferably at the next scheduled visit for a bone scan and at least 6 weeks later. The date of progression is the date of the first bone scan documenting the 2 new lesions. If there is no confirmatory scan this is not PD. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the patient's scheduled visits.

[q] Patients who discontinue study treatment before disease progression should continue follow-up tumour 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. After the initial assessment of progression, whether the patient receives a subsequent therapy or not, the patient should have 1 follow-up scan collected preferably at the next (and no later than the next) scheduled imaging visit, and no less than 6 weeks after the prior assessment of PD.

[r] All anticancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigator's opinion of response to these treatments plus the date of progression, following discontinuation of study treatment, must be recorded.

[s] The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patients' notes, hospital records, contacting the patients' general practitioner, and checking publicly available death registries, if allowable per local regulations. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws (see Section 7.3). In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut-off date) for the survival analysis.

[t] Second progression is based on investigator assessment according to local standard clinical practice and includes radiological, PSA progression 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) and the start of the next-line anticancer therapy.

ADT, Androgen-deprivation therapy; AE, Adverse event; AML, Acute myeloid leukaemia; BP, Blood pressure; BPI-SF, Brief Pain Inventory-Short Form; CT, Computed tomography; ECHO, Echocardiography; ECOG, Eastern Cooperative Oncology Group; ePRO, Electronic patient-reported outcomes; EQ-5D-5L, EuroQol 5-dimension, 5-level, health state utility index; FACT-P, Functional Assessment of Cancer Therapy - Prostate Cancer; FFPE, Formalin-fixed, paraffin-embedded; HOSPAD, An AstraZeneca module used to record resource use during unscheduled hospital visits and admissions; HRR, Homologous recombination repair; INR, International normalized ratio; MDS, Myelodysplastic syndrome; MRI, Magnetic resonance imaging; MUGA, Multigated acquisition scan; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCWG-3, Prostate Cancer Working Group 3; PD, Progressive disease; PFS2, Time to second progression or death; PT, Prothrombin time; PTT, Partial thromboplastin time; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, Serious AE; SSRE, Symptomatic skeletal-related event.

1.2 Synopsis

International Co-ordinating Investigators

CCI

[redacted]

Protocol Title: A Randomised, Double-blind, Placebo-controlled, Multicentre Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men with Metastatic Castration-resistant Prostate Cancer

Short Title: Phase III Study of Olaparib Plus Abiraterone versus Placebo Plus Abiraterone as First-line Therapy in Men with Metastatic Castration-resistant Prostate Cancer

Rationale: PROpel is a Phase III study evaluating the efficacy, safety, and tolerability of olaparib versus placebo when given in addition to abiraterone acetate (henceforth referred to as abiraterone) to genetically unselected patients (ie, an 'all-comers' population) with metastatic castration-resistant prostate cancer (mCRPC) who have not received prior chemotherapy or new hormonal agents (NHAs) for mCRPC (first-line setting). It is proposed that this study will build on the knowledge gained from D081DC00008 (Study 8; NCT01972217) and serve as confirmatory evidence of the clinical benefit, safety, and tolerability of the combination of olaparib and abiraterone in the treatment of patients with mCRPC. Study 8 was a randomised, double-blind, placebo-controlled, multicentre Phase II study of olaparib versus placebo when given in combination with abiraterone, in patients with mCRPC who had received prior chemotherapy containing docetaxel (second-line setting).

The rationale for treating patients with mCRPC with the combination of olaparib and abiraterone is based on the observation, both in cell culture and model systems (Schiewer et al 2012, Asim et al 2017), that polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerisation (PARP) inhibition plus androgen deprivation could significantly reduce the growth of prostate cancer cells independent of HRR gene mutation status.

Following the completion of global enrolment to PROpel, a China cohort will randomise approximately 108 additional patients at sites in China. Data from the China cohort will be analysed separately from the global cohort.

Primary Objective:	**Outcome Measures:**

To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of rPFS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	rPFS, defined as the time from randomisation to 1) radiological progression, assessed by investigator per RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), or 2) death from any cause, whichever occurs first.

mCRPC, Metastatic castration-resistant prostate cancer; NHA, New hormonal agent; PCWG-3, Prostate Cancer Working Group 3; rPFS, Radiological progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid tumours version 1.1.

Secondary Objectives:	**Outcome Measures:**
To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of OS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	OS, defined as the time from randomisation to death from any cause.
To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone as assessed by time to start of first subsequent anticancer therapy or death (TFST) in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	TFST, ie, the time from randomisation to 1) the start of the first subsequent anticancer therapy or 2) death from any cause.[a]
To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone as assessed by time to pain progression (TTPP) in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	TTPP is defined as the time from randomisation to pain progression based on the Brief Pain Inventory-Short Form (BPI-SF) Item 3 “worst pain in 24 hours” and opiate analgesic use (analgesic quantification algorithm [AQA] score).[b]
To further evaluate the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of time to opiate use, time to an SSRE, and PFS2 in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• Time to opiate use: The time from randomisation to the first opiate use for cancer-related pain. • Time to an SSRE: the time from randomisation to the first SSRE. 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 radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention. • PFS2: The time from randomisation to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression or death.

To assess the effect of the combination of olaparib and abiraterone vs placebo and abiraterone on disease related symptoms and HRQoL using BPI-SF and Functional Assessment of Cancer Therapy (FACT) - Prostate Cancer (FACT-P) questionnaires in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• BPI-SF: progression in pain severity domain, change in pain interference domain. • FACT-P total score, FACT-G total score, trial outcome index, functional well-being, physical well-being, prostate cancer subscale, and FACT Advanced Prostate Symptom Index-6 (FAPSI-6).
To evaluate tumour and blood samples collected from patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage for mutations in *BRCA1*, *BRCA2*, *ATM* and 11 other HRR genes. Note: blood samples will not be collected for HRR gene mutation status testing in the China cohort	HRR gene mutation status.
To determine steady-state exposure to abiraterone and its active metabolite Δ4-abiraterone in the presence and absence of olaparib. To determine steady-state exposure to olaparib when co-administered with abiraterone. Note: this objective is not applicable for the China cohort	• Plasma concentration data at steady state for olaparib, abiraterone, and Δ4-abiraterone in the subset of patients evaluable for PK. • If sufficient data are available, PK parameters at steady state (eg, maximum concentration [$C_{max,ss}$], time to $C_{max,ss}$ [$t_{max,ss}$], minimum concentration [$C_{min,ss}$], and partial area under the concentration-time curve [AUC_{0-8}]) will be calculated in the PK patient subset. In addition, the area under the curve at steady state (AUC_{ss}) and the apparent clearance (CL_{ss}/F) for olaparib and the metabolite to parent ratios for $C_{max,ss}$, $C_{min,ss}$ and AUC_{0-8} for Δ4-abiraterone will be determined. The time of last concentration (t_{last}) will also be determined as a diagnostic parameter.

[a] Subsequent systemic anticancer therapies (excluding radiotherapy) will be reviewed prior to data unblinding to assess which represent clinically important treatments intended to control prostate cancer. Any patient not known to have died at the time of the analysis and not known to have had a further anticancer therapy will be censored at the last known time to have not received subsequent therapy, ie, the last follow-up visit where this was confirmed.

[b] Pain progression is defined as follows: 1) for patients who are asymptomatic at baseline, a ≥2-point change from baseline in the average (4-7 days) Brief Pain Inventory-Short Form (BPI-SF) Item 3 score observed at 2 consecutive evaluations (with at least 2 weeks between the end of the initial visit and the start of the subsequent visit) OR initiation of opioid use for pain; 2) for patients who are symptomatic at baseline (average BPI-SF Item 3 score >0 and/or currently taking opioids), a ≥2-point change from baseline in the average BPI-SF Item 3 score observed at 2 consecutive visits and an average worst pain score ≥4, and no decrease in average opioid use (≥1-point decrease in analgesic quantification algorithm [AQA] score from a starting value of 2 or higher) OR any increase in opioid use (eg, 1-point change in AQA score) at 2 consecutive follow-up visits (with at least 2 weeks between the end of the initial visit and the start of the subsequent visit). Any patient who has more than 2 consecutive visits that are not evaluable for pain progression will be censored at the last evaluable assessment.

AQA, Analgesic quantification algorithm; *ATM*, Ataxia-telangiectasia mutated; AUC_{0-8}, Area under the plasma concentration-time curve in 0-8 h; AUC_{ss}, Area under the plasma concentration-time curve at steady state; BPI-SF, Brief Pain Inventory-Short Form; *BRCA1*, Breast Cancer 1 gene; *BRCA2,* Breast Cancer 2 gene; CL_{ss}/F, Clearance at steady state; $C_{max,ss}$, Maximum plasma concentration at steady state; $C_{min,ss}$, Minimum plasma concentration at steady state; FACT G, Functional Assessment of Cancer Therapy – General; FACT-P, Functional Assessment of Cancer Therapy - Prostate Cancer; FAPSI-6, FACT Advanced Prostate Symptom Index-6; HRR, Homologous recombination repair; HRQoL, Health-related quality of life; mCRPC, Metastatic castration-resistant prostate cancer; NHA, New hormonal agent; OS, Overall survival; PFS2, Time from randomisation to second progression or death; PK, Pharmacokinetics; PSA, prostate-specific antigen; SSRE, Symptomatic skeletal-related event; TFST, Time to start of first subsequent anticancer therapy or death; $t_{max,ss}$, Time to $C_{max,ss}$; TTPP, Time to pain progression.

Safety Objective:	**Outcome Measures:**
To evaluate the safety and tolerability of the combination of olaparib and abiraterone vs placebo and abiraterone in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	AEs and SAEs, physical examination findings, vital signs (including BP and pulse rate), ECG findings and laboratory test results (including clinical chemistry and haematology parameters)

AE, Adverse event, BP, Blood pressure; ECG, Electrocardiogram, mCRPC, Metastatic castration-resistant prostate cancer; NHA, New hormonal agent; SAE, Serious adverse event.


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BICR, Blinded independent central review; CR, Complete response; DCR, Disease control rate; DoR, Duration of response; EQ-5D-5L; HRR, Homologous recombination repair; ITT, Intention-to-treat; mCRPC, Metastatic castration-resistant prostate cancer; NHA, New hormonal agent; ORR, Objective response rate; PCWG-3, Prostate Cancer Working Group-3; PR, Partial response; PSA, Prostate-specific antigen; rPFS, Radiological progression-free survival; RECIST, Response Evaluation Criteria in Solid tumours; SD, Stable disease.

Overall design:

PROpel is a randomised, double-blind, placebo-controlled, multicentre Phase III study evaluating olaparib in combination with abiraterone versus placebo in combination with abiraterone as first-line therapy in men with mCRPC.

Approximately 720 patients were planned to be randomised in a 1:1 ratio to treatment with either olaparib in combination with abiraterone or placebo in combination with abiraterone, across approximately 200 study sites worldwide, from approximately 20 countries. Randomisation occurred within 28 days of screening. At the time of this amendment to the protocol, enrolment had completed with a total of 796 patients randomised. Following the completion of global enrolment, the China cohort will randomise approximately 108 additional patients at sites in China. Data from the China cohort will be analysed separately from the global cohort, also in a 1:1 ratio.

Upon site initiation, a consultation with the sponsor may occur during the screening process to ensure appropriate randomisation into the study as per defined eligibility criteria in the protocol, as per Section 5.

Patients will receive oral treatment with olaparib 300 mg twice daily + abiraterone 1000 mg once daily or placebo twice daily + abiraterone 1000 mg once daily. Patients in both treatment groups will also receive either prednisone or prednisolone 5 mg twice daily since abiraterone is indicated in combination with prednisone or prednisolone for the treatment of patients with mCRPC.

The randomisation scheme will be stratified on the following factors:

- Metastases: bone only vs visceral vs other
- Docetaxel treatment at mHSPC stage: yes vs no

The primary endpoint of this double-blind study will be radiological progression-free survival (rPFS) as assessed by investigators using the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1; soft tissue) and Prostate Cancer Working Group 3 criteria (PCWG-3; bone) for all randomised patients.

The key secondary endpoint is overall survival (OS), and other secondary endpoints will include time to start of first subsequent anticancer therapy or death (TFST), time to pain progression (TTPP), time to opiate use for cancer related pain, time to a symptomatic skeletal-related event (SSRE), disease-related symptoms/health-related quality of life (HRQoL), time from randomisation to second progression or death (PFS2), and subgroup analyses by HRR gene mutation status.

Safety assessments will include reporting of adverse events (AEs) and serious adverse events (SAEs), physical examinations, vital signs (including blood pressure [BP] and pulse rate), electrocardiograms (ECGs), and laboratory tests (including clinical chemistry and haematology).

Exploratory endpoints will include the exploration of blood, plasma, tumour and genetic biomarkers for the assessment of resistance mechanisms, predictive biomarkers of efficacy, drug combination mechanism of response, research into factors that may influence development of cancer and/or response to treatment, and investigation into healthcare resource utilisation.

The study schema is depicted in Figure 1.

Study Period:

Global study:

- First patients enrolled Q4 2018 / Last patient enrolled Q1 2020
- Estimated date of last patient completed Q4 2022

China cohort:

- Estimated first patients enrolled Q2 2021 / Estimated last patient enrolled Q3 2022
- Estimated date of last patient completed Q2 2026

Number of Patients:

Approximately 720 patients were planned to be enrolled into this study. At the time of this protocol amendment, enrolment had completed and a total of 796 patients were randomised in a 1:1 ratio to treatment with either olaparib and abiraterone or placebo and abiraterone. In addition, the China cohort will randomise approximately 108 additional patients at sites in China, after the completion of global enrolment.

Target patient population

All patients randomised in the study will be selected based on the following key criteria:

- **Treatment setting:** All patients must have confirmed prostate adenocarcinoma and metastatic status defined as at least 1 documented metastatic lesion on either a bone scan or a computed tomography (CT)/magnetic resonance imaging (MRI) scan. Patients must be treatment naïve at mCRPC stage, eg, patients should not have received any cytotoxic chemotherapy, NHA, or other systemic treatment in the mCRPC setting; androgen-deprivation therapy (ADT) is an exception. Prior to mCRPC stage, treatment with second-generation antiandrogen agents (except abiraterone) without prostate specific antigen (PSA) progression/clinical progression/radiological progression during treatment is allowed, provided the treatment was stopped at least 12 months before randomisation. Treatment with first-generation antiandrogen agents before randomisation is allowed, but there must be a washout period of 4 weeks. Docetaxel treatment is allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at mHSPC stage, as long as no signs of failure or disease progression occurred during or immediately after such treatment. Patients should be candidates for abiraterone therapy with documented evidence of progressive disease defined by PSA progression and/or radiological progression. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment. Prior to randomisation, sites must confirm availability of either an archival formalin-fixed, paraffin-embedded (FFPE) tumour tissue sample, or a new biopsy taken during the screening window, which meets the minimum pathology and sample requirements.
- **Medical conditions:** Patients will not be eligible for the study if they have a known additional malignancy that has had progression or has required active treatment in the last 5 years. Patients should not have myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) or features suggestive of MDS/AML; clinically significant cardiovascular disease in the past 6 months, severe or unstable angina, atrial fibrillation or other cardiac

arrhythmia requiring therapy, or New York Heart Association Class II-IV heart failure or cardiac ejection fraction measurement of <50% during screening as assessed by echocardiography or multigated acquisition scan; a planned or scheduled cardiac surgery or percutaneous coronary intervention procedure; had a prior revascularisation procedure. Patients should not have any chronic medical condition requiring a systemic dose of corticosteroid >10 mg prednisone/prednisolone per day. Patients with brain metastases are not allowed.

- **Prior/concomitant therapy:** Patients should not have received previous treatment with PARP inhibitor and/or CYP17 inhibitor. Patients will not be eligible for the study if they are receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment. Patients should not have major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

Treatments and treatment duration:

Treatments

Patients will receive oral treatment with olaparib 300 mg twice daily + abiraterone 1000 mg once daily or placebo twice daily + abiraterone 1000 mg once daily. Patients in both treatment groups will also receive either prednisone or prednisolone 5 mg twice daily.

Duration of treatment

Patients need to start study treatment as soon as possible after randomisation and ideally on the same day of randomisation.

Randomised patients will continue treatment until unequivocal radiological progressive disease is assessed by investigator (using RECIST 1.1 for soft tissues lesions and PCWG-3 criteria for bone lesions), unacceptable toxicity occurs, or the patient withdraws consent. Following objective disease progression, further treatment options will be at the discretion of the investigator. Patients may be allowed to continue study treatment if the investigator believes, and the AstraZeneca Study Physician concurs, that the patient could continue to receive clinical benefit, the patient is not experiencing serious toxicity, and there is no available better alternative treatment that could benefit the patient. Crossover from placebo+abiraterone to olaparib+abiraterone is not allowed in this study.

Data Monitoring Committee

This study will use an external Independent Data Monitoring Committee (IDMC) to review accumulating study safety data. The committee will also review efficacy data from the planned interim data cut-offs (DCOs).

Statistical methods

The full analysis set (all comers) will be used as the primary population for reporting efficacy and to summarise baseline characteristics. The full analysis set comprises all patients randomised into the study and will be analysed according to randomised treatment

(intention-to-treat [ITT] principle). The safety analysis set will be used for safety analyses. Any important deviations from randomised treatment will be listed and considered when interpreting the efficacy and safety data.

The primary objective of this study is to assess the efficacy of olaparib+abiraterone combination therapy versus placebo+abiraterone in terms of rPFS assessed by the investigator in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA.

Three DCOs are planned. The 1-sided alpha of 0.025 is allocated to the rPFS assessment. If the result for rPFS is statistically significant, the OS hypothesis will be tested in a hierarchical fashion. A multiplicity testing procedure based on the graphical approach in group sequential trials of Maurer and Bretz (Maurer and Bretz 2013), analogous to a simple sequential gatekeeping method, strongly controls the overall family-wise 1-sided error rate of 2.5%.

The rPFS endpoint will be tested at DCO1 and DCO2. The OS endpoint will be tested at DCO1, DCO2 and DCO3. For each endpoint with interim analysis, O'Brien and Fleming spending function (Lan and DeMets 1983, O'Brien and Fleming 1979), calculated based upon actual observed events, will be used to strongly control the overall type 1 error, with the restriction that alpha spend for the OS interim analysis at DCO1 will not exceed 0.0005.

Subgroup analyses will be conducted for rPFS to assess consistency of treatment effect across potential or expected prognostic factors, including HRR gene mutation status.

A sensitivity analysis will be conducted using rPFS as assessed for all patients by blinded independent central review (BICR) per RECIST 1.1 and PCWG-3 criteria.

The secondary endpoint, OS, will be analysed using the same methodology as specified for rPFS. To describe the benefits of olaparib+abiraterone compared to placebo+abiraterone, time to opiate use, SSRE, HRQoL, and PFS2 will also be analysed.

Safety and tolerability data will be summarised using appropriate descriptive measures.

Pharmacokinetic (PK) sampling will be performed in a subset of patients, planned to include approximately 50 patients per treatment group (ie, olaparib+abiraterone or placebo+abiraterone), at specific timepoints after multiple dosing (see Table 1). The plasma concentration-time data will be analysed using non-compartmental analysis (NCA) to determine the PK of olaparib, abiraterone, and Δ4-abiraterone (a metabolite of abiraterone) at steady state and to evaluate the effect of olaparib on abiraterone PK.

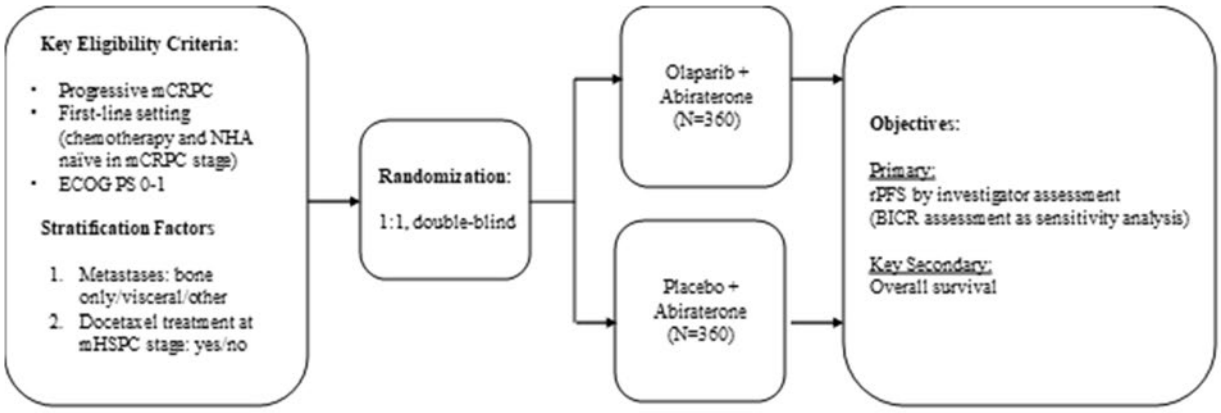
Enrolment in the China cohort will commence after global enrolment is closed, to randomise approximately 108 additional patients from sites in China. The safety and efficacy analyses of

subjects from China will be performed separately (please see Section 9.4.5 for details). Pharmacokinetic samples will not be collected for patients in China.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



BICR, Blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, Metastatic castration-resistant prostate cancer; N, Number of patients; NHA, New hormonal agent; rPFS, Radiological progression-free survival.

Note: Patients will receive 5 mg prednisone or prednisolone twice daily in addition to randomised study treatment (olaparib/placebo twice daily + abiraterone once daily).

Note: China cohort will apply the same study design and will include approximately 108 additional patients randomised in China.

2. INTRODUCTION

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure.

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

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by HRR. Tumours with homologous recombination deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

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

2.1 Study rationale

There is accumulating evidence that second-generation androgen receptor (AR) signalling inhibitors might induce "*BRCA*ness," and there is potential synergy between AR inhibitors and PARP inhibitors in the treatment of mCRPC (Li et al 2017). *BRCA*ness is defined as molecular features that some sporadic cancers share with hereditary *BRCA*-mutation carriers that make them susceptible to similar treatments. The concept for treating mCRPC patients with the combination of olaparib and abiraterone was largely based on the observation that PARP inhibition plus androgen deprivation could significantly reduce the growth of prostate cancer cells independent of HRR gene mutation status, in both in vitro and in vivo model systems (Schiewer et al 2012). Further, the combination of ADT and olaparib have a synergistic effect on inducing synthetic lethality (Asim et al 2017).

Additional rationale for the current study is based on the results of a recent AstraZeneca sponsored study, Study D081DC00008 (Study 8; NCT01972217). Study 8 was designed to explore the hypothesis that PARP inhibition acts synergistically with inhibition of the androgen pathway and that this effect is independent of a cell's HRR gene mutation status, hence the study enrolled post-chemotherapy patients who were genetically unselected (ie, an 'all comers' population). Study 8 was a randomised, double-blind, placebo-controlled,

multicentre Phase II study of olaparib versus placebo when given in combination with abiraterone, in patients with mCRPC who had received prior chemotherapy containing docetaxel (second-line setting).

Part A of the study was a safety run-in, conducted to assess the safety and tolerability of olaparib when given in addition to abiraterone and to recommend a dose of olaparib to be used for Part B of the study, also given in addition to abiraterone. [redacted]

Part B of the study was a randomised, double-blind, placebo-controlled comparison of the efficacy, safety and tolerability of the dose of olaparib selected from Part A, when given in addition to abiraterone, versus placebo in addition to abiraterone. Eligible patients were aged 18 years or older with mCRPC who had previously received docetaxel and were candidates for abiraterone treatment. Patients were excluded if they had received more than 2 previous lines of chemotherapy, or had previous exposure to second-generation antihormonal drugs. Patients (n=142) were randomised (1:1), without stratification, to receive oral olaparib 300 mg twice daily or placebo in combination with oral abiraterone 1000 mg once daily and prednisone or prednisolone 5 mg twice daily. The primary endpoint was investigator-assessed rPFS (based on RECIST 1·1 and PCWG-2). Efficacy analyses were done in the intention-to-treat (ITT) population, which included all randomly assigned patients, and safety analyses included all patients who received at least 1 dose of olaparib or placebo. Median rPFS was 13·8 months (95% Confidence Interval [CI] 10·8–20·4) with olaparib+abiraterone and 8·2 months (5·5-9·7) with placebo+abiraterone (HR 0·65, 95% CI 0·44–0·97, p=0·034). Median OS was 22.7 months (95% CI 17·4–29·4) in the olaparib and abiraterone group compared with 20.9 months (95% CI 17·6–26·3) in the placebo and abiraterone group.

The most common grade 1–2 AEs were nausea (26 [37%] patients in the olaparib group versus 13 [18%] patients in the placebo group, constipation (18 [25%] versus 8 [11%]), and back pain (17 [24%] versus 13 [18%]). Thirty-eight (54%) of 71 patients in the olaparib and abiraterone group and 20 (28%) of patients in the placebo and abiraterone group had grade 3 or worse AEs, including anaemia (in 15 [21%] of 71 patients versus 0 of 71), pneumonia (4 [6%] versus 3 [4%]), and myocardial infarction (4 [6%] versus 0). Increased toxicity seen in the olaparib group compared with the placebo group was expected, with many, but not all, observed AEs being consistent with the current safety profile for olaparib. Serious adverse events were reported by 24 (34%) of 71 patients in the olaparib and abiraterone group and 13 (18%) of 71 patients in the placebo and abiraterone group. Seven (10%) of 71 patients in the

olaparib group had SAEs that were related to study treatment (anaemia [n=3], febrile neutropenia [n=1], pneumonitis [n=1], vomiting [n=1], general deterioration in physical health [n=1]) compared with 1 (1%) of 71 patients in the placebo group (gastroenteritis [n=1]). Seven (10%) of 71 patients in the olaparib and abiraterone group had serious cardiovascular events (myocardial infarction [n=4], fatal cardiac failure [n=1], chronic cardiac failure [n=1], fatal ischaemic stroke [n=1]) compared with 1 patient in the placebo group (thrombotic stroke [n=1]). Time to onset of serious cardiovascular events ranged from 3 to 29 months in the olaparib and abiraterone group. However, notable numerical imbalances were observed in relation to cardiovascular events (myocardial infarction, congestive heart failure, stroke) when olaparib was given in combination with abiraterone. An imbalance was also seen for thrombotic events and those associated with fluid overload, whilst events of congestive heart failure were more severe in the olaparib group. The patients who experienced cardiovascular events of concern were elderly (≥65 years), the events occurred late in the treatment with no apparent chronological pattern and they had a relatively high burden of cardiovascular risk factors. Single or multiple cardiovascular risk factors (eg, hypertension, diabetes mellitus, hyperlipidaemia) were not obviously imbalanced between the treatment groups at baseline. In the myocardial infarction cases, the reported data supported the diagnosis; however, details were limited for the 2 cases of congestive heart failure and the diagnoses were lacking supportive data on file. In this study, meaningful interpretation of the findings in relation to cardiovascular events is limited by the small sample size, some imbalances in relevant demographic and baseline characteristics as well as cardiovascular risk factors, differences in duration of treatment and lack of confirmation of congestive heart failure diagnosis. Further investigation is therefore needed in a Phase III trial with olaparib given in addition to abiraterone.

The current study, PROpel, is a Phase III study evaluating the efficacy, safety, and tolerability of olaparib versus placebo when given in addition to abiraterone in genetically unselected (ie, an 'all-comers' population) patients with mCRPC who have not received prior chemotherapy or NHAs for mCRPC (first-line setting). It is proposed that this study will build on the knowledge gained from Study 8 and serve as confirmatory evidence of the clinical benefit, safety and tolerability of the combination of olaparib and abiraterone in the treatment of patients with mCRPC.

2.2 Background

2.2.1 Advanced prostate cancer and its treatment

Prostate cancer is the fourth most common cancer in both sexes combined and the second most common cancer in men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men. With an estimated 307,000 deaths in 2012, prostate cancer is the fifth leading cause of death from cancer in men (6.6% of the total men deaths) (Globocan 2012).

Prostate cancer is a heterogeneous disease and ADT with luteinising hormone-releasing hormone (LHRH) analogues or orchidectomy is usually initially effective at controlling metastatic disease. However, patients inevitably progress from an androgen sensitive to a castration resistant phenotype which is not curable, and is associated with 90% of overall mortality being attributable to the underlying malignant disease (Scher et al 2015). Since curative therapy is not possible in this setting, reducing disease burden and symptoms are critical objectives of any therapeutic intervention.

Recently, the treatment of mCRPC has significantly altered with the approval of new drugs. Several life-prolonging agents are now approved for the mCRPC population overall, notably including NHAs. NHAs are potent, orally available treatment options with a favourable tolerability profile that have replaced docetaxel as the preferred choice of first-line therapy for mCRPC (Flaig et al 2016). Both abiraterone and enzalutamide have demonstrated robust improvements in progression-free survival (PFS) and OS and have also shown a significantly prolonged time to initiation of cytotoxic chemotherapy (Ryan et al 2013, Beer et al 2014). However, patients eventually progress under available treatment options, eg, median PFS is approximately 16 months, and median OS is approximately 36 months with abiraterone treatment for first-line mCRPC. There is an unmet medical need for new treatment options, either as a single agent for early-line therapy or as combination therapy to improve efficacy (ie, prolong the effective treatment period) and delay resistance.

Abiraterone is a pregnenolone-derived 3-pyridyl steroidal agent that selectively and irreversibly inhibits the CYP17A1 microsomal enzyme, encoded by the CYP17A1 gene. CYP17A1 has 2 separate activating properties: 17-α-hydroxylase (that catalyses the 17 α hydroxylation of C21 steroids, which are needed for the synthesis of cortisol in the adrenal gland); 17,20-lyase (that catalyses the breaking of the C17–21 bond, converting C21 compounds to C19 steroids in the sex steroid synthesis pathway in both the adrenal gland and the testis) (Sonpavde et al 2011, Attard et al 2012).

CYP17A1 inhibition blocks 2 critical stages in testosterone biosynthesis: conversion of pregnenolone to 17-OH-pregnenolone, and conversion of 17-OH-pregnenolone to dehydroepiandrosterone.

Inhibition of CYP17 also results in deficient cortisol synthesis and the upregulation of the hypothalamic–pituitary–adrenal pathway with elevated levels of adrenocorticotropic hormone. This results in an increase in the steroid levels upstream of the CYP17A1 block, including corticosterone and deoxycorticosterone (Attard et al 2012). This metabolic state stimulates both the glucocorticoid and the mineralocorticoid receptor, and their excess prevents adrenocortical insufficiency. However, this secondary effect also results in an excess of secondary mineralocorticoids, which is characterised by fluid retention, hypertension and

hypokalaemia, and often requires intervention. To prevent this side effect, abiraterone is normally administered with prednisone (Pia et al 2013).

2.2.2 Homologous recombination repair genes in prostate cancer

Multiple loss-of-function alterations in genes that are involved in DNA repair, including homologous recombination repair, are associated with response to poly(adenosine diphosphate–ribose) polymerase (PARP) inhibition in patients with prostate and other cancers (de Bono et al 2020).

Between 24% to 30% of mCRPCs have loss of function mutations in genes involved in homologous recombination repair (HRR) of DNA double strand breaks (Abida et al 2017, Armenia et al 2018, Chung et al 2019, Mateo et al 2015, Robinson et al 2015, AstraZeneca data on file). Mutations in the breast cancer susceptibility genes (*BRCA1* and/or *BRCA2*) are the most prevalent HRR gene mutations (HRRm) in mCRPC (with *BRCA2* more prevalent than *BRCA1*) with *ATM* (ataxia telangiectasia mutated) the second most frequently mutated HRR gene in mCRPC (Armenia et al 2018, Chung et al 2019, Mateo et al 2015, Robinson et al 2015). Together the prevalence of *BRCA1/2* and *ATM* mutations in mCRPC ranges from 13% to 26.5%. The next most prevalent HRRm in mCRPC are *CDK12* (1.3% to 8%), *CHEK2* (1.4% to 4%), *PALB2* (0.3% to 3%), and *CHEK1* (0.9% to 2%). The prevalence of other HRR gene mutations is very low (0% to 1.8%). Due to the low prevalence of many of the HRR genes it is challenging to validate them individually. Therefore, based on their common mechanistic role in homologous recombination, and prior evidence from D081DC00007 (PROfound; NCT02987543) cohort B suggesting that patients with PALB2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, RAD51B, RAD51C, RAD51D, and RAD54L mutations collectively benefited from monotherapy olaparib treatment, grouping of the genes together into a HRRm population is supported. PROfound was a randomised, open label, multicentre Phase III study of olaparib monotherapy versus physician's choice of NHA (enzalutamide or abiraterone) that enrolled men with mCRPC who had disease progression on prior treatment with an NHA and who had a qualifying mutation (predicted to be deleterious or suspected deleterious) in one of 15 HRR genes. Of note, nonclinical data have emerged since PROfound was designed, showing weak evidence of PPP2R2A as an HRR gene.

Enrichment of *BRCA1/2*, *ATM* and *CDK12* 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 2013, Castro et al 2015, Chung et al 2019, Mateo et al 2018) rather than these mutations being acquired under treatment with standard therapies (eg, androgen receptor mutations and amplifications [Mateo et al 2018]).

2.2.3 Rationale for evaluating olaparib-abiraterone combination treatment in patients with mCRPC independent of HRR gene mutation status

There is accumulating evidence that second-generation AR signalling inhibitors like abiraterone might induce "*BRCA*ness," and there is potential synergy between AR inhibitors and PARP inhibitors in the treatment of mCRPC (Li et al 2017).

The rationale for treating patients with mCRPC with the combination of olaparib and abiraterone was based on the observation that PARP inhibition plus androgen deprivation could significantly reduce the growth of prostate cancer cells independent of HRR gene mutation status, both in cell culture and model systems (Schiewer et al 2012).

Based on available data, there are 2 plausible mechanisms that may account for the biomarker independent activity of the olaparib-abiraterone combination. The first hypothesis involves PARP-1 transcriptional roles: beyond its function in DNA repair, PARP-1 is implicated in modulation of transcription via various mechanisms (reviewed in Schiewer and Knudsen 2014). PARP-1's transcriptional functions may be especially relevant in hormone dependent cancers such as breast and prostate cancer, as nuclear hormone receptors require catalytically active PARP-1 as a positive co-regulator of target gene expression (Ju et al 2006). PARP-1 co-regulation of AR is supported by the observation that PARP inhibition suppresses transcription of a number of AR targets, and this function is linked to reduced AR target gene expression and improved efficacy in a prostate cancer xenograft model treated with PARP inhibitors and surgical castration when compared with surgical castration or PARP inhibitor alone (Schiewer et al 2012).

The second mechanistic explanation that may account for HRR independent activity of olaparib in combination with abiraterone is induction of an HRR deficient phenotype (or *BRCA*ness) through inhibition of AR signalling. Several lines of evidence support this possibility (Polkinghorn et al 2013, Goodwin et al 2013, Tarish et al 2015, Asim et al 2017, Li et al 2017) including:

- Up-regulation of HRR gene transcripts and protein levels in response to enhanced AR signalling in prostate cancer,
- Increased radioresistance in the presence of functional AR signalling, and
- Conversely, decreased HRR gene expression and DNA repair indices in ADT/NHA treated cells and tumour biopsies, correlated with increased damage sensitivity.

Importantly, in the CRPC setting, inhibition of the AR signalling axis by NHAs such as enzalutamide are still able to induce *BRCA*ness which sensitises cells and xenograft models to olaparib, despite resistance to the initial ADT (Asim et al 2017, Polkinghorn et al 2013, Li et al 2017).

Olaparib in combination with abiraterone (Study 8) provided clinical efficacy benefit for patients with mCRPC compared with abiraterone alone. Although more SAEs were observed in patients who received olaparib and abiraterone than abiraterone alone, no difference in HRQoL outcomes were identified between the groups. The data also suggest that the combination of olaparib and abiraterone might provide an additional clinical benefit to a broad population of patients with mCRPC.

A detailed description of the chemistry, pharmacology, efficacy, and safety of olaparib is provided in the Investigator's Brochure.

2.3 Benefit/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 tumours including those with *BRCA* mutated 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 haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, mean cell volume elevation and increase in blood creatinine), nausea and vomiting, decreased appetite, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), headache, dizziness and cough. Most of these events are generally mild or moderate in intensity.

In a relatively small number of patients, the adverse events of special interest of pneumonitis, MDS/AML, and new primary malignancies have been observed.

The available evidence from across the olaparib clinical development programme supports a conclusion that there is a reasonable possibility of a causal relationship between olaparib and MDS/AML. However, consistent with the low incidence seen across all indications, the incidence in men with mCRPC is <1.5%. MDS/AML is an important identified risk for olaparib. Patients in this study are monitored closely for signs and symptoms of MDS/AML.

Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and pneumonitis or new primary malignancies. These are important potential risks for olaparib and are being kept under close surveillance.

In Study 8, there were no safety findings new to the combination of olaparib and abiraterone that have not already been reported for each agent alone. As expected, there was higher

toxicity in the olaparib+abiraterone group versus placebo+abiraterone, but the nature and severity of these events were consistent with the known safety profiles of olaparib and abiraterone, and were clinically manageable and reversible. A higher percentage of patients had cardiovascular events (myocardial infarction, congestive heart failure, stroke) in the olaparib+abiraterone group compared with the placebo+abiraterone group. Extensive interpretation of the cardiovascular findings in Study 8 is limited by the size of the safety analysis set, some imbalances in relevant demographic and baseline characteristics, differences in duration of treatment, and lack of confirmation of congestive heart failure diagnosis. Based on the available safety data from Study 8, it is considered that the safety and tolerability profile of olaparib+abiraterone is acceptable in patients with mCRPC following docetaxel containing chemotherapy. The statistically significant and clinically meaningful rPFS improvement shown in the olaparib+abiraterone group of Study 8 suggests a positive benefit:risk of olaparib+abiraterone treatment in patients with mCRPC.

Based on the available data on efficacy and safety it is believed that olaparib continues to demonstrate an overall positive benefit/risk balance to support its further clinical evaluation in patients with advanced prostate cancer, and in combination with abiraterone.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of olaparib may be found in the Investigator's Brochure and the Development Safety Update Report.

See Section 9.5 and Appendix C for information regarding the Data Monitoring Committee.

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

3. OBJECTIVES AND ENDPOINTS

Following the completion of global enrolment to PROpel, a China cohort will randomise approximately 108 additional patients at sites in China. Data from the China cohort will be analysed separately from the global cohort (see Section 9.4.5).

3.1 Primary objectives

The primary objectives of the study and associated outcome measures are summarised in Table 3.

Table 3 Primary objective

Primary Objective:	Outcome Measures:
To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of rPFS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	rPFS, defined as the time from randomisation to 1) radiological progression, assessed by investigator per RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), or 2) death from any cause, whichever occurs first.

mCRPC, Metastatic castration-resistant prostate cancer; NHA, New hormonal agent; PCWG-3, Prostate Cancer Working Group 3; rPFS, Radiological progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid tumours version 1.1.

3.2 Secondary objectives

The secondary objectives of the study and associated outcome measures are summarised in Table 4.

Table 4 Secondary objectives

Secondary Objectives:	Outcome Measures:
To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of OS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	OS, defined as the time from randomisation to death from any cause.
To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone as assessed by time to start of first subsequent anticancer therapy or death (TFST) in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	TFST, ie, the time from randomisation to 1) the start of the first subsequent anticancer therapy or 2) death from any cause.[a]
To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone as assessed by time to pain progression (TTPP) in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	TTPP is defined as the time from randomisation to pain progression based on the Brief Pain Inventory-Short Form (BPI-SF) Item 3 “worst pain in 24 hours” and opiate analgesic use (analgesic quantification algorithm [AQA] score).[b]

To further evaluate the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of time to opiate use, time to an SSRE, and PFS2 in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• Time to opiate use: The time from randomisation to the first opiate use for cancer-related pain. • Time to an SSRE: the time from randomisation to the first SSRE. 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 radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention. • PFS2: The time from randomisation to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression or death.
To assess the effect of the combination of olaparib and abiraterone vs placebo and abiraterone on disease related symptoms and HRQoL using BPI-SF and Functional Assessment of Cancer Therapy (FACT) - Prostate Cancer (FACT-P) questionnaires in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• BPI-SF: progression in pain severity domain, change in pain interference domain. • FACT-P total score, FACT-G total score, trial outcome index, functional well-being, physical well-being, prostate cancer subscale, and FACT Advanced Prostate Symptom Index-6 (FAPSI-6).
To evaluate tumour and blood samples collected from patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage for mutations in *BRCA1*, *BRCA2*, *ATM* and 11 other HRR genes. Note: blood samples will not be collected for HRR gene mutation status testing in the China cohort	HRR gene mutation status.
To determine steady-state exposure to abiraterone and its active metabolite Δ4-abiraterone in the presence and absence of olaparib. To determine steady-state exposure to olaparib when co-administered with abiraterone. Note: this objective is not applicable for the China cohort	• Plasma concentration data at steady state for olaparib, abiraterone, and Δ4-abiraterone in the subset of patients evaluable for PK. • If sufficient data are available, PK parameters at steady state (eg, maximum concentration [$C_{max,ss}$], time to $C_{max,ss}$ [$t_{max,ss}$], minimum concentration [$C_{min,ss}$], and partial area under the concentration-time curve [AUC_{0-8}]) will be calculated in the PK patient subset. In addition, the area under the curve at steady state (AUC_{ss}) and the apparent clearance (CL_{ss}/F) for olaparib and the metabolite to parent ratios for $C_{max,ss}$, $C_{min,ss}$ and AUC_{0-8} for Δ4-abiraterone will be determined. The time of last concentration (t_{last}) will also be determined as a diagnostic parameter.

[a] Subsequent systemic anticancer therapies (excluding radiotherapy) will be reviewed prior to data unblinding to assess which represent clinically important treatments intended to control prostate cancer. TFST is defined as the time from randomisation to the earlier of 1) the first subsequent anticancer therapy start date following study treatment discontinuation or 2) death from any cause. Any patient not known to have died at the time of

the analysis and not known to have had a further anticancer therapy will be censored at the last known time to have not received subsequent therapy, ie, the last follow-up visit where this was confirmed.

[b] Pain progression is defined as follows: 1) for patients who are asymptomatic at baseline, a ≥2-point change from baseline in the average (4-7 days) Brief Pain Inventory-Short Form (BPI-SF) Item 3 score observed at 2 consecutive evaluations (with at least 2 weeks between the end of the initial visit and the start of the subsequent visit) OR initiation of opioid use for pain; 2) for patients who are symptomatic at baseline (average BPI-SF Item 3 score >0 and/or currently taking opioids), a ≥2-point change from baseline in the average BPI-SF Item 3 score observed at 2 consecutive visits and an average worst pain score ≥4, and no decrease in average opioid use (≥1-point decrease in analgesic quantification algorithm [AQA] score from a starting value of 2 or higher) OR any increase in opioid use (eg, 1-point change in AQA score) at 2 consecutive follow-up visits (with at least 2 weeks between the end of the initial visit and the start of the subsequent visit). Any patient who has more than 2 consecutive visits that are not evaluable for pain progression will be censored at the last evaluable assessment.

AQA, Analgesic quantification algorithm; *ATM*, Ataxia-telangiectasia mutated; AUC_{0-8}, Area under the plasma concentration-time curve in 0-8 h; AUC_{ss}, Area under the plasma concentration-time curve at steady state; BPI-SF, Brief Pain Inventory-Short Form; *BRCA1*, Breast Cancer 1 gene; *BRCA2,* Breast Cancer 2 gene; CL_{ss}/F, Apparent clearance at steady state; $C_{max,ss}$, Maximum plasma concentration at steady state; $C_{min,ss}$, Minimum plasma concentration at steady state; FACT-G, Functional Assessment of Cancer Therapy - General; FACT-P, Functional Assessment of Cancer Therapy - Prostate Cancer; FAPSI-6; FACT Advanced Prostate Symptom Index-6; HRR, Homologous recombination repair; HRQoL, Health-related quality of life; mCRPC, Metastatic castration-resistant prostate cancer; NHA, New hormonal agent; OS, Overall survival; PFS2, Time from randomisation to second progression or death; PK, Pharmacokinetics; PSA, Prostate-specific antigen; SSRE, Symptomatic skeletal-related event; TFST, Time to start of first subsequent anticancer therapy or death; $t_{max,ss}$, Time to $C_{max,ss}$; TTPP, Time to pain progression.

3.3 Safety objective

The safety objective of the study and associated outcome measures are summarised in Table 5.

Table 5 Safety objective

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of the combination of olaparib and abiraterone vs placebo and abiraterone in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	AEs and SAEs, physical examination findings, vital signs (including BP and pulse rate), ECG findings and laboratory test results (including clinical chemistry and haematology parameters).

AE, Adverse event, BP, Blood pressure; ECG, Electrocardiogram, mCRPC, Metastatic castration-resistant prostate cancer; NHA, New hormonal agent; SAE, Serious adverse event.

3.4 Exploratory objectives

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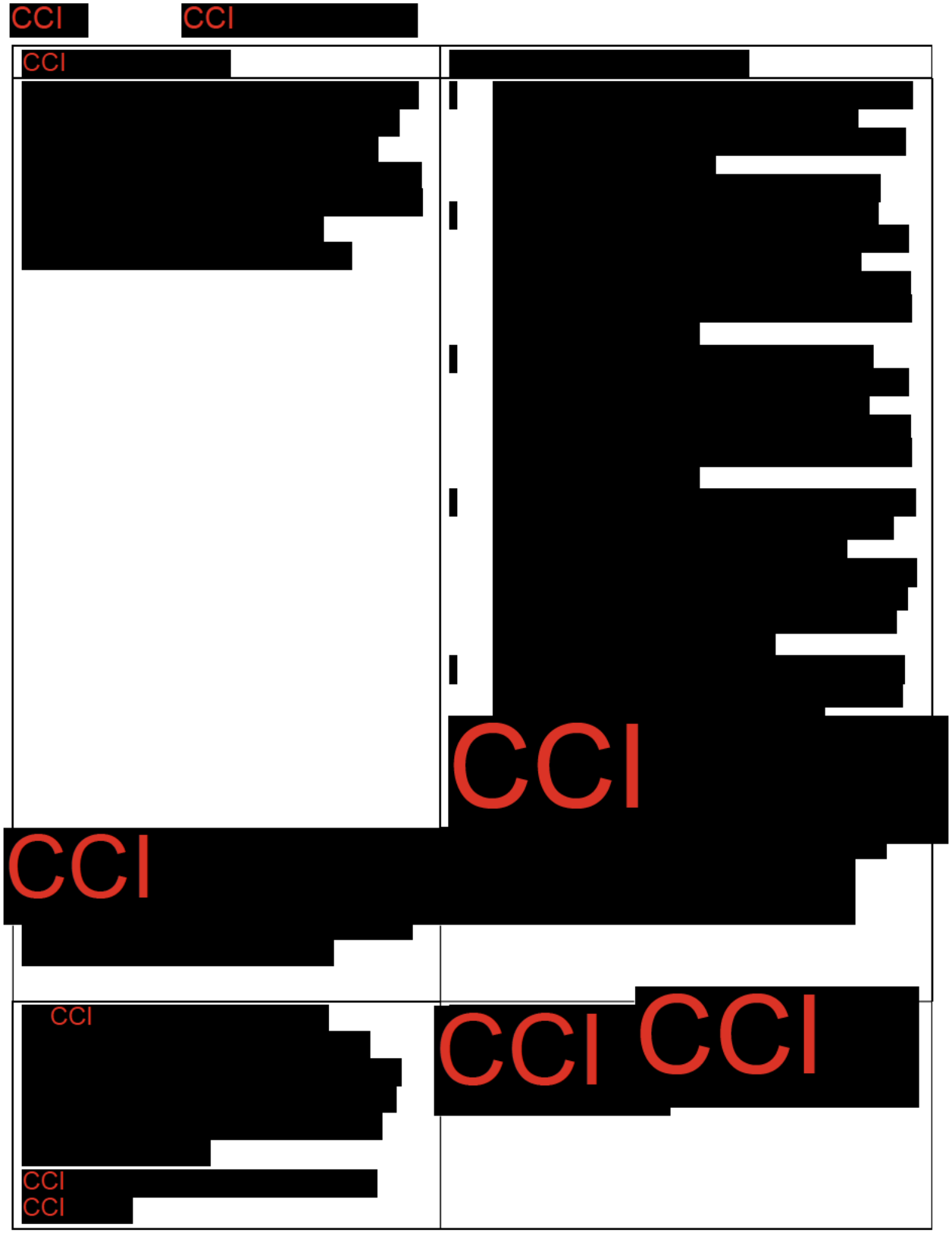
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BICR, Blinded independent central review; CR, Complete response; DCR, Disease control rate; DoR, Duration of response; Intention-to-treat; mCRPC, Metastatic castration-resistant prostate cancer; NHA, New hormonal agent; ORR, Objective response rate; PCWG-3, Prostate Cancer Working Group-3; PR, Partial response; PSA, Prostate-specific antigen; rPFS, Radiological progression-free survival; RECIST, Response Evaluation Criteria in Solid tumours; SD, Stable disease.

4. STUDY DESIGN

4.1 Overall design

This is a randomised, double-blind, placebo-controlled, multicentre Phase III study evaluating the efficacy and safety of the combination of olaparib and abiraterone in patients with mCRPC.

Approximately 720 patients were planned to be randomised in a 1:1 ratio to treatment with either olaparib in combination with abiraterone or placebo in combination with abiraterone. Randomisation occurred within 28 days of screening. Patients will receive oral treatment with olaparib 300 mg twice daily + abiraterone 1000 mg once daily or placebo twice daily +

abiraterone 1000 mg once daily. At the time of this amendment to the protocol, enrolment had completed with a total of 796 patients randomised. Following the completion of global enrolment, the China cohort will randomise approximately 108 additional patients at sites in China, also in a 1:1 ratio.

Upon site initiation, a consultation with the sponsor may occur during the screening process to ensure appropriate randomisation into the study as per defined eligibility criteria in the protocol, as per Section 5.

Abiraterone is indicated in combination with prednisone or prednisolone for the treatment of patients with mCRPC. Hence, patients in both treatment groups will also receive either prednisone or prednisolone 5 mg twice daily with the abiraterone in this study, but throughout this protocol the treatment will be referred to simply as abiraterone.

All patients will attend a screening visit within 28 days before starting study treatment.

Day 1 is defined as the randomisation date; study treatment needs to begin as soon as possible after randomisation, ideally within 24 hours. Randomised patients will continue study treatment until unequivocal radiological progressive disease is assessed by investigator (using RECIST 1.1 for soft tissues lesions and PCWG-3 criteria for bone lesions), unacceptable toxicity occurs, or the patient withdraws consent. Following objective disease progression, further treatment options will be at the discretion of the investigator. Patients may be allowed to continue study treatment if the investigator believes, and the AstraZeneca Study Physician concurs, that the patient could continue to receive clinical benefit, the patient is not experiencing serious toxicity, and there is no available better alternative treatment that could benefit the patient. Crossover from placebo+abiraterone to olaparib+abiraterone is not allowed in this study.

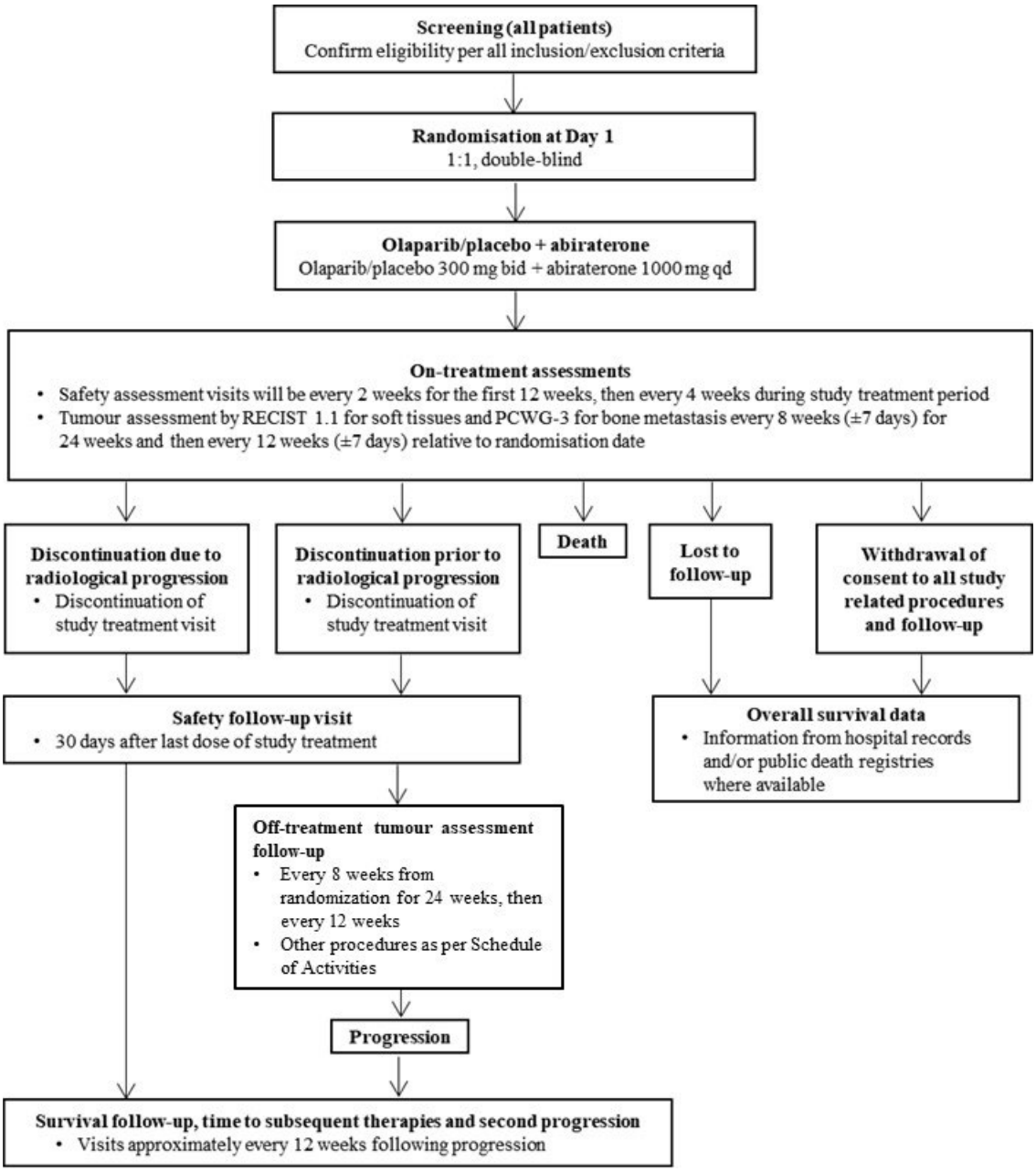
The randomisation scheme will be stratified on the following factors:

- Metastases: bone only vs visceral vs other
- Docetaxel treatment at mHSPC stage: yes vs no

The primary endpoint of this double-blind study will be rPFS as assessed by investigator using RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone) for all randomised patients.

A study flow chart is illustrated in Figure 2 and the study design is summarised in Figure 1.

Figure 2 Study flow chart



Bid, Twice daily; PCWG-3, Prostate Cancer Working Group 3; qd, Once daily; RECIST, Response Evaluation Criteria in Solid Tumours.

There are 3 DCOs planned. The primary endpoint of rPFS will be formally analysed at DCO1 and DCO2. The key secondary endpoint of overall survival (OS) will be tested at DCO1, DCO2 and DCO3. See Section 9 for further details.

The final data cut, DCO3, will occur approximately 48 months after the first patient is randomised, when a minimum follow-up of 32 months would be expected. At DCO3, the

clinical study database will close to all new data (SAEs will continue to be recorded on the AstraZeneca Patient Safety database as described below). Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with study treatment. For patients who do continue to receive treatment beyond the time of this DCO, investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after study treatment is discontinued, in accordance with Section 8.4.1 (Reporting of Serious Adverse Events). If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety. Additionally, as stated in Section 8.3.3 (Follow-up of AEs and SAEs), any SAE or nonserious adverse event that is ongoing at the time of this data cut-off, must be followed up by the investigator for as long as medically indicated.

For an overview of the study design see Figure 1 Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific rationale for study design

Data in Phase II Study 8 demonstrated that in patients with mCRPC (second-line setting), the addition of olaparib to abiraterone results in a statistically significant and clinically meaningful improvement in rPFS over abiraterone alone, with an acceptable safety and tolerability profile.

The PROpel study will build on the knowledge gained from Study 8 and serve as confirmatory evidence of the clinical benefit, safety and tolerability of the combination of olaparib and abiraterone in the treatment of patients with mCRPC who have not received prior chemotherapy or NHA at mCRPC stage (first-line setting). Patients who have had prior docetaxel treatment during neoadjuvant/adjuvant treatment for localised prostate cancer and at mHSPC stage will be permitted to enrol.

The randomised, double-blind design of PROpel reduces potential for bias when assessing whether the combination of olaparib + abiraterone shows improved efficacy compared with abiraterone monotherapy.

The scientific rationale for combining olaparib with abiraterone in a biomarker unselected patient population is described in Sections 2.1 and 2.2.

4.3 Justification for dose

The dose of olaparib used in this study is 300 mg twice daily which is the currently approved dose of olaparib for ovarian cancer given as monotherapy.

CCI [redacted]

Safety data observed from Part B of Study 8 was consistent with the known safety profile of olaparib and abiraterone, and provide further support to use olaparib 300 mg twice daily in combination with abiraterone 1000 mg once daily.

The recommended dose of abiraterone acetate for the treatment of patients with mCRPC, and in this study, is 1000 mg once daily, in combination with prednisone or prednisolone 5 mg twice daily (Zytiga Prescribing Information, Zytiga SmPC). It should be taken on an empty stomach.

In Study 8, the PK assessment conducted in a cohort of 12 patients did not show evidence of a drug-drug interaction (DDI) between olaparib and abiraterone. In addition, the respective metabolic pathways and DDI characteristics of the 2 drugs did not suggest that abiraterone will affect olaparib PK and vice-versa (Zytiga Prescribing Information, Lynparza Prescribing Information).

CCI [redacted]

4.4 End of study definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

- European Union requirements define study completion as the last visit of the last subject for any protocol related activity.
- Food and Drug Administration requirements defines 2 completion dates:

- Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.
- Study Completion Date – is defined as the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

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

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with olaparib.

See Appendix C 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

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

Each patient should meet all the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who sign informed consent. "Randomised" patients are defined as those who undergo randomisation.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in the study protocol.

2 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

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

- Provision of informed consent for genetic research prior to collection of sample.
- Provision of informed consent for biomarker research prior to collection of sample.

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

Age

4 Patients must be ≥18 years of age (or ≥19 years of age in South Korea) at the time of signing the informed consent form. For patients enrolled in Japan who are <20 years of age, written informed consent should be obtained from the patient and from his legally acceptable representative.

Type of patient and disease characteristics

5 Histologically or cytologically confirmed prostate adenocarcinoma.

6 Metastatic status defined as at least 1 documented metastatic lesion on either a bone scan or a CT/MRI scan.

7 First-line mCRPC:

- Patients must be treatment naïve at mCRPC stage, eg, patients should not have received any cytotoxic chemotherapy, NHA, or other systemic treatment (approved drugs or experimental compounds) in the mCRPC setting. ADT is an exception as specified in inclusion criterion 8.
- Treatment with first-generation antiandrogen agents (eg, bicalutamide, nilutamide, and flutamide) before randomisation is allowed, but there must be a washout period of 4 weeks.
- Docetaxel treatment is allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at mHSPC stage, as long as no signs of failure or disease progression occurred during or immediately after such treatment.
- Prior to mCRPC stage, treatment with second-generation antiandrogen agents (except abiraterone) without PSA progression/clinical progression/radiological progression

during treatment is allowed, provided the treatment was stopped at least 12 months before randomisation.

8 Ongoing androgen deprivation with gonadotropin-releasing hormone analogue or bilateral orchiectomy, with serum testosterone <50 ng/dL (<2.0 nmol/L) within 28 days before randomisation. Patients receiving ADT at study entry should continue to do so throughout the study.

9 Candidate for abiraterone therapy with documented evidence of progressive disease. Progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy:

- PSA progression defined by a minimum of two rising PSA levels with an interval of ≥1 week between each determination. The PSA value at the Screening visit should be ≥1 µg/L (1 ng/mL) (per PCWG-3 criteria);
- Soft-tissue disease progression defined by RECIST 1.1;
- Bone progression defined by appearance of 2 or more new lesions on a bone scan (per PCWG-3 criteria).

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

- Haemoglobin ≥10.0 g/dL with no blood transfusion in the past 28 days.
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.
- Platelet count $\geq 100 \times 10^9$/L.
- Total bilirubin ≤1.5×institutional upper limit of normal (ULN). Patients with known Gilbert's disease who have serum bilirubin ≤3×ULN may be enrolled.
- Serum potassium ≥3.5 mmol/L.
- Serum albumin ≥3.0 g/dL.
- Aspartate aminotransferase/alanine aminotransferase ≤2.5×ULN unless liver metastases are present, in which case values must be ≤5×ULN.
- Creatinine clearance ≥51 mL/min, calculated using the Cockcroft-Gault equation for males or based on a 24-hour urine test:

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

11 Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix B), with no deterioration over the previous 2 weeks.

12 The participant has, in the opinion of the investigator, a life expectancy of at least 6 months.

13 Prior to randomisation, sites must confirm availability of either an archival FFPE tumour tissue sample, or a new biopsy taken during the screening window, which meets the minimum pathology and sample requirements in order to enable HRR status subgroup analysis of the primary endpoint rPFS. If there is not written confirmation of the availability of tumour tissue prior to randomisation, the patient is not eligible for the study.

Reproduction

14 Male patients must use a condom during treatment and for 3 months after the last dose of olaparib + abiraterone when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (see Appendix I for acceptable methods) if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

5.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

Medical conditions

1 Has a known additional malignancy that has had progression or has required active treatment in the last 5 years. Exceptions include basal cell carcinoma of the skin, and squamous cell carcinoma of the skin that has undergone potentially curative therapy.

2 Patients with MDS/AML or with features suggestive of MDS/AML.

3 Clinically significant cardiovascular disease as evidenced by myocardial infarction or arterial thrombotic events (eg, stroke) in the past 6 months, severe or unstable angina, atrial fibrillation or other cardiac arrhythmia requiring therapy, or New York Heart Association Class II-IV heart failure or cardiac ejection fraction measurement of <50% during screening as assessed by echocardiography or multigated acquisition scan.

4 Planned or scheduled cardiac surgery or percutaneous coronary intervention procedure.

5 Prior revascularisation procedure (significant coronary, carotid, or peripheral artery stenosis).

6 Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg). Patients with a history of hypertension are allowed provided BP is controlled by antihypertensive treatment.

7 History of uncontrolled pituitary or adrenal dysfunction.

8 Active infection or other medical condition that would make prednisone/prednisolone use contraindicated.

9 Any chronic medical condition requiring a systemic dose of corticosteroid >10 mg prednisone/prednisolone per day.

10 Patients who are considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, active pneumonitis, extensive interstitial bilateral lung disease on high-resolution CT scan, or any psychiatric disorder that prohibits obtaining informed consent and following the study procedures.

11 Persistent toxicities (Common Terminology Criteria for Adverse Events [CTCAEs] grade >2) caused by previous cancer therapy, excluding alopecia.

12 Patients with brain metastases. A scan to confirm the absence of brain metastases is not required.

13 Patients with spinal cord compression are excluded unless they are considered to have received definitive treatment for this and have evidence of clinically stable disease for 4 weeks.

14 Patients who are unevaluable 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 nonmeasurable) that can be assessed by RECIST.

15 Patients who are unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

16 Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus.

17 Patients with known active hepatitis infection (ie, hepatitis B or C).

Prior/concomitant therapy

18 Any previous treatment with PARP inhibitor, including olaparib.

19 Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment. Patients who receive palliative radiotherapy need to stop radiotherapy 1 week before randomisation.

20 Any previous exposure to a CYP17 (17α-hydroxylase/C17,20-lyase) inhibitor (eg, abiraterone, orteronel).

21 Concomitant use of known strong CYP3A 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 study treatment is 2 weeks.

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

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

24 Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).

Prior/concurrent clinical study experience

25 Participation in another clinical study with an investigational product or investigational medical devices within 1 month of randomisation.

26 History of hypersensitivity to olaparib or abiraterone, any of the excipients of olaparib or abiraterone, or drugs with a similar chemical structure or class to olaparib or abiraterone.

Other exclusions

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

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

29 Previous randomisation in the present study.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

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

Patients will be required to fast from at least 2 hours before until 1 hour after each dose of abiraterone, due to an effect of food on absorption. Water can be allowed as desired.

On olaparib PK sampling day, patients should fast from 1 hour before taking the olaparib dose to 2 hours after (see Section 6.1.1). Note: PK samples will not be collected for patients in China.

5.3.2 Contraception

Patients must use a condom when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients must use one highly effective form of contraception (as described in Appendix I) if they are of childbearing potential. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 3 months after the last dose of olaparib, or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix I). Patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

For details of acceptable methods of contraception refer to Appendix I Acceptable Birth Control Methods.

5.3.3 Blood donation

Patients should not donate blood or plasma while participating in this study and for 3 months following the last dose of study treatment.

5.4 Screen failures

Screen failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded in the electronic case report form (eCRF) (ie, patient does not meet the required inclusion/exclusion criteria) and the patient should also be registered in the randomisation and trial supply management system (interactive response technology) (RTSM [IRT]) as 'screen failed'. This reason for study withdrawal is only valid for screen failures (not randomised patient).

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once, upon the AstraZeneca Study Physician's approval and agreement. Re-screened patients should be assigned the same patient number (enrolment code [E-code]) as for the initial screening. Re-screening should be documented (in the eCRF/RTSM [IRT] and source data) so that its effect on study results, if any, can be assessed.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to olaparib, placebo or abiraterone.

6.1 Treatments administered

6.1.1 Investigational products

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply the olaparib and matching placebo to the investigator as film-coated tablets. Details of the investigational product (IP) is shown in Table 7.

Patients will be administered olaparib or placebo orally at a dose of 300 mg twice daily. The initial dosage of 300 mg twice daily will be composed of 2 x 150 mg tablets per dose which should be taken at the same time each day, approximately 12 hours apart with 1 glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

CCI [redacted]

Olaparib and matching placebo will be provided in high-density polyethylene bottles with child-resistant closures. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement.

Table 7 Identity of investigational product (olaparib)

Investigational product	Dosage form and strength
Olaparib	100 mg tablet
Olaparib	150 mg tablet
CCI [redacted]	[redacted]
Placebo to olaparib 150 mg	Placebo to match olaparib 150 mg tablet

Olaparib should be dosed fasted on PK sampling days (from 1 hour before taking the olaparib dose to 2 hours after). If vomiting occurs shortly after the olaparib or placebo tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient randomised on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time. CCI [redacted]

Once patients have been discontinued from study treatment, further treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. Crossover from placebo+abiraterone to olaparib+abiraterone is not allowed in this study.

6.1.2 Additional study drugs – abiraterone and prednisone/prednisolone

Abiraterone with supportive prednisone or prednisolone is background treatment; these will be sourced locally or centrally as commercially available materials. Patients will be administered abiraterone 1000 mg once daily. The initial dosage of 1000 mg once daily will be in combination with prednisone or prednisolone 5 mg administered orally twice daily. **Abiraterone must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone is taken and for at least 1 hour after the dose of abiraterone is taken. The tablets should be swallowed whole with water and not crushed or chewed, in full accordance with local prescribing information**.

Adverse events management and dose modifications strategies of abiraterone and prednisone or prednisolone during the study is at the investigators' discretion based on local prescribing information of abiraterone.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients randomised in the study may receive study treatment and only authorised site staff may dispense study treatment. At site, all study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

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

Unused study treatment should be destroyed as per site/country local regulations and guidelines.

6.3 Measures to minimise bias: randomisation and blinding

All patients will be centrally assigned to randomised study treatment using an RTSM (IRT). Before the study is initiated, the telephone number and call-in directions for the RTSM (IRT) and/or the log-in information and directions for the RTSM (IRT) will be provided to each site.

Eligible patients will be randomised in a 1:1 ratio (treatment 1: treatment 2). The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the RTSM (IRT) database. The randomisation scheme will be produced by a computer software program called AZRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers.

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the investigator (or nominated assistant) should contact the RTSM (IRT) Centralised Randomisation Centre for allocation of randomised therapy. Patients will be identified to the Centralised Randomisation Centre using E-code (and patient initials/date of birth, if permissible under local regulations).

It is recommended that patients commence study treatment as soon as possible after randomisation and ideally on the same day of randomisation.

If a patient withdraws from the study, then his enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

If a patient is continuing to derive benefit from olaparib at the end of the study, then they may continue to receive treatment as open labelled drug via manual supply once the RTSM (IRT) has been closed. Following objective disease progression, further treatment options will be at the discretion of the investigator. Patients may be allowed to continue study treatment if the investigator believes, and the AstraZeneca Study Physician concurs, that the patient could continue to receive clinical benefit, the patient is not experiencing serious toxicity, and there is no available better alternative treatment that could benefit the patient. Crossover from placebo+abiraterone to olaparib+abiraterone is not allowed in this study. At the end of the study (ie, at final analysis) the study will be unblinded.

6.3.1 Methods for ensuring blinding

The study will be conducted in a double-blind manner. The study medications will be identical and presented in the same packaging to ensure blinding of the study medication.

The patient, the investigator and study centre staff will be blinded to study drug allocation.

No member of the extended study team at AstraZeneca, at the investigational centres, or any Contract Research Organisation (CRO) handling data will have access to the randomisation scheme until the study is formally unblinded as a result of meeting the primary objective. Exceptions are relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package study drug, the drug safety departments at AstraZeneca, and personnel providing the analysis of PK samples. Investigators will only be unblinded to treatment allocation in cases of medical emergency.

The treatment codes and results will be kept strictly within AstraZeneca to safeguard the integrity of the blind, and hence to minimise any possible bias in data handling.

An independent third-party vendor will provide unblinded data to the IDMC for their review per the IDMC charter but AstraZeneca and CRO staff and investigators involved in the study will remain blinded at this time. See Section 9.5.1 for further details.

6.3.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) at the study centre from the RTSM (IRT). Routines for this will be described in the RTSM (IRT) user manual that will be provided to each centre. The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to a patient to the AstraZeneca staff. Overdose will not normally be considered a reason for breaking the blind. If the treatment code is broken the investigator(s) must document and report to AstraZeneca. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented. If the blind is broken, the date, time and reason will be recorded in the RTSM (IRT), and any associated AE report. If a patient's study drug is unblinded by the investigator, or designee, the patient will be withdrawn from study drug as described in Section 7.3. The study will be centrally unblinded at the time of first meeting the primary objective, but patients and investigators will remain blinded until after the database is verified and closed.

For the BICR, blinded data will be provided.

6.4 Treatment compliance

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

Exception: Tablet counts do not have to be recorded on eCRF for locally supplied drug, but all study drug usage, including any missing doses, still needs to be recorded in the appropriate Section of the eCRF.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF.

Patients must return all containers and any remaining tablets at the end of the study. For overdosing see Section 8.4.3.

6.5 Concomitant therapy

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

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

Anti-emetics/Anti-diarrhoeals

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

Prohibited and restricted concomitant medications and therapies

Prohibited and restricted concomitant mediation and therapies are described in Table 8 and Table 9.

Avoid concomitant strong CYPsA4 inducers and CYP2D6 substrates with abiraterone; for more details of restrictions and cautions required when administering concomitant medications with abiraterone, please refer to abiraterone local prescribing information.

Table 8 Prohibited medications

Prohibited medication/class of drug:	
Anticancer therapy: Chemotherapy Immunotherapy Radiotherapy (except palliative) Biological therapy Other novel agents	Patients must not receive any other concurrent anticancer therapy, including investigational agents, while on study treatment. **However, continuous ADT with an LHRH agonist/antagonist (unless bilateral orchiectomy) must be continued during the trial.** 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.
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.

ADT, Androgen-deprivation therapy; LHRH, Luteinising hormone-releasing hormone.

Restricted concomitant medications

Table 9 Restricted concomitant medications and therapies

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which the medication is allowed):
Strong CYP3A inhibitors: eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, and telaprevir Moderate CYP3A inhibitors: eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, and verapamil	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the eCRF 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: eg, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide, and St John's wort Moderate CYP3A inducers: eg, bosentan, efavirenz, and modafinil	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers is 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 they must be monitored carefully for any change in efficacy of olaparib.
CYP3A4 substrates with narrow therapeutic margin: eg, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, and warfarin Sensitive CYP3A4 substrates: eg, buspirone, felodipine, fluticasone, lovastatin, quetiapine, saquinavir, sildenafil, and simvastatin CYP2B6 substrates: eg, bupropion and efavirenz OATP1B1 substrates: eg, bosentan, glibenclamide, repaglinide, statins, and valsartan OCT1, MATE1 and MATE2K substrates: eg, metformin OCT2 substrates: eg, cimetidine and metformin OAT3 substrates: eg, furosemide and methotrexate BCRP substrates: eg, methotrexate and rosuvastatin P-gp substrates: eg, simvastatin, pravastatin, dabigatran, digoxin, and colchicine	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6 (and potentially substrates of CYP2C9, CYP2C19, and P-gp). The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered. Appropriate clinical monitoring is recommended for patients receiving P-gp substrates or CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Table 9 Restricted concomitant medications and therapies

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which the medication is allowed):
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; 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. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (eg, apixaban and rivaroxaban) if possible.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

INR, International normalised ratio.

Subsequent therapies for cancer

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

Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, 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 10, Table 11 and Table 12.

Table 10 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 11 Dose reduction for olaparib if patient develops moderate renal impairment

Initial Dose	Moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test, between 31 and 50 mL/min): Dose reduction
300 mg twice daily	200 mg twice daily

Table 12 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 AEs (including renal impairment) refer to Section 8.4.4.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Section 6.5.

When dose reduction is necessary due to olaparib-related AEs, patients will take 1 x 150 mg tablet and 1 x 100 mg tablet twice daily or 2 x 100 mg tablet twice daily (see Section 8.4.4). In the case that a patient has to take a strong or moderate CYP3A inhibitor, dose reduction is necessary and the patient will take 1 x 150 mg tablet twice daily or 1 x 100 mg tablet twice daily (see Section 6.5). These dose reductions should be documented in the eCRF. Dose re-escalation is allowed after the discontinuation of the strong or moderate CYP3A inhibitor, provided there are no olaparib-related AEs of grade 2 or above.

6.6.2 Dose reductions for abiraterone

In case dose reductions are necessary for abiraterone, the investigator should refer to abiraterone local prescribing information for further details. These dose reductions should be documented in the eCRF.

6.7 Treatment after final DCO before the end of the study

AstraZeneca will continue to supply olaparib within the current study after final DCO until either olaparib is licenced in that country, or it is determined that the benefit to risk profile

does not support continued development of olaparib, or the national health authority has deemed the drug not approvable.

AstraZeneca will continue to supply olaparib in the continued access phase of this study while, in the opinion of the Investigator, the participant is benefiting.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the participant(s) to alternative supply, where possible.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participant(s) currently receiving treatment with olaparib may then be transitioned to such a study, and the current study would reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable. Participants are to be followed in accordance with the Medical Standard of Care and as deemed appropriate by the investigators. It is recommended that investigators continue to observe ongoing participants at the frequency employed prior to the DCO.

Protocol dose modification and stopping criteria are to be followed while a participant is receiving olaparib. A change in the dose/schedule of olaparib should only occur for safety reasons, based on the investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from study treatment in the following situations. Note that discontinuation from study treatment does NOT equal complete withdrawal from the study (all efforts should be made to keep patients who withdraw from treatment on study):

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event
- Severe non-compliance with the Clinical Study Protocol
- Bone marrow findings consistent with MDS/AML
- Radiological progressive disease is confirmed by the investigator (RECIST 1.1 or PCWG-3 criteria), unless in the investigator's opinion, and the AstraZeneca Study

Physician concurs, that the patient is benefiting from the treatment, provided patient does not meet any other discontinuation criteria as outlined in this section.

See the schedule of activities (SoA; Section 1.1) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

All reasons for discontinuation of study treatment must be documented in the eCRF (see Section 7.1.1).

7.1.1 Procedures for discontinuation of study treatment

The investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All study treatment should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the investigator.

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

After discontinuation of 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 7.2). 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 8.4.1) 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 AEs after the 30-day follow-up period see Section 8.3.2.1.

Any patient who has not yet shown objective radiological disease progression at withdrawal from study treatment should continue to be followed as per RECIST 1.1 and PCWG-3 as detailed in Section 8.1.1.1.

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

Discontinuation of study treatment, for any reason, does not impact on the patient's participation in the study. The patient should continue attending subsequent study visits and

data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient**,** a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Note: Patients who discontinue 1 of the study treatments, eg, discontinue abiraterone and remain on olaparib, or vice versa, should continue to be seen and have assessments performed as outlined in the SoA (see Section 1.1). Once both olaparib and abiraterone treatment are permanently discontinued, procedures should be followed for the discontinuation and follow-up visits.

The date and reasons for discontinuation of study treatment should be captured in the eCRF.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient or next of kin by eg, repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 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 randomised patients ie, the patient does not meet the required inclusion/exclusion criteria for the study.
- Patient lost to follow-up (see Section 7.2).
- Death

A patient may withdraw from the study (eg, withdraw consent), at any time (investigational product **and** assessments) at his own request, without prejudice to further treatment.

A patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

If the patient 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 patient withdraws from the study, he may request destruction of any samples taken, and the investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The investigator will follow up patients as medically indicated. The patient will be asked to return electronic patient-reported outcome (ePRO) devices.

AstraZeneca or its delegate will request investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patient is crucial for the integrity of the study.

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

- To further participation in the study including any further follow-up (eg, survival calls)
- Withdrawal of consent to the use of their study generated data
- Withdrawal to the use of optional and/or mandatory biological samples (all biomarker samples that are not already analysed can be requested to be destroyed)

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

See SoA, Table 1, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

After withdrawal from the study, patients will continue to receive standard treatment according to their own doctor's discretion.

7.4 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (see Section 1.1).

The investigator will ensure that data are recorded on the eCRF. The web-based data capture system will be used for data collection and query handling.

The investigator ensures the accuracy and completeness for eCRFs, which includes legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRF will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed approximately 300 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 Imaging tumour assessment

In this study the preferred assessment of soft tissue lesions are CT/MRI scans using the RECIST 1.1 criteria and the bone lesions are assessed on bone scintigraphy scans using the PCWG-3 criteria. The RECIST 1.1 and PCWG-3 assessments should follow the same schedule. 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 randomisation/treatment assignment. Following the baseline assessment, subsequent assessments should be performed every 8 weeks (± 7 days) until week 24 and every 12 weeks (± 7 days) thereafter, relative to the date of randomisation, until objective radiological disease progression is confirmed by the investigator. After the initial assessment of progression, whether the patient receives a subsequent therapy or not, the patient should have 1 follow-up scan collected preferably at the next (and no later than the next) scheduled imaging visit, and no less than 6 weeks after the prior assessment of progression of disease (PD). The assessments by different imaging modalities, for example CT and bone scintigraphy, 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 Section 1.1, SoA Table 1). However, tumour assessment can be performed at any time when PD is suspected. If the scans are performed outside of scheduled visit window interval, and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points.

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

8.1.1.1 RECIST 1.1 assessments (soft tissue lesions)

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 patients. During the assessments subsequent to baseline any other sites at which new disease is suspected should also be appropriately imaged. The modality of assessment of tumour burden used at baseline must be

used at each subsequent visit. In this study, bone lesions will not be included in the RECIST soft tissue assessment.

8.1.1.2 PCWG-3 assessment (bone lesions assessment)

Bone lesions will be assessed on whole body bone scintigraphy (bone scans). Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions. Bone lesions will be assessed on bone scan only and will not be part of the RECIST 1.1 malignant soft tissue assessment.

8.1.2 Tumour evaluation

Disease progression will be deemed to have occurred if 1 or more of the following criteria is met:

- Soft tissue disease progression as defined by RECIST 1.1
- Bone lesion progression by PCWG-3 (Table 13)
- Death

RECIST 1.1 and PCWG-3 criteria will be used together to assess patient response to treatment by determining PFS times. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria are presented in Appendix A, together with the PCWG-3 guidelines.

8.1.2.1 Soft tissue lesions evaluation

Categorisation of objective tumour response assessment on soft tissue lesions will be based on the RECIST 1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease), NED (no evidence of disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, and SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

For patients with non-measurable soft tissue lesions only at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PD and Non-CR/Non-PD.

Patients with bone metastasis only and no soft tissue disease at baseline will still be assessed according to RECIST criteria. The only RECIST visit response possible will be NED if the patient remains without soft tissue lesion, PD if a new soft tissue lesion is identified or not evaluable (NE) in rare situations when insufficient data exist.

If the investigator is in doubt as to whether progression has occurred, particularly with regard to non-target lesions or the appearance of a new lesion, it is advisable to continue treatment and reassess the tumour burden at the next scheduled assessment or sooner if clinically indicated. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression. New bone lesions should not be counted in the RECIST assessment.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

8.1.2.2 Bone lesions evaluation

Categorisation of tumour progression of bone lesions will be based on the PCWG-3 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 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 other 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 radiological 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 summarised in Table 13.

Table 13 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 tumours.

It is important to follow the assessment schedule as closely as possible. Please refer to the study schedule in Table 1.

8.1.2.3 Central reading of scans

An independent review of all scans used in the assessment of tumours will be conducted. All imaging assessments including unscheduled visit scans should be collected in DICOM format on an ongoing basis and sent to an AstraZeneca appointed CRO to enable BICR. Results of this independent review will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST 1.1 and PCWG-3 assessment conducted by the investigator.

All treatment decisions will be based on site assessment of scans. After the primary PFS analysis, central review of scans will no longer be required, and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Note this

also applies to the China Cohort, following the final rPFS analysis for the China Cohort, which will occur after the analysis for the global study.

8.1.3 Patient-reported outcomes

The following patient-reported outcomes (PRO) questionnaires will be electronically administered in this study: Brief Pain Inventory-Short Form (BPI-SF), Functional Assessment of Cancer Therapy-Prostate Cancer (FACT-P); and the EuroQol 5-dimension, 5-level health state utility index (EQ-5D-5L).

Patients must complete the PRO questionnaires in the following order: First the BPI-SF and analgesic log, then the FACT-P questionnaire, and then the EQ-5D-5L. If the participant does not complete the PROs, the REVPRDI form must be completed during a site visit by a site staff to capture the reason the assessment was not completed by the patient.

8.1.3.1 BPI-SF

The BPI-SF (see Appendix J) is a validated, 15-item domain-specific instrument designed to assess the severity of pain and the impact/interference of pain on daily functions (Cleeland and Ryan 1994). The BPI-SF will be scored according to the user guide (Cleeland 2009). All BPI-SF pain items including "worst pain" is scored on a 0-10 numeric rating scale (NRS) with 0=No Pain and 10=Worst Pain Imaginable. This instrument consists of 2 domains: pain severity and pain interference. The pain severity domain consists of 4 items (item #3, item #4, item #5, and item #6) which assess pain at its "worst," "least," "average," and "now" (current pain) respectively on the 11-point NRS. These 4 items may be averaged as a composite pain severity score or they may be interpreted individually (Dworkin et al 2005, Turk et al 2006, Dworkin et al 2008, Food and Drug Administration 2009). In this study, the "worst pain" (item 3) will be used as a single item in assessing pain progression. A composite pain severity score from all the 4 items will also be evaluated as 'pain severity progression'. A 2- or more point change in the average pain severity or in "worst pain" item is considered clinically meaningful.

The pain interference domain score is a mean of 7 items: general activity (item #9A), mood (item #9B), walking ability (item #9C), normal work (item #9D), relations with other people (item #9E), sleep (item #9F), and enjoyment of life (item #9G), each scored on an 11-point NRS from 0 (Does not interfere) to 10 (Completely interferes). Based on the BPI-SF scoring manual, the following items are not used in scoring pain severity or pain interference domains: items #1, #2, #7 and #8. Item #7 (a free text field) describing pain medication use is captured separately in more detail using the Analgesic Log.

The BPI-SF analgesic log (captured on ePRO device) will be completed by the patient as specified in the SoA (Section 1.1).

8.1.3.2 Analgesic log

The analgesic log will be implemented using the ERT Medication Module™, a component of the ERT eCOA System that serves for accurately tracking patient consumption of concomitant and/or rescue medications. The Medication Module allows medication data capture via the ERT eCOA Universal App, followed by the review and management of that data by sites and sponsors. The Medication Module provides a consistent, easier-to-use and more efficient tool as compared to paper-based reporting. Using the module, patients will record all analgesic medication dosages and dosage times. The Medication Module includes the 2 main components and a report:

(a) Global Master Medication List – This list will be developed collaboratively by ERT and AstraZeneca and will contain all approved analgesic drug names including generic names and formulations. The list will be updated over the course of the study via an approval workflow process, when necessary.

(b) eCOA Universal App Medication Diary – The medication diary will allow patients to record analgesic medications between visits and identify when any new medications not previously approved have been taken.

(c) Medication Report – This interactive report allows sites to see when their patients have taken new medications, resolve those medications through an approval workflow, and remotely update the tailored list of medications available on a patients' eCOA Universal App.

The analgesic log is study specific (not generic) and screenshots will be available and submitted along with the Clinical Study Protocol to the Institutional Review Board (IRB)/Ethics Committees (ECs).

8.1.3.3 Analgesic use scoring

Although information on all analgesics used by patients in pain control will be collected using the analgesic log, only changes in opiate are considered in pain progression evaluation in line with FDA recommendation. Opiates consumed by patients will be converted into oral morphine equivalents (OMEs) as defined in Chung et al 2014. The analgesic quantification algorithm (AQA) developed by Chung et al 2014 will be used to quantify and score analgesic use in the study. The AQA is an 8-point scale that assigns a score as follows:

- 0=No analgesic
- 1=Non-opioid analgesics
- 2=Weak opioids (eg, codeine, tramadol)
- 3=Strong opioids ≤75 mg OME per day

- 4=Strong opioids >75–150 mg OME per day
- 5=Strong opioids >150–300 mg OME per day
- 6=Strong opioids >300–600 mg OME per day
- 7=Strong opioids >600 mg OME per day

Opiate analgesic use (AQA score) will be assessed at timelines specified in the SoA (Section 1.1). The average daily OME will require at least 4 days of data and will be used to assign the AQA score. An increase of 1 point or more in the AQA score from a starting value of 1 or higher OR ≥ 2 points in AQA score from a starting value of 0 is considered a clinically meaningful increase in opiate use. Similarly, a decrease of 1 point or more in the AQA score from a starting value of 2 or higher is considered a clinically meaningful decrease in opiate use.

8.1.3.4 FACT-P

The FACT-P (Appendix J) is a disease-specific 39-item questionnaire included for the purpose of assessing HRQoL and prostate cancer-specific symptoms. It is a well-established measure of HRQoL/health status commonly used in prostate cancer clinical studies. The FACT-P was developed specifically for patients with advanced prostate cancer and has been found to be reliable and valid in this population (Esper et al 1997). The FACT-P consists of 5 subscales: Physical Well-Being (PWB; 7 items), Functional Well-Being (FWB; 7 items), Emotional Well-Being (EWB; 6 items), Social Well-Being (SWB; 7 items), and Additional Concerns or Prostate Cancer Subscale (PCS) specific to prostate cancer (12 items). All FACT-P questions are scored on a 5-point Likert scale from 0 to 4 (0 being not at all and 4 being very much). Negatively stated items are reversed by subtracting the response from 4. For all subscales, symptoms index, and individual item scores, the higher the score, the better the HRQoL/symptom. In addition to the Total and Subscale scores, the FACT-P also supports the calculation of the Functional Assessment of Cancer Therapy-General (FACT-G) total score (sum of PWB, SWB, EWB and FWB scores), a Trial Outcome Index (TOI) score (the sum of the PWB, FWB and PCS scores), and the FACT Advanced Prostate Symptom Index-6 (FAPSI-6), a symptom score made up of 6 items from within the FACT-P (3 pain items, 1 fatigue item, 1 weight loss item, and 1 condition getting worse item).

FACT-P assessments will be at timelines as specified in the SoA (Section 1.1). Scoring of the FACT-P will be based on the user manual.

8.1.3.5 EQ-5D-5L

The EQ-5D is a standardised measure of health status developed by the European Quality of Life (EuroQoL) Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990), see Appendix J. Applicable to a wide range of

health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQol Group 2013). Since 2009, the EuroQoL group has been developing a more sensitive version of the EQ5D (the EQ-5D-5L), which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the 5 level (5L) version improves upon the properties of the 3 level (3L) measure in terms of reduced ceiling effect, increased reliability, and an improved ability to differentiate between different levels of health (Pickard et al 2007, Janssen et al 2008a, Janssen et al 2008b). The patient will be asked to indicate his current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with zero being the worst imaginable health state.

EQ-5D-5L assessments will be at timelines as specified in the SoA (Section 1.1).

8.1.3.6 Administration of PRO questionnaires

During the study, each patient will take 1 handheld device home for completing all ePRO assessments (ePROs will be self-administered by the patients using these handheld devices). The analgesic use log using the ERT Medication Module™ will also be administered electronically alongside the ePROs.

All assessments should be completed according to the following parameters:

- Without assistance from site staff or relatives/friends according to the assessment schedules (see SoA, Section 1.1).
- Before any other study procedures are conducted at a given visit.
- Before being seen by a study nurse or physician.

Each centre must allocate the responsibility for the administration of the ePROs to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent. Approximately 15 to 30 minutes is required for patients to complete the questionnaires. Patients may complete some of the ePROs (FACT-P and EQ-5D-5L [see Sections 8.1.3.4 and 8.1.3.5]) at study sites if the assessment time point coincides with a scheduled site visit; otherwise, patients may complete the ePROs at home. Similarly, during the post-progression period, patients should complete ePROs at home or at the study site if a scheduled visit coincides with the time point. If patients have had scans or

other tests at an outside facility or missed a scheduled data collection site visit, ePROs should still be completed by the patient at home for that scheduled visit within the window period.

The significance and relevance of the data should be explained carefully to participating patients so that they are motivated to comply with data collection. Reminders should be sent to patients at home as needed to ensure compliance with the assessment schedules.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- PRO questionnaires completed at site visits must be completed prior to treatment administration and ideally before any discussions of health status to avoid biasing the patient's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias.

- When each instrument is due to be completed, the following order should be observed: BPI-SF, Analgesic Log, FACT-P, and then EQ-5D-5L.

- PRO questionnaires must be completed by the patient in private.

- The research nurse or appointed site staff must explain to the patient the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patients have any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must train the patient on how to use the ePRO device, using the materials and training provided by the ePRO vendor, and provide guidance on whom to call if there are problems with the device if the patient is completing the ePRO at home.

- The research nurse or appointed site staff should remind patients that there are no right or wrong answers.

- The research nurse or appointed staff must avoid clarifying items in order to avoid bias.

- The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a patient uses visual aids (eg, spectacles or contact lenses) for

reading and does not have them when he attends the clinic, the patient will be exempted from completing the PROs at the clinic.

- Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient is exempted from completing PRO questionnaires and may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff.

- The patient should be given sufficient time to complete the PRO questionnaires at his own speed.

The research nurse or appointed site staff must monitor compliance to ensure all data is captured. Compliance must be checked at each study visit to identify problems early. If a patient's compliance drops below 85%, they will be flagged in the routine compliance report generated by the ePRO system and a check-in call from the site to ask the patient if he has any difficulties is highly recommended.

8.1.4 Other assessments

8.1.4.1 Time to first subsequent anticancer therapy or death (TFST)

All anticancer treatments (including, but not limited to, chemotherapy and targeted agents), and the investigator's opinion of response to these treatments plus the date of progression, following discontinuation of study treatment, must be recorded.

Subsequent systemic anticancer therapies (excluding radiotherapy) will be reviewed prior to data unblinding to assess which represent clinically important treatments intended to control prostate cancer. Any patient not known to have died at the time of the analysis and not known to have had a further anticancer therapy will be censored at the last known time to have not received subsequent therapy, ie, the last follow-up visit where this was confirmed.

8.1.4.2 Overall survival (OS)

Assessments for survival will be conducted every 12 weeks following objective disease progression or treatment discontinuation; see Figure 2.

Survival information may be obtained via telephone contact with the patient, patient's family, by contact with the patient's current physician, or local death registries as described in Section 7.3.

8.1.4.3 Time to second progression or death (PFS2)

Following the progression event used for the primary variable rPFS (the first progression), patients will be assessed every 12 weeks for second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression or death (PFS2). The patient's status at first progression will be

used as the reference for assessment of PFS2. RECIST 1.1 and PCWG-3 assessments will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of progression status (progressed or nonprogressed) at each assessment will be recorded in the eCRF.

8.1.4.4 Symptomatic skeletal-related event (SSRE)

Assessments for SSREs will be conducted at every visit from randomisation up to the discontinuation visit as defined in the SoA (Section 1.1).

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.1).

8.2.1 Clinical safety laboratory assessments

See Table 14 for the list of clinical safety laboratory tests to be performed and the SoA (Section 1.1) for the timing and frequency. All protocol-required laboratory assessments, as defined in Table 1 must be conducted in accordance with the laboratory manual and the SoA.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

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, haematology and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 14 Laboratory safety variables

Haematology (whole blood)	Chemistry: electrolytes (serum/plasma)	Chemistry: liver function (serum/plasma)
B-Haemoglobin (Hb)	S/P-Potassium	S/P-Creatinine
B-Haematocrit (Hct)	S/P-Calcium, total	S/P-Bilirubin, total
B-Red blood cell (RBC) count	S/P-Sodium	S/P-Bilirubin, direct
B-White blood cell (WBC) count with differential	S-Carbon dioxide (CO_2) or bicarbonate (HCO_3^-)	S/P-Alkaline phosphatase (ALK-P)

B-Leukocyte count	S-Chloride (Cl)	S/P-Aspartate aminotransferase (AST)
B-Absolute neutrophil count	S-Magnesium	S/P-Alanine aminotransferase (ALT)
B-Absolute lymphocyte count	S-Phosphorus	Amylase
B-Platelet count		S/P-Albumin
B-Mean cell volume (MCV)	**Fasting glucose (plasma/whole blood)**	S/P-Urea or blood urea nitrogen (BUN)
	P/B-Fasting glucose	S/P-Total protein
Coagulation factors		S/P-Lactate dehydrogenase (LDH)
Prothrombin (PT)	**Serum lipids**	S-Gamma-glutamyl transferase (GGT) (at screening only)
Activated partial thromboplastin time (aPTT)	S-Cholesterol	
International normalised ratio (INR)	S-High density lipoprotein (HDL)	
	S-Low density lipoprotein (LDL)	
Urinalysis (dipstick)	S-Triglycerides	
U-Hb/erythrocytes/blood		**Additional tests**
U-protein/Albumin		S-Prostate specific antigen (PSA)
Microscope examination of abnormalities		S-Testosterone, total

NB. In case a patient shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix G 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.
ULN, Upper limit of normal.

8.2.1.1 Coagulation

Tests for prothrombin time (PT), partial thromboplastin time (PTT), and international normalised ratio (INR) will be performed at timelines as specified in the SoA (Section 1.1).

Patients 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 the eCRF.

8.2.1.2 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 8.4.4.1.

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 Patient Safety database. These data are not required to be entered into eCRF.

8.2.2 Physical examinations

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

A symptom-directed physical examination will be performed at other timelines as specified in the SoA (Section 1.1).

A symptom-directed physical examination will be additionally performed if clinically indicated at any other time for all patients. Patients with hypertension at baseline need to be monitored closely, and BP must be recorded at all visits.

Investigators should pay special attention to clinical signs related to previous serious illnesses; new or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details.

8.2.3 Vital signs

Vital signs (including blood pressure, pulse rate and body temperature) will be assessed at timelines as specified in the SoA (Section 1.1).

Weight will be assessed at timelines as specified in the SoA (Section 1.1).

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

Any changes in vital signs should be recorded as an AE, if applicable. For information on how AEs based on changes in vital signs should be recorded and reported, see Section 8.3.7.

8.2.4 Electrocardiogram

Twelve-lead resting ECGs will be performed at timelines as specified in the SoA (Section 1.1).

Twelve-lead resting ECGs are required within 7 days of start of study treatment and will be additionally performed every 12 weeks during the study treatment period, study treatment

discontinuation visit, 30-days follow-up visit, and if clinically indicated at any other time for all patients.

The investigator or designated physician will review each of the timed 12-lead resting ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

8.2.5 Other safety assessments

8.2.5.1 ECHO or MUGA

Assessments will be performed at screening and thereafter as clinically indicated. Patient must have a left ventricular ejection fraction measurement of at least 50% by echocardiogram (ECHO) (preferable) or multigated acquisition scan Cardiology A (MUGA), a maximum of 14 days prior to randomisation. The same method used for pre-randomisation assessment preferably should also be used when clinically indicated later.

8.3 Collection of 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 D.

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

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse events, including SAEs, will be collected from time of signature of informed consent form, throughout the treatment period, including study treatment discontinuation (+7 days of

last study drug dose), and the 30-day (+7 days) follow-up after last study drug dose. Assessments may be conducted by phone if not tied to a scheduled visit.

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix D. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix D.

8.3.2.1 Adverse events after the 30 day follow-up period

For Pharmacovigilance purposes and characterisation, 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 patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

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

Otherwise, after study treatment completion (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 patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post-treatment follow-up period (30 days).

8.3.3 Follow up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAE/non-serious AEs/AEs of special interest (as defined in Appendix D and Section 8.3.13) will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate 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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Any SAE or non-SAE that is ongoing at the time of the 30-day follow-up, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

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
- Investigator causality rating against the olaparib/placebo (yes or no)
- Action taken with regard to olaparib/placebo and abiraterone, prednisone or prednisolone
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

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

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

- Causality assessment to other medication
- Description of AE

8.3.5 Causality collection

The investigator will assess causal relationship between study treatment 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 olaparib or abiraterone?'

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

A guide to the interpretation of the causality question is found in Appendix D to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study 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.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the Investigational Product.

If deterioration in a laboratory value/vital sign 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, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study (see Sections 8.3.9 and 8.3.10).

8.3.8 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3xULN together with total bilirubin ≥2xULN will need to be reported as SAEs if criteria for Potential Hy's Law (PHL) are met. Please refer to Appendix G for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.9 Disease progression

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

8.3.10 New cancers

The development of a new primary cancer should be reported as an AE (see Section 8.3.13 Olaparib adverse events of special interest) and would in most cases meet seriousness criteria (with the exception of some non-melanoma skin cancers). New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

8.3.11 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.

8.3.12 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 8.4.1 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

Deaths with an unknown cause should always be reported as a SAE. A post-mortem 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 within the usual timeframes.

8.3.13 Olaparib adverse events of special interest

Adverse events of special interest (AESIs) 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. AESIs for olaparib are the Important Identified Risk of MDS/AML, and the Important Potential Risk of new primary malignancy (other than MDS/AML), and the Potential Risk of pneumonitis. All AESIs will be recorded in the eCRF.

A questionnaire will be sent to any investigator reporting an AESI to the safety database, 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.

8.3.14 Safety data to be collected following the final DCO of the study

For patients, continuing to receive olaparib + abiraterone or abiraterone treatment after the final DCO, it is recommended that the patients continue site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with olaparib + abiraterone or abiraterone in order to manage AEs in accordance with the olaparib or abiraterone dose modification and toxicity management guidelines (see Section 8.4.4).

China cohort: All data after the final DCO and database closure will be recorded in the patient notes, with the exception of SAEs and pregnancy will not otherwise be reported for the purposes of this study. All SAEs that occur in participants still receiving Olaparib (or within the 30 days following the last dose of Olaparib) after the final DCO must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

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** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 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** of 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 investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

The reference document for definition of expectedness/listedness is the Investigators Brochure for olaparib and the European Union SmPC for the abiraterone, prednisone and prednisolone.

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

8.4.1.1 Paternal exposure

Patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

Pregnancy of the patients' partners 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 until 3 months after the last dose should, if possible, be followed up and documented.

8.4.2 Medication Error, Drug Abuse, and Drug Misuse

8.4.2.1 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 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 8.4.2) and **within 30 days** for all other events

8.4.2.2 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 D 8.

8.4.2.3 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 D 8.

8.4.2.4 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 D 8.

8.4.3 Reporting Overdose

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established. In the event of overdose with abiraterone, please see local prescribing information.

Olaparib 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 for olaparib is 300 mg twice daily (tablet). Abiraterone must be used according to local prescribing information.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated Aes is recorded as the AE diagnosis/symptoms on the relevant AE modules in the Ecrf and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an I**MP 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 he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.2) and **within 30 days** for all other overdoses.

8.4.4 Management of adverse events related to olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of olaparib or dose reductions (Table 17). 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 olaparib should be discontinued.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 6.5).

For management of toxicities for patients treated with abiraterone see Section 8.4.5.

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

8.4.4.1 Management of haematological toxicity

Management of anaemia

Anaemia should be managed as described in Table 15.

Table 15 Management of anaemia

Haemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dL (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg, transfusion) *or* interrupt dose for a maximum of 4 weeks. Olaparib can be restarted if Hb has recovered to >9 g/dL. Subsequent occurrences: If Hb <10 *but* ≥9 g/dL investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* dose interrupt (for max 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 max 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) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥9 g/dL. Upon recovery dose reduce 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.

CTCAE, Common Terminology Criteria for Adverse Events; Hb, Haemoglobin.

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2-week interruption/delay in olaparib due to CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to guidance later in this section for the management of this.

Management of neutropenia, leukopenia and thrombocytopenia

Neutropenia, leukopenia and thrombocytopenia should be managed as described in Table 16.

Table 16 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Olaparib dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation

Toxicity	Olaparib dose adjustment
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. 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

CTCAE, Common Terminology Criteria for Adverse Events.

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

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, olaparib 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 hours (7 days for pegylated G-CSF) of the last dose of olaparib unless absolutely necessary.

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

For cases where patients develop prolonged haematological toxicity (≥2-week interruption/delay in olaparib due to CTCAE grade 3 or worse), refer to guidance later in this section for the management of this.

Management of prolonged haematological toxicities while on olaparib

If a patient develops prolonged haematological toxicity such as:

- ≥2-week interruption/delay in olaparib due to CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in olaparib due to CTCAE grade 3 or worse neutropenia (ANC <1 x 10^9/L)
- ≥2-week interruption/delay in olaparib due to CTCAE 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 patient should be referred to a haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Olaparib should be discontinued if blood counts do not recover to CTCAE 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 an SAE and full reports must be provided by the investigator to AstraZeneca

Patient Safety. Olaparib should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

8.4.4.2 Management of non-haematological 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 olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Olaparib can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Olaparib 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 olaparib.

Management of new or worsening pulmonary symptom

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in olaparib 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 olaparib can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. 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 olaparib treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. 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 patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg, dopamine receptor antagonist, antihistamines or dexamethasone.

Interruptions for intercurrent non-toxicity related events

Dose interruption of olaparib for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart olaparib 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.

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

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

Olaparib should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Olaparib 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, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Table 17 Dose reductions for olaparib

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

8.4.4.3 Renal impairment

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

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test 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 twice daily.

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 patients with severe renal impairment (creatinine clearance ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease it is recommended that olaparib be discontinued.

8.4.5 Management of toxicities related to abiraterone

Please refer to the respective, locally applicable prescribing information (eg, Zytiga Prescribing Information, Zytiga SmPC) for further details.

8.5 Pharmacokinetics

Pharmacokinetic sampling will be performed in a subset of patients, planned to include approximately 50 patients per treatment group (ie, olaparib+abiraterone or placebo+abiraterone), at specific timepoints after multiple dosing. The PK analysis of the plasma concentration data for olaparib, abiraterone and Δ4-abiraterone will be performed at AstraZeneca Research & Development or by a clinical research organisation identified by AstraZeneca Research & Development. The actual sampling times will be used in the PK calculations.

The plasma concentration-time data will be analysed using non-compartmental analysis (NCA) to determine the PK of olaparib, abiraterone, and Δ4-abiraterone (a metabolite of abiraterone) at steady state and to evaluate the effect of olaparib on abiraterone PK. PK samples are to be taken as a blood sample for determination of plasma concentrations of olaparib, abiraterone and Δ4-abiraterone per the SoA (Section 1.1). The actual date and time of dosing on the PK study day must be recorded in the eCRF and source data. IP dosing confirmation for the 3-day-period prior to the PK study day should be recorded in source data.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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

Note: these samples will not be collected from patients in China.

8.5.1 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by analytical test sites on behalf of AstraZeneca, using appropriate validated bioanalytical methods and analytical methods. Samples collected at pre-dose, 30 minutes, 2 hours, 5 hours, and 8 hours post-dose will be used to analyse olaparib plasma concentration. Samples collected at

pre-dose, 30 minutes, 2 hours, 3 hours, 5 hours, and 8 hours post-dose will be used to analyse abiraterone and Δ4-abiraterone concentrations. Full details of the analytical methods used will be described in a separate bioanalytical report.

Full instructions for collection, labelling, storage and shipment of samples are provided in the Laboratory manual. Results will only be reported for samples shipped within a timeframe for which the stability of olaparib in the samples has been validated and shown to be acceptable.

8.5.2 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be destroyed or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

[redacted]

8.6 Pharmacodynamics

Please refer to Sections 8.7 and 8.8 for pharmacodynamic parameters evaluated in this study.

8.7 Genetics

8.7.1 Collection of mandatory genetic samples

The patient's consent to participate in the genetic research components of the study is mandatory.

The baseline blood samples for genetic research (germline and circulating tumour DNA [ctDNA], respectively), and archival or newly collected tumour tissue sample that meets the specimen guidelines outlined in the Laboratory Manual will be obtained from the patients at timelines as specified in the SoA (Section 1.1). Upon randomisation, the tumour specimen should be shipped to the central laboratory per the instructions specified in the Laboratory Manual.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual. In the event of a tumour tissue test failure, a replacement tumour sample may be requested from the patient. If a replacement sample is not available, the patient can continue in the study.

Note: FFPE samples for central tissue HRR testing will be collected for the China cohort.

8.7.1.1 Determination of HRR gene mutation

AstraZeneca or designated organisations will investigate the genetic samples for alterations in genes in the HRR pathway. These analyses are required to establish the presence or absence of a deleterious or suspected deleterious HRR gene mutation in the germline or tumour. Other hereditary or sporadic cancer linked genes will be tested as part of these commercial next generation sequencing tests. Data and samples collected as part of the study may be used for development of current or future diagnostic tests, as required.

Genetic samples (ctDNA and tumour tissue) will be tested for mutations in the following 14 genes: *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L.*

Germline blood testing (Myriad myRisk) will be performed to determine germline versus somatic HRRm status in the following genes: *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CHEK2*, *PALB2*, *RAD51C*, and *RAD51D*. The Myriad myRisk test is not able to assess mutations in *CDK12*, *CHEK1*, *FANCL*, *RAD51B*, and *RAD54L*.

Mutation status

Mutation status will be determined using a ctDNA-based test (FoundationOne Liquid CDx) or a tumour tissue test (FoundationOne CDx).

Patients will be classified into one of three categories of mutation status:

- HRRm: Any deleterious or suspected deleterious HRR gene mutation detected.
- Non-HRRm: No deleterious or suspected deleterious HRR gene mutation detected.
- Unknown: Patients where mutation testing was not performed or where mutation testing failed.

HRRm testing for the China cohort

For the China cohort, HRR mutation status will be determined using a tissue based HRR test at a China-based central laboratory. Although the genetic testing (HRR) is retrospective, the provision of tumour sample is mandatory. Patients must consent to the use of tumour samples for HRRm analysis and future diagnostic development work. Sample requirements will be provided in the Laboratory Manual.

In addition to the defined 14 HRR genes (*ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*), CCI [redacted] These analysis will only be conducted after approval of relevant local authorities.

8.7.2 Optional exploratory genetic sample

CCI [redacted]

CCI [redacted]

8.7.3 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. Samples for genetic analysis are a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

For China, the remaining samples collected from Chinese patients will be destroyed or repatriated within one year of final CSR publication.

No personal details identifying the individual will be available to AstraZeneca or designated organisations working with the samples.

8.8 Biomarkers

Mandatory collection of samples for other biomarker research is also part of this study. The samples may also be used for current or future diagnostic development. The following samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA Section 1.1:

- Blood samples for PSA measurements will be collected and evaluated by the local testing laboratory at timelines as specified in the SoA (Section 1.1). The proportion of patients 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), will be evaluated as part of the PSA response endpoint.
- CCI [redacted] CCI
- Whole blood samples will be collected at timelines as specified in the SoA (Section 1.1) and the response assessments centrally processed to plasma.
  - CCI [redacted]
- A whole blood sample will be collected at radiological progression, and centrally processed to plasma. CCI [redacted]

An optional sample for biomarker research that should be collected from patients in the study where possible is as follows:

- Optional tumour biopsies will be taken at radiological progression for investigation of biomarkers associated with, eg, resistance to olaparib and abiraterone. Note: this sample will not be collected from patients in China.

Please refer to the Central Laboratory Services Manual for further details regarding blood sample collection, shipping and storage.

Unless otherwise specified in the protocol, biomarker data will not be reported to sites unless specifically requested. Frequently, biomarker data are generated retrospectively towards the end of the study. Any sample material remaining after completion of analyses to fulfil the study objectives may be used to develop methods, assays, prognostics, and/or diagnostic tests related to cancer, disease process, pathways associated with disease state, PARP, and or mechanism of action of olaparib in combination with abiraterone and/or used for optional exploratory research.

8.8.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

For China, the remaining samples collected from Chinese patients will be destroyed or repatriated within one year of final CSR publication.

8.9 Medical resource utilisation and health economics

8.9.1 Healthcare resource use

Healthcare resource use will be captured including inpatient admissions, opiate use, intensive care unit and hospital length of stay. Appropriate analyses of resource use will be undertaken to examine the impact of disease and treatment on resource use to primarily support the health economic evaluation of AstraZeneca therapies.

The following will be assessed: number of, types of, and reasons for hospitalisations and hospital attendances; procedures conducted; and hospital length of stay (collected via Hospital Admission [HOSPAD], an AstraZeneca module used to record resource use during unscheduled hospital visits and admissions). All healthcare resource will be recorded in the eCRF.

From visit 2 onwards, assessments will be completed by site staff at each hospitalisation and unscheduled visit.

9. STATISTICAL CONSIDERATIONS

Analyses will be performed by AstraZeneca or an appointed CRO. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. A comprehensive statistical analysis plan (SAP) will be developed and finalised before the first database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Any changes to this plan will be recorded in the SAP before the first database lock and will be reported in the clinical study report.

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19 infection, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatments, and other protocol deviations) may be generated. More detail will be provided in the SAP.

9.1 Statistical hypotheses

The efficacy of the combination of olaparib plus abiraterone and placebo plus abiraterone will be assessed through the primary and the key secondary endpoints, as described in Section 3.1.

Two hypotheses will be tested at three DCOs:

Primary endpoint

rPFS H_{a0}: HR=1 vs H_{a1}: HR<1

Key secondary endpoint

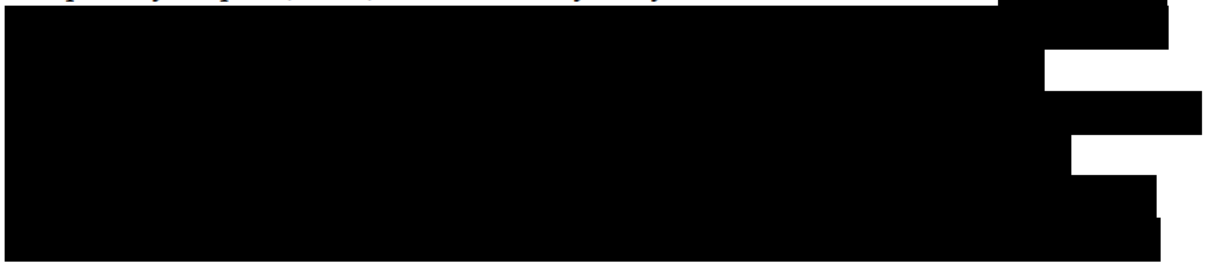
OS H_{b0}: HR=1 vs H_{b1}: HR<1

Further details on the analyses are given in Section 9.4.

9.2 Sample size determination

Approximately 720 patients were planned to be enrolled into this study. At the time of this protocol amendment, enrolment had completed with a total of 796 patients randomised in a 1:1 ratio to treatment with either olaparib and abiraterone or placebo and abiraterone. The study accrual period is approximately 16 months. Three DCOs are planned.

The primary endpoint, rPFS, will be formally analysed at DCO1 and DCO2. CCI



The key secondary endpoint, OS, will be formally analysed at DCO1, DCO2 and DCO3 (See Section 9.4.4 and Table 22).

9.3 Populations for analyses

For purposes of analysis, the populations described in Table 18 and Table 19 are defined. The China cohort will not be included in the main efficacy and safety analysis populations.

Table 18 Analysis populations – Global study

Population	Description
Full Analysis Set	The full analysis set comprises all patients randomised into the study and will be analysed according to randomised treatment (ITT principle). Any important deviations from randomised treatment will be listed and considered when interpreting the efficacy and safety data.
EFR Analysis Set	This is a subset of the FAS, who have measurable disease at baseline as per the RECIST 1.1 criteria. Measurable disease will be defined using the investigator assessment for analyses of investigator data, as well as using the BICR assessment data for analyses of BICR assessment. ORR, DCR, DoR and BoR will be analysed using the EFR set.
Safety Analysis Set	The safety analysis set will consist of all randomised patients who received any amount of olaparib, placebo or abiraterone. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment received. If a patient receives at least one dose of olaparib study treatment they will be summarised in the olaparib and abiraterone arm for safety summaries. If a patient randomised to olaparib and abiraterone receives placebo and abiraterone (or abiraterone only), they will be summarised in the placebo and abiraterone treatment group for safety summaries.

Population	Description
PK Analysis Set Note: This analysis is not applicable for the China cohort	All patients who received at least 1 dose of randomised study drug and provided at least 1 post-dose analysable plasma sample for PK analysis will be included in the PK analysis set. Patients with major protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK may be excluded from the PK analysis set.

BICR, Blinded independent central review; BoR, Best overall response; DCR, Disease control rate; DoR, Duration of response; EFR, Evaluable for response; FAS, Full analysis set; ITT, Intention-to-treat; PK, Pharmacokinetics.

Table 19 Analysis populations – China cohort

Population	Description
China Full Analysis Set	The China full analysis set comprises all patients randomised into the study in China and will be analysed according to randomised treatment (ITT principle). Any important deviations from randomised treatment will be listed and considered when interpreting the efficacy and safety data.
China Safety Analysis Set	The safety analysis set will consist of all randomised patients in the China cohort who received any amount of olaparib, placebo or abiraterone. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment received. If a patient receives at least one dose of olaparib study treatment they will be summarised in the olaparib and abiraterone arm for safety summaries. If a patient randomised to olaparib and abiraterone receives placebo and abiraterone (or abiraterone only), they will be summarised in the placebo and abiraterone treatment group for safety summaries.

FAS, Full analysis set; ITT, Intention to treat

9.4 Statistical analyses

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of study drug, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomisation.

Results of all statistical analysis will be presented using a 95% CI and p-value, unless otherwise stated.

9.4.1 Efficacy analyses

9.4.1.1 Primary endpoint: radiological progression-free survival (rPFS)

Progression-free survival is defined as the time from randomisation until the earlier date of radiological progression or death (by any cause in the absence of progression), regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to progression.

Patients who have not progressed (ie, who have a CR, PR, or SD by RECIST 1.1, and non-progressive disease by PCWG-3) and not died at the time of analysis will be censored at the time of the earliest date of their last evaluable RECIST assessment (taking the latest target lesion, non-target lesion or new lesion scan date) or bone scan assessment that showed non-progressive disease (compared to week 8 or compared to baseline at the week 8 visit) (if the RECIST and bone scans are at different visits). If the RECIST and bone scan assessments are performed at the same visit, then the patient will be censored at the latest of the previous RECIST1.1 and bone scan assessments.

However, if the 2 or more consecutive scheduled radiological assessments immediately prior to progression or death were not evaluable, the patient will be censored at the time of the latest evaluable RECIST 1.1 and bone scan assessment prior to the 2 or more missed assessments. If the patient has no evaluable visits or does not have baseline data, he will be censored at Day 1 (the date of randomisation) unless he dies within 2 visits of baseline (in which case the patient's date of death will be used). The rPFS time will always be derived based on scan/assessment dates, not visit dates.

The overall visit response will be derived using the algorithm shown in Appendix A Table 26. The definitions for the visit bone progression status for bone lesions are shown in Appendix A Table 28.

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

Analysis methods

The primary objective of this study is to assess the efficacy of olaparib+abiraterone combination therapy vs placebo+abiraterone in terms of rPFS assessed by the investigator in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA.

The rPFS will be analysed using a log rank test stratified by the following factors if applicable:

- Metastases: bone only vs visceral vs other
- Docetaxel treatment at mHSPC stage: yes vs no

Although it is expected that there will be enough rPFS events in each stratum to allow a meaningful analysis, if a stratum for either treatment arm contains less than 5 events, then a pooling strategy will be employed. The levels of strata will be collapsed until the minimum 5 event criterion is achieved for the primary rPFS endpoint. Once the pooling strategy is decided, unless there are less than 5 events in a stratum in either treatment, all sensitivity and secondary efficacy analyses will be conducted in accordance with the corresponding final pooling strategy. The details will be provided in the SAP.

Stratification variables will be defined according to data from the RTSM (IRT). If there are any patients who were mis-stratified, a sensitivity analysis may be carried out using the baseline data collected in the eCRF.

The HR and CI will be estimated using a Cox Proportional Hazards Model (with ties=Efron and the stratification variables as covariates) and the 2-sided CI will be calculated using a profile likelihood approach.

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

A Kaplan-Meier (KM) plot of rPFS will be presented by treatment group. Summaries of the number and percentage of patients 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 same analysis model will be used for the subgroup analysis and sensitivity analysis described in the following sections, unless indicated otherwise.

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 investigator assessment of rPFS using all scans regardless of whether they were scheduled or not.

Subgroup analysis

To assess the consistency of treatment effect across potential or expected prognostic factors, the HRs and associated 2-sided CIs will be estimated using a Cox proportional hazard model that contains treatment term, subgroup, and treatment-by-subgroup interaction term for the subgroups described below. If there are too few responders or events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 5 events in either treatment group per subgroup), the relationship between that subgroup and the endpoint will not be formally analysed. In this case, only descriptive summaries will be provided.

The stratification factors in the primary analysis model are not included for the subgroup analyses.

The primary analysis of rPFS will be repeated for the following subgroups, based upon the randomisation stratification factors:

- Metastases (bone only, visceral or other)
- Docetaxel treatment at mHSPC stage (yes or no)

Values collected on the eCRF will be used to define subgroups for stratification factors.

The following subgroup analyses will also apply (HRRm subgroups are defined in Section 8.7.1.1):

- HRRm status subgroup (HRRm, non-HRRm, unknown) based on a ctDNA-based test (FoundationOne Liquid CDx)
- HRRm status subgroup (HRRm, non-HRRm, unknown) based on a tissue test (FoundationOne CDx)
- HRRm status subgroup (HRRm, non-HRRm, unknown) based on a germline blood test (Myriad my Risk) (when data are available)
- Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0 or 1)
- Age at randomisation (<65, ≥65)
- Region (Asia, Europe, North and South America)
- Race (White, Black/African-American, Asian, Other)

- Baseline Prostate specific antigen (PSA) (above/below median baseline PSA of the patients across both treatment groups)

Sensitivity analysis

A sensitivity analysis will be conducted using rPFS as assessed for all patients by BICR per RECIST 1.1 and PCWG-3 criteria. In addition, to assess the sensitivity of the primary rPFS analysis, the following supportive analyses will be performed:

a) Evaluation-time bias

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable assessment (RECIST or PCWG-3) will be analysed as described for the primary analysis of rPFS. Note that midpoint values resulting in non-integer values should be rounded down. For patients whose death was treated as a rPFS event, the date of death will be used to derive the rPFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric schedules (Sun and Chen 2010).

b) Attrition bias

Attrition bias will be assessed by repeating the primary rPFS analysis except that the actual rPFS event times, rather than the censored time, of patients who progressed or died in the absence of progression immediately following 2, or more, missed tumour assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

c) Censoring bias

A Kaplan-Meier plot of the time to censoring will be produced where the censoring indicator of the primary rPFS analysis is reversed.

d) Sensitivity analysis using unequivocal clinical progression in addition to radiological progression

Repeating primary rPFS analysis with the addition of unequivocal progression as an event. Where unequivocal clinical progression is defined as, cancer pain requiring initiation of opioids, need to initiate cytotoxic chemotherapy, radiation therapy or surgical intervention for complications due to tumour progression or deterioration in ECOG performance to ≥ Grade 3.

e) Sensitivity analysis for confirmation of bone progression

Repeat primary rPFS analysis with revised confirmation criteria for bone progression where bone progression accompanied by unequivocal clinical progression does not require a confirmatory bone scan.

f) Sensitivity analysis censoring patients with subsequent therapy or discontinuation of study drug

g) Deviation bias

If greater than 10% of patients in either treatment group have important protocol deviations that may affect the efficacy, the rPFS analysis will be repeated excluding these patients. Details are described in the SAP.

9.4.1.2 Key secondary endpoint: overall survival

Overall survival is defined as the time from randomisation to death from any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. Note: Survival calls will be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO.

Analysis methods

Analysis of OS will be performed using the same methods as in the analysis of rPFS, similarly stratified by metastases category and docetaxel treatment at mHSPC stage.

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

Subgroup Analysis

The subgroup analyses described in Section 9.4.1.1 for rPFS will be repeated for OS.

9.4.2 Safety analyses

Safety and tolerability will be assessed in terms of AEs and SAEs, physical examination findings, vital signs (including BP and pulse rate), ECG findings and laboratory test results (including clinical chemistry and haematology parameters). These will be collected for all patients.

Analysis methods

The analyses for the safety variables described in this section will be presented using the safety analysis set and will be investigated using descriptive statistics by count and percentage for discrete variables and by minimum, maximum, mean, median, and standard deviation for continuous variables.

9.4.2.1 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. All AEs will be coded using the MedDRA® dictionary to provide the system organ class and preferred term for each AE. 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, until the time of the final analysis (rPFS).

9.4.2.2 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 discontinuation of investigational product due to adverse event (DAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

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

9.4.2.3 Concomitant medications

Concomitant medications will be classified and summarised according to the WHO Drug Dictionary.

Concomitant medications will be classed as either:

1. Concomitant medications starting prior to first dose (pre-study)

2. 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.

The number of subjects receiving a medication will be summarised by treatment group. A subject is only counted once if receiving the medication more than once. Disallowed medications will be listed.

9.4.2.4 Exposure

Study drug exposure (days) will be defined as time from first dose of the study drug to last dose. Exposure will be defined as:

Last dose date – first dose date + 1.

The duration of exposure, interruptions, and reductions of study treatment will be summarised. The percentage of the actual dose delivered relative to the intended dose through the end of treatment and the percentage of the actual dose delivered relative to the intended dose until progression will also be summarized.

9.4.3 Other analyses

9.4.3.1 Secondary endpoint: Time to first subsequent anticancer therapy or death (TFST)

Time to first subsequent anticancer therapy is defined as the time from randomisation to the earlier of the first subsequent anticancer therapy start date following study treatment discontinuation or death from any cause. Any patient not known to have died at the time of the analysis and not known to have had a further anticancer therapy will be censored at the last known time to have not received subsequent therapy, ie, the last visit where this was confirmed.

Analysis methods

Time to first subsequent anticancer therapy will be analysed using the same methods as in the analysis of rPFS, stratified by metastases category and docetaxel treatment at mHSPC stage.

A KM plot of time to first subsequent anticancer therapy will be presented by treatment group. Summaries of the number and percentage of patients with subsequent anticancer therapy will be provided along with median time to first subsequent anticancer therapy for each treatment arm.

9.4.3.2 Secondary endpoint: Time to pain progression (TTPP)

Time to pain progression is defined as time from randomisation to pain progression based on the BPI-SF Item 3 “worst pain in 24 hours” and opiate analgesic use (AQA score).

Pain progression is defined as follows:

1 For patients who are asymptomatic at baseline, a ≥2 point change from baseline in the average (4-7 days) BPI SF Item 3 score observed at 2 consecutive evaluations (with at least 2 weeks between the end of the initial visit and the start of the subsequent visit) OR initiation of opioid use for pain;
2 For patients who are symptomatic at baseline (average BPI SF Item 3 score >0 and/or receiving opioids), a ≥2 point change from baseline in the average BPI SF Item 3 score observed at 2 consecutive visits and an average worst pain score ≥4, and no decrease in average opioid use (≥1-point decrease in AQA score from a starting value of 2 or higher) OR any increase in opioid use (eg, 1 point change in AQA score) at 2 consecutive follow-up visits (with at least 2 weeks between the end of the initial visit and the start of the subsequent visit). Any patient who has more than 2 consecutive visits that are not evaluable for pain progression will be censored at the last evaluable assessment.
3 Patients with insufficient data to derive a time to event/censoring will be censored at Study Day 1.

Analysis methods

Time to pain progression will be analysed using the same methods as in the analysis of rPFS, stratified by metastases category and docetaxel treatment at mHSPC stage.

A KM plot of time to pain progression will be presented by treatment group. Summaries of the number and percentage of patients experiencing pain progression will be provided along with median time to pain progression for each treatment arm.

9.4.3.3 Secondary endpoint: Time to opiate use

Time to opiate use is defined as the time from randomisation to the first opiate use for cancer-related pain. Patients 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. Patients receiving opiates at baseline will not be included in this analysis.

Analysis methods

Time to opiate use will be analysed using the same methods as in the analysis of rPFS, stratified by metastases category and docetaxel treatment at mHSPC stage.

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

9.4.3.4 Secondary endpoint: Time to first symptomatic skeletal-related event (SSRE)

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

- 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 is required
- Orthopaedic surgical intervention for bone metastasis

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

Analysis methods

Time to first symptomatic skeletal–related event will be analysed using the same methods as in the analysis of rPFS, stratified by metastases category and docetaxel treatment at mHSPC stage.

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

9.4.3.5 Secondary endpoint: Time to second progression or death (PFS2)

Time to second progression or death is defined as the time from randomisation to second progression on next-line anticancer therapy following study treatment discontinuation, by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression or death, whichever occurs earlier.

Analysis methods

Time from randomisation to second progression will be analysed using the same methods as in the analysis of rPFS, stratified by metastases category and docetaxel treatment at mHSPC stage.

A KM plot of time to second progression will be presented by treatment group. Summaries of the number and percentage of patients experiencing second progression will be provided along with median time to second progression for each treatment arm.

9.4.3.6 Secondary endpoint: Pain severity and worst pain

Pain severity is based on the BPI-SF pain severity domain. Worst pain is based on BPI-SF Item 3 "worst pain in 24 hours" item. Absolute and change from baseline scores of pain severity and worst pain will be evaluated.

Analysis methods

Change from baseline in the BPI-SF pain severity domain will be analysed using a mixed model for repeated measures (MMRM) analysis of all the post-baseline pain severity scores for each visit. The study discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include treatment, visit and treatment by visit interaction as explanatory variables and the baseline pain severity score as a covariate, along with the baseline pain severity score by visit interaction and the stratification variables determined by the primary pooling strategy. Treatment, visit, treatment by visit interaction, baseline pain severity score, baseline pain severity score by visit interaction, and the stratification variables will be fixed effects in the model. All model terms, including treatment by visit interaction, will remain in the model regardless of significance. The analysis will be repeated for the BPI-SF worst pain. The details will be described in the SAP.

9.4.3.7 Secondary endpoint: Pain interference

The BPI-SF pain interference domain includes 7 items: general activity (item #9A), mood (item #9B), walking ability (item #9C), normal work (item #9D), relations with other people (item #9E), sleep (item #9F), and enjoyment of life (item #9G). The pain interference domain is scored as the mean of the 7 interference items. The mean can be used if more than 50% of the total items, or 4 of 7, have been completed on a given administration (Cleeland 2009). Absolute and change from baseline scores of pain interference will be evaluated.

Analysis methods

Change from baseline in BPI-SF pain interference domain will be analysed using MMRM as per the pain severity endpoint (Section 9.4.3.6).

9.4.3.8 Secondary endpoint: FACT-P

FACT-P total score, FACT-G total score, TOI, FWB, PWB, PCS, and FAPSI-6, absolute and change from baseline scores for each time point will be calculated for each treatment group.

Table 20 details how visit responses will be defined for the FACT-P total, FACT-G total, TOI, FAPSI-6, PCS, PWB, and FWB scores (Cella et al 2009, Webster et al 2003).

A visit response of 'Improved', 'No Change', 'Worsened' or 'Not evaluable', as defined according to Table 20 and Table 21 will be calculated for each patient for scales assessing

prostate cancer symptoms, impact on FWB etc: FACT-P Total, FACT-G Total, TOI, FAPSI-6, PCS, PWB, and FWB subscales.

Table 20 Definition of visit response for FACT-P, FACT-G, FAPSI-6, TOI, PCS and FWB

FACT-P scale	Maximum change from baseline
FACT-P-Total	10
FACT-G-Total	7
FAPSI-6	3
TOI	9
PCS	3
FWB, PWB	3

FACT-G, Functional Assessment of Cancer Therapy-General; FACT-P, Functional Assessment of Cancer Therapy-Prostate Cancer; FAPSI-6, Functional Assessment of Prostate Cancer Symptoms Index-6; FWB, Functional Well-Being; PCS, Prostate cancer symptoms; PWB, Physical Well-Being; TOI, Trial outcome index.

The criteria shown in Table 21 will be used to assign a best QoL response based on individual visit responses in accordance with the score thresholds in Table 20 (further details will be provided in the SAP). Patients with no evaluable baseline or no post-baseline PRO assessments with be assigned to 'non-evaluable' for best QoL response.

Table 21 Overall score response criteria

Overall score response	Criteria
Non-evaluable	Has no evaluable baseline or no post-baseline PRO assessments.
Improved	Two consecutive visit responses of 'improved'
No change	Does not qualify for overall score response of 'improved'. Two consecutive visit responses of either 'no change', or 'improved' and 'no change'
Worsened	Does not qualify for overall score response of 'improved' or 'no change'. A visit response of 'worsened'
Other	Does not qualify for 1 of the above

Analysis methods

FACT-P total score, FACT-G total score, TOI, FWB, PWB, PCS, and FAPSI-6, will be summarised using mean, standard deviation, median and range by treatment group for each visit until there are less than one third of patients with evaluable data. The absolute and change from baseline scores for each time point will be calculated by treatment group. Change from baseline in FACT-P total score, FACT-G total score, TOI, FWB, PWB, PCS, and FAPSI-6 will be analysed using MMRM as per the pain severity endpoint (Section 9.4.3.6).

The proportion of patients with best responses of 'Improved', 'No Change' and "Worsened" will be summarised descriptively as number of patients and corresponding percentages for each category by treatment group. Responses will be compared between treatment groups using logistic regression, adjusting for metastases status, docetaxel treatment at mHSPC stage. Patients who died or discontinued prior to assessment will be classified as 'Other'. Overall improvement rate will be defined as the proportion of patients with a best overall QoL response of "Improved" based on Table 21.

Time to deterioration in FACT-P (FACT-P total score, FACT-G total score, TOI, FWB, PWB, PCS, and FAPSI 6) will be analysed using the same method as in the analysis of rPFS. The HRs and 95% CIs will be presented on a forest plot. Patients who died or discontinued prior to assessment will be censored at Study Day 1.

9.4.3.9 Secondary endpoint: Pharmacokinetics

Pharmacokinetic sampling will be performed in a subset of at least 50 patients per treatment group (ie, olaparib+abiraterone or placebo+abiraterone) at specific timepoints after multiple dosing according to the schedule of assessments.

Analysis methods

The plasma concentration-time data will be analysed using NCA to determine the PK of olaparib, abiraterone, and Δ4-abiraterone at steady state and to evaluate the effect of olaparib on abiraterone PK. The effect of HRRm status on the PK of olaparib, abiraterone, and Δ4-abiraterone will be evaluated if deemed feasible.

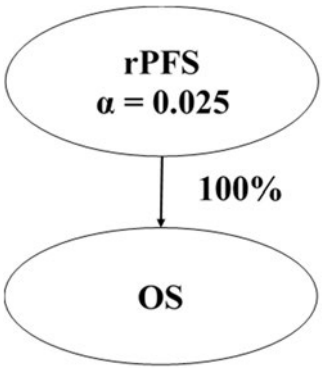
9.4.4 Multiplicity strategy for primary and key secondary endpoints

The statistical hypotheses are described and defined in Section 9.1. The 1-sided alpha of 0.025 is fully allocated to H_{a0} (rPFS). If the result for rPFS is statistically significant, H_{b0} (OS) will be tested in a hierarchical fashion. A multiplicity testing procedure based on the graphical approach in group sequential trials of Maurer and Bretz (Maurer and Bretz 2013), analogous to a simple sequential gatekeeping method, strongly controls the overall family-wise 1-sided error rate of 2.5%.

The rPFS endpoint will be tested at DCO1 and DCO2. The OS endpoint will be tested at DCO1, DCO2 and DCO3. For each endpoint with interim analysis, O'Brien and Fleming spending function (Lan and DeMets 1983, O'Brien and Fleming 1979), calculated based upon actual observed events, will be used to strongly control the overall type 1 error, with the restriction that alpha spend for the OS interim analysis at DCO1 will not exceed 0.0005.

The multiplicity strategy is illustrated in Figure 3:

Figure 3 Multiplicity strategy maintaining overall type 1 error rate



OS, Overall survival; rPFS, Radiological progression-free survival.

9.4.5 China cohort

Following the completion of global enrolment, the China cohort will randomise approximately 108 additional patients at sites in China. The safety and efficacy data collected will be summarised and analysed separately to the global study safety and efficacy analysis sets (as defined in Section 9.3).

The primary analysis of efficacy for the China cohort will be an assessment of radiological progression (rPFS) (RECIST 1.1 and PCWG-3) on the China full analysis set, as defined in Section 9.3. Where data permit, summaries and analysis of secondary supportive efficacy endpoints (including at least but not limited to ORR, time to pain progression, TFST, PFS2 and OS) will be performed for the China cohort. Efficacy analyses for the China cohort will be performed when the rPFS data from the patients in this cohort are of similar maturity to those of the global cohort where significant clinical efficacy is established in the global cohort. The detailed analysis plan will be documented in the China supplementary SAP.

When assessing safety and tolerability, summaries will be produced separately for the China cohort based on the China safety analysis set. The China safety analysis set includes all patients who are randomised as part of the China cohort and receive at least one dose of randomised study treatment.

9.5 Interim analyses

The interim efficacy analyses will be monitored and reviewed by the IDMC at DCO1. When pre-specified interim efficacy boundaries are achieved, AstraZeneca will be contacted, and the Unblinded Review Committee may be activated. More details can be found in the Unblinded Review Committee Charter and in Section 9.5.1. The AZ study team remain blinded during this initial review period, as described in Section 6.3.1.

Table 22 summarises details of the estimated number of events and power at each DCO with associated, estimated, allowable type I error (alpha).

CCI [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Alpha presented 1-sided

DCO, Data cut-off; HR, Hazard ratio; N/A, Not applicable; OS, Overall survival; rPFS, Radiological progression-free survival.

9.5.1 Independent Data monitoring committee (IDMC)

This study will use an external IDMC to review accumulating study safety data (see Appendix C 5). The committee will also review efficacy data from the planned interim DCO1 as described in the previous section. Committee members will include therapeutic area experts, a cardiologist, and a statistician who are not employed by AstraZeneca or by any participating study group and who do not have any major conflict of interest. An unblinded IDMC review of all myocardial infarction, congestive heart failure, and arterial thrombosis events will be conducted by the expert cardiologist. Following each review, the committee will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Committee membership and responsibilities will be detailed in a committee charter.

The IDMC will separately assess the safety of the olaparib and abiraterone combination therapy in Japanese patients for the initial data review meetings. Further details will be provided in the IDMC charter.

10. REFERENCES

Abida et al 2017
Abida W, Armenia J, Gopalan A, Brennan R, Walsh M, Barron D, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis 2017 July;2017.

Armenia et al 2018
Armenia J, Wankowicz SAM, Liu D, Gao J, Kundra R, Reznik E, et al. The long tail of oncogenic drivers in prostate cancer. Nat Genet 2018 May;50(5):645-51. Erratum in: Nat Genet 2019;51(7):1194.

Asim et al 2017
Asim M, Tarish F, Zecchini HI, Sanjiv K, Gelali E, Massie CE, et al. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat Commun. 2017;8(1):374.

Attard et al 2012
Attard G, Reid AH, Auchus RJ, Hughes BA, Cassidy AM, Thompson E, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J Clin Endocrinol Metab. 2012;97(2):507-16.

Beer et al 2014
Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424-33.

Castro et al 2013
Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline *BRCA* mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31(14):1748-57.

Castro et al 2015
Castro E, Goh C, Leongamornlert D, Saunders E, Tymrakiewicz M, Dadaev T, et al. Effect of *BRCA* mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol. 2015 Aug;68(2):186-93.

Cella et al 2009
Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy-Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health. 2009 Jan-Feb;12(1):124-9.

Chung et al 2014
Chung KC, Barlev A, Braun AH, Qian Y, Zagari M. Assessing analgesic use in patients with advanced cancer: development of a new scale--the Analgesic Quantification Algorithm. Pain Med 2014;15(2):225-32.

Chung et al 2019
Chung JH, Dewal N, Sokol E, Matthew P, Whitehead R, Millis SZ, et al. Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. JCO Presic Oncol 2019;3.

Cleeland 2009
Cleeland CS. The Brief Pain Inventory User Guide. 2009;1-63.

Cleeland and Ryan 1994
Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994 March;23(2):129-138.

de Bono et al 2020
de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer N Engl J Med 2020; 382:2091-2102.

Dworkin et al 2005
Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.

Dworkin et al 2008
Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008 Feb;9(2):105-21.

Esper et al 1997
Esper P, Mo F, Chodak G, Sinner M, Cella DF, Pienta KJ. Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy-Prostate instrument. Urology. 1997;50:920-8.

EuroQol Group 1990
EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.

EuroQol Group 2013
EuroQol Group. EQ-5D-5L user guide: basic information on how to use the EQ-5D-5L instrument, version 2.0, October 2013. Available from: URL:

http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D5L_v2.0_October_2013.pdf. Accessed 21 November 2013.

Food and Drug Administration 2009
Food and Drug Administration: Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims; Availability. Federal Register 2009;74:65132-3.

Flaig et al 2016
Flaig TW, Potluri RC, Ng Y, Todd MB, Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med 2016;5:182-91.

Globocan 2012
Globocan FactSheet 2012. Available at: http://globocan.iarc.fr/old/FactSheets/cancers/prostate-new.asp. Accessed on 19 April 2018.

Goodwin et al 2013
Goodwin JF, Schiewer MJ, Dean JL, Schrecengost RS, de Leeuw R, Han S, et al. A hormone-DNA repair circuit governs the response to genotoxic insult. Cancer Discov. 2013;3(11):1254-71.

Herdman et al 2011
Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-36.

Janssen et al 2008a
Janssen MF, Birnie E, Haagsma JA, Bonsel GJ. Comparing the standard EQ-5D three-level system with a five-level version. Value Health 2008;11(2):275-84.

Janssen et al 2008b
Janssen MF, Birnie E, Bonsel GJ. Quantification of the level descriptors for the standard EQ-5D three-level system and a five-level version according to two methods. Qual Life Res 2008;17(3):463-73.

Ju et al 2006
Ju BG, Lunyak VV, Perissi V, Garcia-Bassets I, Rose DW, Glass CK, et al. A topoisomerase IIbeta-mediated dsDNA break required for regulated transcription. Science. 2006;312(5781):1798-802.

Lan and DeMets 1983
Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70(3):659-63.

Li et al 2017
Li L, Karanika S, Yang G, Wang J, Park S, Broom BM, et al. Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. Sci Signal 2017;10(480). pii: eaam7479.

Lynparza Prescribing Information
US prescribing information for lynparza (olaparib) tablets for oral use. AstraZeneca Pharmaceuticals LP. Accessed on: 09 April 2018. Available at: https://www.azpicentral.com/lynparza_tb/pi_lynparza_tb.pdf#page=1

Mateo et al 2015
Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R et al. DNA repair defects and PARP inhibition in metastatic prostate cancer. N Engl J Med. 2015 Oct 29;373(18):1697-708.

Mateo et al 2018
Mateo J, Carreira S, Seed G, Chandler R, Dolling D, Figueredo I et al. Genomic profiling of primary prostate tumors from patients who develop metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2018;36(Suppl 15; May 20): 5013.

Maurer and Bretz 2013
Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Statistics in Biopharmaceutical Research 2013;5(4):311-20.

O'Brien and Fleming 1979
O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-556.

Pia et al 2013
Pia A, Vignani F, Attard G, Tucci M, Bironzo P, Scagliotti G, et al. Strategies for managing ACTH dependent mineralocorticoid excess induced by abiraterone. Cancer Treat Rev. 2013;39(8):966-73.

Pickard et al 2007
Pickard AS, De Leon MC, Kohlmann T, Cella D, Rosenbloom S. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. Med Care 2007;45(3):259-63.

Polkinghorn et al 2013
Polkinghorn WR, Parker JS, Lee MX, Kass EM, Spratt DE, Iaquinta PJ, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. Cancer Discov. 2013;3(11):1245-53.

Robinson et al 2015
Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015 May 21;161(5):1215-28.

Ryan et al 2013
Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138-48.

Scher et al 2015
Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model. PLoS One 2015;10:e0139440.

Schiewer et al 2012
Schiewer MJ, Goodwin JF, Han S, Brenner JC, Augello MA, Dean JL, et al. Dual roles of PARP-1 promote cancer growth and progression. Cancer Discov. 2012;2(12):1134-49.

Schiewer and Knudsen 2014
Schiewer MJ, Knudsen KE. Transcriptional roles of PARP1 in cancer. Mol Cancer Res. 2014;12(8):1069-80.

Sonpavde et al 2011
Sonpavde G, Attard G, Bellmunt J, Mason MD, Malavaud B, Tombal B, et al. The role of abiraterone acetate in the management of prostate cancer: a critical analysis of the literature. Eur Urol. 2011;60(2):270-8.

Sun and Chen 2010
Sun X, Chen C. Comparison of Finkelstein's Method with the conventional approach for interval censored data analysis. Stat Biopharm Res. 2010;2:97-108.

Tarish et al 2015
Tarish FL, Schultz N, Tanoglidi A, Hamberg H, Letocha H, Karaszi K, et al. Castration radiosensitizes prostate cancer tissue by impairing DNA double-strand break repair. Sci Transl Med. 2015;7(312):312re11.

Turk et al 2006
Turk DC, Dworkin RH, Burke LB, Gershon R, Rothman M, Scott J et al. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain 2005 Dec 5;125(3):208-15.

Webster et al 2003
Webster K, Cella D, Yost E. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health and Quality of Life Outcomes. 2003;1(1):79.

Zytiga Prescribing Information
US Prescribing information for ZYTIGA (abiraterone acetate) tablets for oral administration. Janssen Pharmaceutical Companies. Accessed on 26 April 2018. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ZYTIGA-pi.pdf.

Zytiga SmPC
Summary of Product Characteristics for ZYTIGA 500 mg film-coated tablets. Janssen-Cilag International NV. Accessed on 26 April 2018. Available at: https://www.medicines.org.uk/emc/product/2381/smpc.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours) 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 D081SC00001 study with regards to assessment of tumour burden including protocol-specific requirements for this study.

ASSESSMENT OF SOFT TISSUE DISEASE USING RECIST 1.1 CRITERIA

Definition of measurable, non-measurable, target and non-target lesions

In this study, bone lesions will not be included in the RECIST assessment as target lesions, non-target lesions (NTL) or new lesions. The guidelines for bone lesion assessments are defined in the bone lesion section of this appendix document.

Measurable:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline*).
- Truly non-measurable lesions include the following: leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**

* Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Special cases:

- 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 subject, these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline (except bone lesions which will be assessed as defined in bone lesion section of this appendix).

Methods of assessment

The same method of assessment and the same technique should be used to characterise each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 23 Summary of methods of assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred) MRI	CT (preferred) MRI X-ray, Chest x-ray	CT (preferred) MRI X-ray, Chest x-ray Ultrasound FDG-PET

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D081SC00001 study it is recommended that CT examinations of the chest, abdomen and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI

should be used where CT is not feasible or it is medically contraindicated. For brain lesion assessment, MRI is the preferred method.

Every effort should be made to maintain the radiologic imaging modality used at baseline throughout subsequent assessments.

Chest X-ray

In the D081SC00001 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Ultrasound

In the D081SC00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the D081SC00001 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Tumour markers

In the D081SC00001 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

In this study the following marker (PSA) are being collected for separate analysis. However, the results will not contribute to tumour response based on RECIST 1.1 assessment.

Cytology and histology

In the D081SC00001 study histology and cytology will not be used for tumour response assessments as per RECIST 1.1 and tumour response assessments will be performed on radiological criteria only.

FDG-PET scan

In the D081SC00001 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding

to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinically indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

Tumour response evaluation

Schedule of evaluation

Baseline assessments 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 subjects and 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 randomisation within the first 24 weeks, and then every 12 weeks until objective disease progression assessed by investigator as defined by RECIST 1.1 (soft tissue) or PCWG-3 (bone). Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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 minimise any unintentional bias caused by some subjects being assessed at a different frequency than other subjects.

Target lesions (TL)

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis 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, which can be measured reproducibly, should be selected.

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

Special cases:

- For TL 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.
- 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 longest diameter should be recorded as 0 mm.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TL 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 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.
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 24 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

Non-target lesions (NTL)

Evaluation of non-target lesions

All other lesions (or sites of disease), except for bone lesions, not recorded as TL should be identified as NTL 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. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 25 Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of 1 or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. 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.
Not Evaluable (NE)	Only relevant when 1 or some of the non-target lesions were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For subjects without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New lesions

Details of any new soft tissue lesions will also be recorded with the date of assessment. The presence of 1 or more new lesions is assessed as progression.

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

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

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Evaluation of overall visit soft tissue response

The overall visit response will be derived using the algorithm shown in Table 26.

Table 26 Overall visit soft tissue response

Target lesions	Non-Target lesions	New Lesions	Overall soft tissue response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NA	NA	No	NED
NE	Non PD or NE	No	NE
NA	NE	No	NE

Target lesions	Non-Target lesions	New Lesions	Overall soft tissue response
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NED = no evidence of disease, NA = not applicable (only relevant if there were no TL and/or NTLs at baseline).

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 D081SC00001 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.

Tumour 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 randomisation within the first 24 weeks, and then every 12 weeks 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 summarised in Table 27.

Table 27 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.

Visit Date	Criteria for Bone Progression	Criteria for Soft Tissue Progression
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 tumours.

Evaluation of bone progression status

Table 28 provides the definitions for the visit bone progression status for bone lesions.

Table 28 Bone progression status

Bone progression status	
Non Progressive Disease (Non-PD)	No evidence of progression, or appearance of 1 new bone lesion, or non-fulfilment of the progression criteria including new lesions without confirmation of progression
Progressive Disease (PD)	Bone lesions fulfilling the requirements for at least 2 new lesions and confirmation of progression
Not Evaluable (NE)	Only relevant if a follow-up bone scan is not performed

CENTRAL REVIEW

The Contract Research Organisation (CRO) appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

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 B ECOG Performance Status

Example of performance status (ECOG scale)

DESCRIPTION	ECOG GRADE
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework, office work.	1
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Appendix C Regulatory, Ethical and Study Oversight Considerations

C 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 (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, 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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

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 they become 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 EMA 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 (e-mail address or telephone number) provided by AstraZeneca.

C 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.

C 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the patient or his legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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 patient was enrolled in the study and the date and time the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Patients 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 patient or the patient's legally authorised representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he will not be excluded from other aspects of the study.

If a patient's partner becomes pregnant during 3 months after the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

If subjects will be asked to consent to optional exploratory research using the remainder of mandatory samples, include text that addresses the use of remaining mandatory samples for optional exploratory research.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples have already been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

C 4 Data protection

Each patient will be assigned a unique identifier by the sponsor. Any patient records or data sets transferred to the sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient 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 must also be explained to the patient.

The patient must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

C 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 Clinical Study Protocol and letters to investigators.

C 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com *and* https://www.clinicaltrialsregister.eu/ as will the summary of the D081SC00001 study results when they are available. The clinical trial and/or summary of D081SC00001 study results may also be available on other websites according to the regulations of the countries in which the D081SC00001 study is conducted.

C 7 Data quality assurance

All patient data relating to the study will be recorded on an eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

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.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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 in accordance with local regulations after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

C 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on 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.

C 9 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 multicentre studies only in their entirety and not as individual site data. In this case, a coordinating 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 D Adverse Event Definitions and Additional Safety Information

D 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product 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 it's considered related to the medicinal product.

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 treatment has been administered.

D 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent 1 of the outcomes listed above.

D 3 Life-threatening

'Life-threatening' means that the patient 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 patient'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).

D 4 Hospitalisation

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

D 5 Important medical event or medical treatment

Medical and scientific judgement 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, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent 1 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 judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous 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 anaemia requiring blood transfusion) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

D 6 Intensity rating scale:

The grading scales found in the revised National Cancer Institute CTCAE version 4.03 will be utilised 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 D 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 D 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 D 2.

D 7 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 patient 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 re-challenge.
- 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 limited or insufficient information in the case, it is likely that 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.

D 8 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 intercepted before the 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, for example, 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 fridge when it should be at room temperature
- Wrong participant received the medication (excluding RTSM [IRT] errors)
- Wrong drug administered to participant (excluding RTSM [IRT] errors)

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

- Errors related to or resulting from RTSM (IRT) - including those which lead to 1 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

Clinical Study Protocol – Final AstraZeneca

Olaparib (AZD2281, KU 0059436) - D081SC00001

CONFIDENTIAL AND PROPRIETARY 168 of 202 Form Doc Number: AZDoc0070547 Parent Doc Number: AZDoc0017426

· 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 E Handling of Human Biological Samples

E 1 Chain of custody of biological samples

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

The investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

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

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

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle. This is not applicable in China since clinical samples will not be exported out of China.

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

E 2 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

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 eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and

packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix F Genetics

F 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient´s DNA, ie, the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on Study treatment or Study treatments of this class or indication continues but no longer than 15 years from Last Patient Last Visit or other period as per local requirements.

F 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**: provide informed consent for the genetic sampling and analyses.

Exclusion criteria
Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or the following:

- Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)

Withdrawal of consent for genetic research:
Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for genetic research
The blood sample for genetic research will be obtained from the patients at Visit 2 randomisation. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples
The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of Last Patient Last Visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements
The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix D.

Informed consent
The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection
AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, or general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his genetic data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management
Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can

only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

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

Study and site closure

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
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

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

G 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Potential Hy's Law (PHL) and Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 8.3.8 of the Clinical Study Protocol.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets 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 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 total bilirubin from a local laboratory.

The investigator will also review Adverse Event (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 the 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 investigational product (IP).

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

G 2 Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3 × ULN **together with** total bilirubin ≥ 2 ×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP 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 total bilirubin, but there is no specified time frame within which the elevations in transaminases and total bilirubin must occur.

G 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 patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- Total bilirubin ≥ 2 × ULN

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Appendix G 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

G 4 Follow-up

G 4.1 Potential Hy's Law criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

G 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section8.4 Safety Reporting)

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For patients that met PHL criteria prior to starting IP, the investigator is not required to submit an SAE of PHL unless there is a significant change* in the patient's condition

The AstraZeneca Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated, and completes the follow-up SAE Form as required
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the AstraZeneca Study Physician
- Complete the three Liver CRF Modules as information becomes available

*A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) 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 AstraZeneca Study Physician if there is any uncertainty.

G 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 AstraZeneca 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 IP, to ensure timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were 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 must follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and total bilirubin 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, the investigator must record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, the investigator must update the previously submitted PHL SAE and AE CRFs accordingly with the new information (reassessing event term, causality and seriousness criteria) following the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin elevations other than the IP, the investigator must:

- Send an 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, and the investigator must:

- Provide any further update to the previously submitted PHL SAE (report term now 'Hy's Law case') ensuring causality assessment is related to IP and seriousness criteria is 'Medically important', according to the 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 the 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.

G 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

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

At the first on-study treatment occurrence of PHL criteria being met, the investigator will determine if there has been a **significant change** in the patients' 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 Appendix D 5.
- *A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) 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 AstraZeneca Study Physician if there is any uncertainty.

G 7 Actions required for repeat episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment 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 patient meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix G 6?

- If **No**: Follow the process described in Appendix G 4.1 for reporting a PHL case as an SAE.
- If **Yes**: Determine if there has been a significant* change in the patient'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 Appendix G 4 for reporting a PHL case as an SAE

*A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) 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 AstraZeneca Study Physician if there is any uncertainty.

Appendix H Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

Appendix I Acceptable Birth Control Methods

Male patients must use a condom when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients must use at least 1 highly effective form of contraception if they are of childbearing potential (as listed below). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 3 months after the last dose of olaparib, or they must totally/truly abstain from any form of sexual intercourse (see below). Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

Highly effective methods of contraception, defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in the list below. 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, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Non-hormonal highly effective methods of contraception:

- Total/true abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 3 months after last dose for male patients. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.]
- Vasectomised sexual partner PLUS male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia).
- Tubal occlusion PLUS male condom.
- Intrauterine device (provided coils are copper banded) PLUS male condom.

Hormonal highly effective methods of contraception:

- Combined pill PLUS male condom: Normal and low-dose combined oral pills.
- Mini pill PLUS male condom: Progesterone-based oral contraceptive pill using desogestrel. Cerazette (Merck Sharp & Dohme) is currently the only highly efficacious progesterone-based pill available.
- Injection PLUS male condom: Medroxyprogesterone injection (eg, Depo-Provera [Pfizer]).
- Implants PLUS male condom: Etonorgestrel-releasing implants (eg, Nexplanon [Merck Sharp & Dohme]).

- Patch PLUS male condom: Norelgestromin/ethinyl estradiol transdermal system (eg, Xulane).
- Levonorgestrel-releasing intrauterine system (eg, Mirena [Bayer]) PLUS male condom.
- Intravaginal devices (eg, ethinyl estradiol-/etonogestrel-releasing intravaginal devices such as NuvaRing [Merck Sharp & Dohme]) PLUS male condom.

Appendix J Patient-Reported Outcomes

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

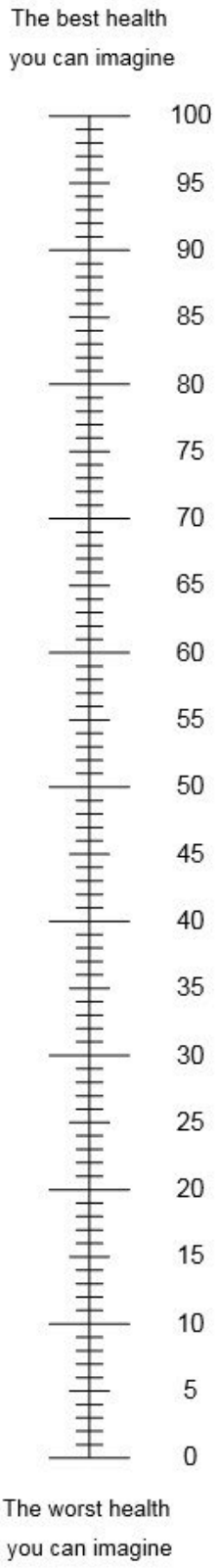
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07.01.05

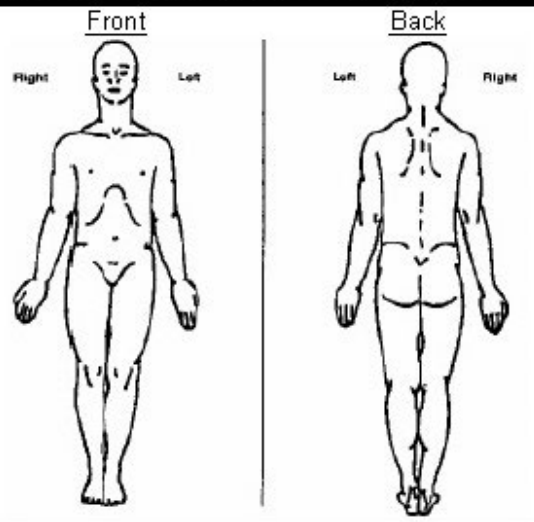
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07.01.05

PLEASE USE BLACK INK PEN

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Page 2 of 2

Appendix K 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 patients 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 patients will allow adverse events 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 patients themselves.

Appendix L Olaparib/placebo 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/placebo.

L 1 Study Participant Risks during COVID-19

The risk-benefit balance should be carefully assessed for each patient enrolling 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 patients and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

L 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.

L 2.1 Olaparib/placebo: Product-specific Guidance in Relation to the COVID-19 Pandemic

- Patients 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/placebo 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 haemoglobin, neutrophils and lymphocytes
  - Benefit risk for the individual patients including curative vs palliative intent of treatment and response to olaparib/placebo

- If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib/placebo 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/placebo 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.

L 3 Reference

Brahmer et al 2018
Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10;36(17):1714-1768.

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