Statistical Analysis Plan	
Study Code	D081SC00001
Edition Number	China supplementary - 1
Date	21st May 2021

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

- China supplementary statistical analysis plan

TABLE OF CONTENTS

LIST OF TABLES

No table in this document.

LIST OF FIGURES

No figure in this document.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse events of special interest
ATM	Ataxia-telangiectasia mutated
BICR	Blinded independent central review
BoR	Best objective response
BP	Blood pressure
BPI-SF	Brief Pain Inventory-Short Form
BRCA1	Breast Cancer 1 gene
BRCA2	Breast Cancer 2 gene
CI	Confidence interval
CR	Complete response
CTC	Circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour DNA
CV%	Coefficient of variation
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFR	Evaluable for response
EQ-5D-5L	EuroQol 5 dimension, 5 level, health state utility index
FACT-P	Functional Assessment of Cancer Therapy - Prostate Cancer
FAS	Full analysis set
HR	Hazard ratio
HRR	Homologous recombination repair
KM	Kaplan-Meier
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Not evaluable
NHA	New hormonal agent
ORR	Objective response rate

Abbreviation or special term	Explanation
OS	Overall survival
PCWG-3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS2	Time from randomisation to second progression or death
PID	Percentage intended dose
PK	Pharmacokinetics
PR	Partial response
PRO	Patient Reported Outcome
PSA	Prostate specific antigen
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid tumours version 1.1
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SDev	Arithmetic standard deviation
SOC	System organ class
SSRE	Symptomatic skeletal related event
TFST	Time to start of first subsequent anticancer therapy or death
TTPP	Time to pain progression

AMENDMENT HISTORY

Date	Brief description of change
	N/A

1 STUDY DETAILS

This supplementary statistical analysis plan (SAP) outlines the further country-specific pre-planned analyses to be conducted for the China cohort of AstraZeneca study D081SC00001. Full details of all analyses can be found in the global study SAP for study D081SC00001.

Throughout this SAP, the China cohort will consist of all patients randomised (approximately 108) at sites in China. This cohort will enable standalone safety and efficacy analyses to support Chinese regulatory requirements. Patients from China will not be included in the Full Analysis Set for the global study analysis.

In addition, all of the statistical analyses defined in this SAP will be performed using all patients randomised at sites in Asian countries (South Korea and Japan) excluding China, to be designated the Asian subgroup analysis. Different data cut-offs for China analysis in China cohort and Asian subgroup/global analysis in Global cohort are used since all subjects randomised in the China sites will be recruited after the last global subject was randomised. This will also support Chinese regulatory requirements

1.1 Study objectives

1.1.1 Primary objective

Refer to Section 1.1.1 of the global study SAP.

1.1.2 Secondary objectives

Refer to Section 1.1.2 of the global study SAP.

Note that the secondary objectives HRR gene mutation status by blood samples and PK are not applicable for China or Asian analysis.

1.1.3 Safety objective

Refer to Section 1.1.3 of the global study SAP.

1.1.4 Exploratory objectives

Refer to Section 1.1.4 of the global study SAP. All exploratory objectives defined in global SAP are not applicable for China or Asian Analysis.

1.2 Study design

Refer to Section 1.2 of the global study SAP.

1.3 Number of subjects

Refer to Section 1.3 of the global study SAP.

There will be approximately 108 patients randomised in China cohort. The analyses of the China cohort will be performed at the same maturity as the global primary analysis.

In total, 133 patients from Japan and South Korea have been randomised in the Asian subgroup. The analyses of the Asian subgroup will be performed using the same data cut-offs for different endpoints as the global primary analysis.

2 ANALYSIS SETS

2.1 Definition of analysis sets

Refer to Section 2.1 of the global study SAP.

The Full Analysis Set (FAS) and the Safety Analysis Set as defined for the global study are applicable for China cohort and Asian subgroup.

2.2 Violations and deviations

Refer to Section 2.2 of the global study SAP.

3 PRIMARY AND SECONDARY VARIABLES

Refer to Section 3 of the global study SAP.

3.1 Derivation of RECIST and PCWG-3 Visit Responses

Refer to Section 3.1 of the global study SAP.

3.1.1 Target lesions – site investigator data

Refer to Section 3.1.1 of the global study SAP.

3.1.2 Non-target lesions and new lesions – site investigator data

Refer to Section 3.1.2 of the global study SAP.

3.1.3 Overall visit response – site investigator data

Refer to Section 3.1.3 of the global study SAP.

3.1.4 Bone Lesion Progression using PCWG-3

Refer to Section 3.1.4 of the global study SAP.

3.1.5 Blinded independent central review (BICR) with RECIST 1.1 and PCWG-3 criteria

Refer to Section 3.1.5 of the global study SAP.

3.2 Primary endpoint – Radiographic progression free survival (rPFS)

Refer to Section 3.2 of the global study SAP.

3.3 Secondary endpoints

3.3.1 Overall survival

Refer to Section 3.3.1 of the global study SAP.

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

Refer to Section 3.3.2 of the global study SAP.

3.3.3 Time to pain progression (TTPP)

Refer to Section 3.3.3 of the global study SAP.

3.3.4 Time to opiate use

Refer to Section 3.3.4 of the global study SAP.

3.3.5 Time to first symptomatic skeletal related event (SSRE)

Refer to Section 3.3.5 of the global study SAP.

3.3.6 Time to second progression or death (PFS2)

Refer to Section 3.3.6 of the global study SAP.

3.3.7 Pain severity

Refer to Section 3.3.7 of the global study SAP.

3.3.8 Pain interference

Refer to Section 3.3.8 of the global study SAP.

3.3.9 Functional Assessment of Cancer Therapy- Prostate Cancer (FACT-P)

Refer to Section 3.3.9 of the global study SAP.

3.3.10 Homologous recombination repair (HRR) gene mutation status

Mutation status will be determined using a tumour tissue test.

Patients will be classified into three subgroups based on HRR gene 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

3.4 Exploratory endpoints

All exploratory endpoints are not applicable for China and Asian analysis.

3.5 Patient Reported Outcome (PRO) Variables

Refer to Section 3.5 of the global study SAP.

3.5.1 BPI-SF

Refer to Section 3.5.1 of the global study SAP.

3.5.2 Analgesic use scoring

Refer to Section 3.5.2 of the global study SAP.

3.6 Safety variables

3.6.1 Exposure

Refer to Section 3.6.1 of the global study SAP.

3.6.2 Dose intensity

Refer to Section 3.6.2 of the global study SAP.

3.6.3 Adverse events

Refer to Section 3.6.3 of the global study SAP.

3.6.4 Concomitant medications

Refer to Section 3.6.4 of the global study SAP.

3.6.5 Laboratory assessments

Refer to Section 3.6.5 of the global study SAP.

3.6.6 Vital signs

Refer to Section 3.6.6 of the global study SAP.

3.6.7 Physical examination

Refer to Section 3.6.7 of the global study SAP.

3.6.8 Electrocardiogram (ECG)

Refer to Section 3.6.8 of the global study SAP.

3.7 Pharmacokinetic Variables

All PK endpoints are not applicable for China and Asian analysis.

4 ANALYSIS METHODS

4.1 General principles

Refer to Section 4.1 of the global study SAP.

Most listings created for Global study will be produced for China cohort. No additional listings will be produced for the Asian subgroup, because individual Asian patient data can be found in the global listings.

4.2 Analysis methods

Refer to Section 4.2 of the global study SAP.

Summaries and analysis of the rPFS and other efficacy endpoints will be performed for the China cohort and Asian subgroup as described.

In these supplementary analyses, exploratory p-values will be presented. The rule from the global study SAP that no formal statistical analysis of time to event outcomes will be performed unless sufficient events are available (at least 5 events) will be relaxed so that the consistency of treatment effect can be assessed. Interpretation of the rPFS analysis in the China cohort and Asian subgroup will be limited due to a very small number of rPFS events expected.

4.2.1 Multiplicity

Not applicable for the analysis in China cohort and Asian subgroup.

4.2.2 Analysis of the primary variable (rPFS)

The analysis performed on the China cohort is to support evaluation of drug effect in China. The Asian subgroup analysis is to provide supportive evidence as well.

The primary analysis for the China cohort will be performed based on the investigators' assessment of rPFS using all scans regardless of whether they were scheduled or not, when the China data has the same maturity as global cohort data cut-offs. If the global analysis is positive at DCO1, the China data will be analysed at the same maturity as global DCO1. If the global analysis is negative at first DCO and will be performed at DCO2, the China data will be analysed at the same maturity as global DCO2. The primary analysis for Asian subgroup will be performed based on the investigators' assessment of rPFS when global analysis is conducted.

A nominal p-value in the China cohort and Asian subgroup will be obtained using a log rank test, stratified the same variables (Metastases and Docetaxel treatment at metastatic hormone-sensitive prostate cancer stage) determined by the global pooling strategy. If the model cannot converge due to the small number of events or response so that the model does not provide a valid estimate, then an option to remove stratification factors will be applied for the China cohort and Asian subgroup based on the global pooling strategy described in Section 4.2.2 of the global study SAP.

The effect of olaparib+abiraterone combination therapy versus placebo+abiraterone will be estimated by the hazard ratio (HR) and the corresponding 95% confidence interval (CI). This analysis will be performed using a Cox Proportional Hazards Model with the Efron approach being used for handling ties and the same stratification variables used for the stratified log-rank test. The 2-sided 95% CIs will be calculated using the profile likelihood method and a HR less than 1 will favour olaparib+abiraterone combination therapy.

A Kaplan-Meier (KM) plot of rPFS will be presented by treatment group for the China cohort and Asian subgroup. Summaries of the number (%) 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. For each treatment arm, the rPFS rate and its 95% CI will be summarized every 6 months using the KM method for the China cohort and Asian subgroup.

The treatment status of patients at the time of analysis will be summarised for the China cohort and Asian subgroup. This will include the number (%) of patients who were on

treatment at the time of progression, the number (%) of patients who discontinued study treatment prior to progression, the number (%) of patients who have not progressed and were on treatment or discontinued treatment. This will also provide distribution of number of days prior to progression for the patients who have discontinued treatment.

4.2.2.1 Subgroup analysis

rPFS analysis for subgroup based on other covariates will not be conducted for the China cohort or the Asian subgroup.

4.2.2.2 Sensitivity analysis

Sensitivity analyses for ascertainment bias and deviation bias will be conducted for the China cohort and the Asian subgroup.

4.2.3 Analysis of secondary variables

4.2.3.1 Overall survival

An analysis of overall survival (OS) for the China cohort and Asian subgroup will be performed using the same methods as in the analysis of rPFS, stratified in accordance with the primary pooling strategy as described in Section 4.2.2 of the global study SAP.

A KM plot of OS will be presented by treatment group for the China cohort and Asian subgroup. Summaries of the number (%) of deaths and those alive and censored will be provided along with median time to death for each treatment arm. For each treatment arm, the percentage of those alive and its 95% CI will be summarized every 6 months using the KM method for the China and Asian subgroups.

OS analysis for subgroup based on other covariates will not be conducted for the China cohort or Asian subgroup.

4.2.3.2 Time to first subsequent anticancer therapy or death

Time to first subsequent anticancer therapy for the China cohort and Asian subgroup will be analysed using the same methods as in the analysis of rPFS, stratified in accordance with the pooling strategy.

In addition, medians and a KM plot of the time to the start of subsequent therapy will be presented by treatment arm and the time between progression and starting subsequent therapy will be summarised per treatment arm for the China cohort and Asian subgroup. For each treatment arm, the percentage of those with no subsequent anticancer therapy and its 95% CI will be summarized every 6 months using the KM method for the China cohort and Asian subgroup.

In patients who received a subsequent anti-cancer therapy, a summary table of first subsequent anti-cancer therapies by treatment arm will be provided for the China cohort and Asian subgroup, as well as best response to first subsequent anti-cancer therapy by treatment arm.

4.2.3.3 Time to pain progression (TTPP)

TTPP for the China cohort and Asian subgroup will be analysed using the same methods as in the analysis of rPFS, stratified in accordance with the primary pooling strategy.

A KM plot of TTPP will be presented by treatment group for the China cohort and Asian subgroup. Summaries of the number (%) of patients experiencing pain progression will be provided for the China cohort and Asian subgroup along with median TTPP for each treatment arm. For each treatment arm, the percentage of those with no pain progression and its 95% CI will be summarized every 6 months using the KM method for the China cohort and Asian subgroup.

4.2.3.4 Time to opiate use

Time to opiate use for the China cohort and Asian subgroup will be analysed using the same methods as in the analysis of rPFS, stratified by in accordance with the primary pooling strategy.

A KM plot of time to opiate use will be presented by treatment group for the China cohort and Asian subgroup. Summaries of the number (%) of patients using opiate will be provided for the China cohort and Asian subgroup along with median time to opiate use for each treatment arm. For each treatment arm, the percentage of those with no opiate use and its 95% CI will be summarized every 6 months using the KM method for the China cohort and Asian subgroup.

4.2.3.5 Time to first symptomatic skeletal related event (SSRE)

Time to first SSRE for the China cohort and Asian subgroup will be analysed using the same methods as in the analysis of rPFS, stratified in accordance with the primary pooling strategy.

A KM plot of time to SSRE will be presented by treatment group for the China cohort and Asian subgroup. Summaries of the number (%) of patients experiencing SSRE and those who are censored will be provided along with median time to SSRE for each treatment arm. For each treatment arm, the percentage of those with SSRE free and its 95% CI will be summarized every 6 months using the KM method.

4.2.3.6 Time to second progression or death (PFS2)

Time from randomisation to second progression on next-line (immediately after study treatment) anticancer therapy for the China cohort and Asian subgroup will be analysed using

the same methods as in the analysis of rPFS, stratified in accordance with the primary pooling strategy.

A KM plot of PFS2 will be presented by treatment group for the China cohort and Asian subgroup. Summaries of the number (%) of patients experiencing second progression or death and those who are censored will be provided along with median time to second progression for each treatment arm. For each treatment arm, the percentage of those with event free and its 95% CI will be summarized every 6 months using the KM method.

4.2.3.7 Pain severity

Descriptive analysis for the BPI-SF pain severity domain will be provided for the China cohort and Asian subgroup.

4.2.3.8 Pain interference

Descriptive analysis for the BPI-SF pain interference domain will be provided for the China cohort and Asian subgroup.

4.2.3.9 Functional Assessment of Cancer Therapy- Prostate Cancer (FACT-P)

Descriptive analysis for the FACT-P will be provided for the China cohort and Asian subgroup.

4.2.3.10 HRR gene mutation status

HRR gene mutation status will be summarised descriptively as number of patients and corresponding percentages by treatment group using tumour tissue test.

These analyses will be performed at the time when the data become available.

4.2.4 Analysis of exploratory variables

All exploratory endpoints are not applicable for China and Asian analysis.

4.2.5 Concordance between investigator and BICR assessments for rPFS (FAS)

Disagreements between investigator and BICR assessment of RECIST and bone (PCWG-3) progression of each treatment group in the China cohort and Asian subgroup will be presented for RECIST progression, PCWG-3 progression, overall progression separately.

The number (%) of patients in each category listed below will be presented for the China cohort and Asian subgroup:

- Progression declared by investigator and central review
- Progression declared by investigator but not central review

- Progression declared by central review but not investigator
- No progression by both central review and investigator

The summary will include the early discrepancy rate which is the frequency of investigator review progressions declared before the BICR (≥2 weeks earlier and including progressions declared by investigator but not BICR) as a proportion of all investigator review progressions, and the late discrepancy rate which is the frequency of investigator review progressions declared after the BICR (≥2 weeks later and including progressions declared by BICR but not investigator) as a proportion of all discrepancies (including early and late discrepancies).

4.2.6 EQ-5D-5L

This endpoint will not be analysed for the China cohort and Asian subgroup.

4.2.7 Patient reported outcomes (PROs)

4.2.7.1 BPI-SF

Descriptive analysis for BPI-SF will be conducted for China cohort and Asian subgroup.

BPI-SF compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

4.2.7.2 Analgesic use scoring

Descriptive analysis for AQA score will be performed for China cohort and Asian subgroup.

4.2.8 Safety

Safety analyses will be presented for China cohort and Asian analysis in the safety analysis set and will be investigated using descriptive statistics. Safety profiles will be assessed in terms of AEs, vital signs (including blood pressure (BP) and pulse rate), laboratory data (clinical chemistry and hematology), and physical examination.

4.2.8.1 General considerations for safety assessments

Refer to Section 4.2.8.1 of the global study SAP.

4.2.8.2 Adverse events

All AEs, both in terms of MedDRA preferred term and CTCAE grade, will be summarised for the China cohort and Asian subgroup descriptively by count (n) and percentage (%) and treatment group. MedDRA dictionary will be used for coding.

Summary information (the number [%] of patients by treatment) in the China cohort and Asian subgroup will be tabulated by system organ class (SOC), preferred term and treatment group for:

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

For the corresponding rows of the above list "related to olaparib/placebo/abiraterone" will be broken down into the following sub-types:

- Related to study treatment
- Related to olaparib/placebo
- Related to olaparib/placebo only
- Related to abiraterone only
- Related to prednisone/prednisolone only

An overall summary of the number (%) of patients in each category listed above will be presented, as will an overall summary of the number of episodes in each category.

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

AEs will be assigned CTCAE grades (NCI CTCAE version 4.03) and summaries of the number (%) of patients will be provided for the China cohort and Asian subgroup by maximum reported CTCAE grade, SOC, preferred term and actual treatment group.

Deaths

A summary of deaths for the China cohort and Asian subgroup will be provided with number (%) of patients by actual treatment group categorised as:

- Death related to disease under investigation only
- AE with outcome of death only
- AE with outcome of death only (AE start falling after 30-day follow up)
- Number of subjects with death related to disease and AE outcome of death
- Other deaths

Adverse events of special interest (AESI)

For the definition of the AESI, refer to Section 3.6.3 of the global study SAP.

Summaries of the AESI categories for the China cohort and Asian subgroup will include number (%) of patients who have:

- At least one AESI presented by outcome
- At least one AESI leading to discontinuation of study medication

4.2.8.3 Laboratory assessments

Laboratory data (clinical chemistry and haematology) will be summarized for the China cohort and Asian subgroup. Shift tables will be provided for select tests, where shift from baseline to the worst value within the study will be summarized for the China cohort and Asian subgroup.

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

Shift tables for laboratory values by worst CTCAE grade will be produced for the China cohort and Asian subgroup, within each part of the study and overall, and for specific parameters separate shift tables indicating hyper- and hypo- directionality of change will be produced for the China cohort and Asian subgroup. For parameters with no CTCAE grading,

shift tables from baseline to worst value on-treatment will be provided (i.e., on-treatment is defined as data collected up until the last dose of study treatment) for the China cohort and Asian subgroup.

4.2.8.4 Vital signs

Vital signs, including BP (mmHg), body temperature (°C), pulse (beats/minute) and weight (kg), at baseline will be summarized for the China cohort and Asian subgroup using the descriptive statistics.

4.2.8.5 Exposure

Exposure data will be summarised for the China cohort and Asian subgroup apan subset, the following summaries will be produced:

- Summary of duration of exposure of study treatment, relative dose intensity (RDI) and percentage intended dose (PID)
- Summary of interruptions and reductions of study treatment

4.2.8.6 Electrocardiogram (ECG)

Overall ECG evaluation and the clinically significance of abnormal ECG finding will be summarised for the China cohort and Asian subgroup using descriptive statistics at each scheduled assessment time by actual treatment group.

4.2.9 Pharmacokinetic data

This endpoint is not applicable for China and Asian analysis.

4.2.10 Concomitant medications

Summary of concomitant medications will be produced for China cohort and Asian subgroup in the FAS.

4.2.11 Demographics and baseline characteristics

The following will be summarized for China cohort and Asian subgroup in the FAS (unless otherwise specified) by treatment group:

- Patient disposition
- Important protocol deviations
- Stratification factors
- Demographics (age, age group[< 65, ≥ 65], sex, race and ethnicity)
- Patient characteristics at baseline (weight)

- Previous disease-related treatment modalities
- Previous chemotherapy prior to this study
- Disease characteristics at baseline (primary tumour location, histology type, gleason score [grade 1, grade 2], TNM classification at baseline time from initial diagnosis in months, time from CRPC to randomization in months, time from mCRPC to randomization in months, prior local therapy with curative intent for prostate cancer, prior treatment with antiandrogen agents, prior docetaxel treatment, type of prostate cancer progression [PSA progression, radiographic progression, both], ECOG performance status, baseline pain score [BPI-SF Item 3 score: 0-1, 2-3, >3], baseline PSA, haemoglobin, alkaline phosphatase, lactate dehydrogenase, abumin and creatinine)
- Extent of disease at baseline
- Time from most recent disease progression to randomisation
- Post-discontinuation cancer therapy

5 INTERIM ANALYSES

China analyses will be performed at approximately the same maturity as the global cohort. If the global analysis is positive at DCO1, the China data will be analysed at the same maturity as global DCO1. If the global analysis is negative at first DCO and will be performed at DCO2, the China data will be analysed at the same maturity as global DCO2. Asian analyses will be performed upon the same data-offs as the global analyses.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Refer to Section 6 of the global study SAP.

7 REFERENCES

Refer to Section 7 of the global study SAP.

8 APPENDIX

Not applicable.