**Janssen Research & Development**

# Statistical Analysis Plan

## A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for the Treatment of Participants with Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-Mutated Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

**AMPLITUDE**

**Protocol 67652000PCR3002; Phase 3**

**CJNJ-67652000 (niraparib/abiraterone acetate fixed dose combination)**

| | |
|---|---|
| **Status:** | Approved |
| **Date:** | 30 January 2025 |
| **Prepared by:** | Janssen Research & Development, LLC |
| **Document No.:** | EDMS-RIM-1198089, 5.0 |

**Compliance:** The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

# TABLE OF CONTENTS

## AMENDMENT HISTORY

| SAP Version | Issue Date |
|---|---|
| Original | 20 June 2020 |
| Amendment 1 | 23 May 2024 |
| Amendment 2 | 23 December 2024 |
| Amendment 3 | 30 January 2025 |

### Amendment 3 (30 January 2025)

**The overall reason for amendment 3:**

(a) To align with the FDA feedback received on 27 January 2025 to maintain the timing of the final analysis of OS to be event-driven per SAP amendment 1, the previously proposed cap on the total study duration in SAP amendment 2 is removed. Sections 1.4.1 and 2.1, are revised.

(b) To prespecify exploratory analyses on the association of the duration of prior AAP or docetaxel use with key efficacy endpoints. Section 1.8 is revised.

### Amendment 2 (23 December 2024)

**The overall reason for amendment 2:**

(a) Per protocol, when a subject reaches radiographic progression, the investigator may request unblinding of the treatment assignment to determine subsequent therapy in the context of multiple PARP inhibitors being granted regulatory approval for mCRPC with HRR alterations such as BRCA1/2 alterations. At this stage, the Sponsor anticipates a substantial increase in requests for unblinding of subject treatment assignments after documented disease progression and switch to subsequent therapies. Further, in subjects with HRR alterations, who have poorer prognosis and shorter survival [Castro (2013)] than those without HRR alterations, ~4-year median follow-up for the final OS analysis is expected to be sufficient, based on consistency with reporting OS in the unselected mCSPC setting [Fizazi (2019), Chi (2021), Armstrong (2022)], and balances maturity of the data on OS with the effect from different subsequent anti-cancer therapies or crossover at later stages of the study.

Therefore, a cap on the total study duration will be implemented so that the final analysis for the secondary endpoint OS in this study will be conducted approximately 5.5 years from randomization of the first subject (i.e., ~4 years of median follow-up and a follow-up of more than 3 years for all subjects). The remaining alpha available after the second interim analysis will be applied to the OS final analysis, and the overall type I error rate will remain controlled at 0.05.

(b) To clarify that the planned analysis of rPFS excluding subjects with MPD (major protocol deviations) will be a sensitivity analysis. To also clarify that the full analysis set of all randomized participants will be used for the formal analysis of primary and secondary endpoints following an intent-to-treat principle. This is in reference to the Information Request from FDA regarding the SAP amendment 1 received on 08 August 2024.

(c) To further characterize the treatment effect by adding PSA90 response rate and PSA undetectable rate as exploratory endpoints, as well adding pre-specified subgroups based on baseline PSA, LDH and ALP values.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 1.4.1 Number of Events for Secondary Endpoints | The final OS analysis timing is further specified. |
| 1.8 Definition of Subgroups | Subgroups based on baseline PSA, baseline LDH, and baseline ALP are defined. |
| 4.1.3 General Analysis Considerations | the full analysis set of all randomized participants will be used for the formal analysis of primary and secondary endpoints following an intent-to-treat principle |
| 4.2.3 Analysis Methods | To clarify that the rPFS analysis by excluding subjects with major protocol (MPD) deviations if MPD>20% is a sensitivity analysis |
| 4.4 Other Efficacy Variables | PSA90 response rate and PSA undetectable rate (PSA<0.2 ng/mL) are added as exploratory analyses. External emerging data suggests that deep PSA decline may be associated with improved clinical outcomes in subjects with mCSPC [Chowdhury (2023)]. |

**Amendment 1 (23 May 2024)**

**The overall reason for amendment 1:**

(a) To align with protocol amendment 4 (28 August 2023), the study's secondary endpoint has been updated from symptomatic progression-free survival to time to symptomatic progression. Sample size justification and number of events for the secondary endpoints have also been updated based on emerging data from external clinical studies.

(b) The statistical testing procedure is modified to formally evaluate the primary and secondary endpoints first in participants with BRCA mutations, followed by those with alterations in the HRR effector genes (BRCA1, BRCA2, BRIP1, PALB2, RAD51B, and RAD54L - based on the biology of synthetic lethality and molecular association of these genes), and then finally in the All HRR population, in a hierarchical manner.

(c) To prespecify sensitivity analyses in subgroups which consists of all randomized participants excluding individuals who: i) were enrolled with a single gene CHEK2 alteration identified by a liquid biopsy but were negative for HRR gene alterations by paired tissue testing, ii) were enrolled with a single gene CHEK2 alteration identified by a liquid biopsy with negative or no available paired tissue testing.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 1.1 Objectives Endpoints and Estimands | Modify the secondary efficacy endpoint from “Symptomatic progression free survival” to “Time to symptomatic progression”. To capture a patient-centered endpoint and be consistent with the protocol. As death for any cause is captured in radiographic progression-free survival (rPFS) and overall survival, it was removed from the endpoint related to symptomatic progression |
| 1.1 Objectives Endpoints and Estimands | “Overall response” to “Objective response”. To align the SAP with protocol and Response Evaluation Criteria in Solid Tumors (RECIST) terminology |
| 1.4. Sample Size Justification | To stay consistent with Protocol this section was modified. The overall rationale for revising the sample size is based on emerging data from results of other clinical trials external to AMPLITUDE with PARP inhibitors in prostate cancer. |
| 1.4.1 Number of Events for Secondary Endpoints | The number of events for analyzing TSP is updated based on the new testing hierarchy and updated assumptions. |

| | |
|---|---|
| 1.8 Definition of HRR effector Subgroups | Safety and efficacy will be evaluated in BRCA and HRR effector gene mutated subgroups. The complementary subgroups will be evaluated as well (non-BRCA, non-HRR effectors).<br>The risk/benefit of PARP inhibition in patients harboring BRCA mutations have been well established across solid tumors, including in mCRPC, both alone and in combination with AR pathway inhibitors. To assess the risk/benefit of niraparib + AAP in mCSPC patients with BRCA mutations, AMPLITUDE will evaluate the primary and secondary endpoints in the BRCA subgroup.<br>The response to PARP inhibition has been observed to be more heterogeneous in other HRR gene alterations. Therefore, there is a need to refine the understanding of which patients may derive benefit from PARP inhibition through rationally designed studies based on the biology of synthetic lethality. The genes included in AMPLITUDE play diverse roles in the HRR pathway. Specifically, one of the critical steps in HRR is the formation of the RAD51 nucleoprotein filament around the 3' end of DNA double strand breaks (DSBs). This necessary step is directly mediated by BRCA1, which is an upstream regulator of BRCA2. PALB2 directly binds to BRCA1 and mediates the interaction between BRCA1 and BRCA2, thus serving as the molecular scaffold for the BRCA1/PALB2 genes. BRCA2 then recruits and binds RAD51 at the DSB, guiding the complex to the site of DNA damage and providing the central mediator function of RAD51. RAD51B and RAD54L both enhance the stability of the RAD51 nucleoprotein filament. BRIP1 directly binds to BRCA1 and provides the critical function of resecting the DNA ends at the DSB, necessary for HRR.<br>A recent pooled analysis of multiple mCRPC clinical trials investigated the efficacy of PARPi in individual HRR genes (Fallah et al). The results demonstrated that the treatment effect to PARPi is heterogeneous across different HRR genes and suggest that the heterogeneity in response may be related to gene function. Thus, it may be appropriate to group genes by their function in homologous recombination repair. Therefore, the Sponsor proposes to define and prespecify the "HRR effector" subgroup, consisting of participants harboring BRCA1, BRCA2, BRIP1, PALB2, RAD51B and RAD54L gene alterations, to assess the risk/benefit of niraparib + AAP in this group of mCSPC patients. These genes compose the immediate effectors of HRR at the site of the DNA DSB (ie, they are not upstream regulators) and alterations in these genes are hypothesized to be subject to synthetic lethality in combination with PARP inhibition. |
| 4.1.1.1 Multiplicity Adjustment for Testing of Primary and Key Secondary Endpoints | The testing hierarchy has been updated for formal evaluation of the primary endpoint and secondary endpoints in participants with BRCA, HRR effectors, and all HRR gene alterations, respectively. |
| 2.1 Interim Analysis | Interim analysis section has been updated to include 2 interim analyses and one final analysis for OS. |
| 5.1 Adverse Events | The definition of Treatment-Emergent Adverse Event (TEAE) is updated based on updated internal standard. Any new or worsening AE occurring at or after the initial administration of study treatment through the day of the last dose plus [30] days or prior to the start of subsequent anticancer therapy, whichever is earlier, or the follow-up AE (linked to an existing TEAE) with onset date and time beyond [30] days after the last dose of study treatment but prior to the start of subsequent therapy is considered to be treatment emergent. If any event is considered related to study medication, then this event will be assumed to be treatment emergent. |

## ABBREVIATIONS

| | |
|---|---|
| AA-P | abiraterone acetate plus prednisone |
| ADT | androgen deprivation therapy |
| AE | adverse event |
| BICR | blinded independent central review |
| BPI-SF | brief pain inventory-short form |
| CDK | cyclin-dependent kinase |
| CI | confidence interval |
| COVID-19 | Coronavirus Disease 2019 |
| CRF | case report form |
| CSR | Clinical Study Report |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DRD | DNA-repair gene defects |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EQ-5D-5L | Euro-QoL questionnaire |
| FACT-P | Functional Assessment of Cancer Therapy-Prostate questionnaire |
| FDA | Food and Drug Administration |
| HR | hazard ratio |
| HRD | homologous recombination deficiency |
| HRR | homologous recombinant repair |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| ITT | intent-to-treat |
| IWRS | interactive web response system |
| LDH | lactate dehydrogenase |
| LDL | low density lipoprotein |
| mCRPC | metastatic castration-resistant prostate cancer |
| mCSPC | metastatic castration-sensitive prostate cancer |
| mPC | metastatic prostate cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| OS | overall survival |
| PCWG3 | Prostate Cancer Working Group 3 |
| PD | Pharmacodynamic |
| PI | principal investigator |
| PK | pharmacokinetic(s) |
| PRO | patient-reported outcome(s) (paper or electronic as appropriate for this study) |
| PSA | prostate-specific antigen |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| rPFS | Radiographic progression-free survival |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| TEAE | treatment-emergent adverse event |
| TSP | Time to symptomatic progression |
| TST | Time to subsequent therapy |
| US NCI | United States National Cancer Institute |
| WHO | World Health Organization |
| WHO-DD | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

This document describes the planned statistical analyses for protocol 67652000PCR3002: A phase 3 randomized, placebo-controlled, double-blind study of niraparib in combination with abiraterone acetate and prednisone versus abiraterone acetate and prednisone for the treatment of participants with deleterious germline or somatic HRR gene mutated mCSPC. This statistical analysis plan (SAP) is intended to supplement the study protocol. Any deviations from this analysis plan will be described in the clinical study report.

## 1.1. Objectives Endpoints and Estimands

The overall objectives and endpoints/assessments for the study are provided in Table 1.

**Table 1: Objectives and Endpoints/Assessments**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To determine if niraparib and AA plus prednisone compared with AA plus prednisone in participants with deleterious germline or somatic HRR gene-mutated mCSPC provides superior efficacy in improving rPFS | • rPFS, as determined by investigator based on PCWG3 |
| **Secondary** | |
| • To assess the clinical benefit of niraparib and AA plus prednisone compared with AA plus prednisone in participants with deleterious germline or somatic HRR gene-mutated mCSPC | • OS[a]<br>• Time to symptomatic progression[b]<br>• Time to subsequent therapy[c] |
| • To characterize the safety profile of niraparib and AA plus prednisone compared with AA plus prednisone in participants with deleterious germline or somatic HRR gene-mutated mCSPC | • Incidence and severity of adverse events |
| **Other** | |
| • To evaluate other efficacy assessments and determine the clinical benefit of niraparib and AA plus prednisone compared with AA plus prednisone in participants with deleterious germline or somatic HRR gene-mutated mCSPC | • PFS2[d]<br>• Objective response[e]<br>• Time to PSA progression[f] |
| • To characterize the PK of niraparib when administered as niraparib/AA FDC plus prednisone | • Observed plasma concentrations of niraparib and estimated population PK and exposure parameters for niraparib |
| • To show the effect of niraparib and AA plus prednisone is similar to AA plus prednisone on quality of life | • The FACT-P, the EQ-5D-5L, BPI-SF (including Time to pain progression), and the PRO-CTCAE |
| • To evaluate biomarkers predictive of response | • Objective response, rPFS, and PSA response across deleterious germline or somatic HRR gene mutations |

**Table 1: Objectives and Endpoints/Assessments**

AA=abiraterone acetate; BPI-SF=Brief Pain Inventory Short Form; CDK12=cyclin dependent kinase 12;DR=EQ-5D-5L=Euro-QoL; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FDC=fixed-dose combination; HRR=homologous recombinant repair; mCSPC=metastatic castration-sensitive prostate cancer; OS=overall survival; PCWG3=Prostate Cancer Working Group 3; PFS2=progression-free survival 2; PK=pharmacokinetic; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors

[a]OS: defined as the time from date of randomization to date of death from any cause.

[b]Time to symptomatic progression is defined as time from the date of randomization to the date of any of the following (whichever occurs first):

-The use of external beam radiation therapy for skeletal or pelvic symptoms. *Note:* Only radiation planned prior to randomization will not be considered as symptomatic progression

-The need for tumor-related orthopedic surgical intervention

-Other cancer-related procedures (eg, nephrostomy insertion, bladder catheter insertion, external beam radiation therapy, or surgery for tumor symptoms)

-Cancer-related morbid events (ie, fracture [symptomatic and/or pathologic], cord compression, urinary obstructive events)

-Initiation of a new systemic anti-cancer therapy because of cancer symptoms.

[c]Time to Subsequent Therapy: defined as the time from date of randomization to the date of initiation of subsequent therapy for prostate cancer.

[d]PFS2: defined as time from date of randomization to date of first occurrence of disease progression on first subsequent therapy for prostate cancer or death, whichever comes first.

[e]Objective Response: defined as achieving a complete or partial response according to modified RECIST 1.1

[f]Time to PSA progression: defined as the time from the date of randomization to the date of PSA progression based on PCWG3 criteria.

## 1.2. Trial Design

This is a phase 3, randomized, double-blind, multicenter study to assess the efficacy and safety of niraparib 200 mg in combination with AA 1000 mg plus prednisone 5 mg daily (AAP), compared to AAP in participants with deleterious germline or somatic HRR gene-mutated mCSPC.

The study will consist of 4 phases: a Prescreening Phase for biomarker evaluation only, a Screening Phase, a Treatment Phase, and a Follow-up Phase. The biomarker status for all participants will be assessed using the sponsor's approved assays during the Prescreening Phase. In lieu of prescreening, prior local HRR testing performed in a Clinical Laboratory Improvement Amendment-certified (CLIA) or equivalent laboratory may be used. The sponsor must approve participant's HRR alteration status prior to randomization based on receipt of a redacted biomarker report(s). A treatment cycle is defined as 28 days. Imaging will be performed at approximately Day 1 of Cycle 3, Cycle 5, and then every 4 cycles. All participants will be monitored for safety during the Prescreening, Screening, and Treatment Phases, and for 30 days after the last dose of niraparib/placebo and AA study medications. Treatment will be administered daily and is planned to be continuous until disease progression, unacceptable toxicity, death, or the sponsor terminates the study.

After discontinuing study medication, participants will be contacted every 4 months until death or termination of the study. In addition to survival follow up, data will continue to be collected to evaluate all the secondary and other endpoints. Patient-reported outcomes (PROs) questionnaires (ie, EQ-5D-5L) will also be administered every 4 months for up to 1 year after treatment discontinuation.

## 1.3. Statistical Hypotheses for Trial Objectives

The hypothesis is that niraparib and AA plus prednisone (niraparib + AAP) will demonstrate improved rPFS compared with AA plus prednisone (AAP) in participants with deleterious germline or somatic HRR mutated mCSPC, and/or in the pre-specified target subgroup(s) of participants (eg, BRCA) based on emerging external data.

### 1.3.1. Target Subgroups

As AMPLITUDE is a biomarker-selected study it is critical to apply a statistical design that allows for the formal evaluation of primary and secondary endpoints in subgroups of participants who will benefit the most from the niraparib + AAP treatment. The overall population is defined as all enrolled and randomized participants. Target subgroups of the overall population are defined below.

#### BRCA

BRCA1 and BRCA2 are the most well characterized genes in the HRR pathway. BRCA mutations leading to HRD are associated with aggressive disease, rapid progression rates, the emergence of treatment resistance, and poor prognosis across multiple solid tumor types. Patients harboring BRCA mutations have also been shown to have the most consistent and profound benefit with PARP inhibition compared to those with other HRR gene alterations or those without HRR gene alterations in multiple cancer types, including mCRPC. Therefore, patients with BRCA1 or BRCA2 gene alterations will compose the first tier in the testing hierarchy.

#### HRR Effectors

The HRR effectors group is composed of eligible genes that serve as immediate effectors of HRR at the site of DNA double strand breaks (DSBs). These genes – BRIP1, PALB2, RAD51B, RAD54L, in addition to BRCA1 and BRCA2 – directly bind to or interact with one another at the DSBs and perform critical roles necessary for HRR and are thus hypothesized to be subject to synthetic lethality in the context of PARP inhibition. A recent pooled analysis of multiple mCPRC clinical trials demonstrated that the treatment effect to PARPi is heterogeneous across multiple HRR genes and that response may be related to the function of the genes in homologous recombination repair (Fallah et al.). The results suggest that it may be appropriate to group genes by their function in homologous recombination repair. Therefore, the HRR effectors group will be the second tier in the testing hierarchy.

## 1.4. Sample Size Justification

Approximately 692 participants will be randomized in a 1:1 ratio to receive niraparib + AAP or AAP, and it is estimated that approximately half of all enrolled participants will have BRCA mutations. The primary endpoint of rPFS is assumed to follow an exponential distribution with a constant hazard rate. It is estimated that approximately CCI will be required in the All HRR population to provide 91% power for detecting a HR of 0.64 CCI treatment arm versus CCI treatment arm) at a 2-sided significance level of 0.025. With a C -month accrual period and an additional C months of follow-

up, the study duration to reach the required number of rPFS events is projected to be approximately [redacted] months.

Additionally, as summarized in Table 2, at the planned sample size and study duration:

- Approximately 146 rPFS events are projected to be observed in the target subgroup of participants with BRCA mutations at the time of rPFS primary analysis, which will provide 95% power to detect a HR of 0.55 for rPFS (33 versus 60 months) at a 2-sided significance level of 0.05.
- Approximately 185 rPFS events are projected to be observed in the target subgroup of participants with HRR effector gene mutations, which will provide 96% power to detect a HR of 0.55 [redacted] vs 60 months) at a 2-sided significance level of 0.025.

**Table 2: rPFS power justification summary**

| Population | rPFS events | Significance level (2-sided) | HR assumption | Power |
|---|---|---|---|---|
| BRCA | 146 expected | 0.05 | 0.55 | 95% |
| HRR effectors | 185 expected | 0.025 | 0.55 | 96% |
| All HRR | [redacted] required | 0.025 | 0.64 | 91% |

### 1.4.1. Number of Events for Secondary Endpoints

In the All HRR population, 389 OS events are expected at the time of final OS analysis (interim and final analyses are described in Section 2.1) after a study duration of approximately 79 months, with 80% power to detect an underlying true HR of 0.75 for OS (53 versus 70.7 months) at a 2-sided significance level of 0.05.

Approximately 170 OS events are expected to be observed at the time of the rPFS primary analysis (i.e., the first OS interim analysis).

The second interim analysis is planned to occur after 255 OS events are observed in the All HRR population with 199 TSP events projected to be observed at that time (more details in Section 2.1).

## 1.5. Randomization and Blinding

### 1.5.1. Randomization

Participants who meet all the inclusion criteria and none of the exclusion criteria will be stratified and then randomized in a 1:1 ratio to receive niraparib + AAP or AAP using permuted block randomization. Participants will be stratified by HRR gene status (BRCA2 altered vs CDK12 altered vs all other pathogenic alterations), prior docetaxel use (yes vs no), and volume of disease (high vs low). Blinded treatments will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

## 1.6. Pooling Algorithm

### 1.6.1. Pooling Algorithm for Stratification Factors

The stratification factors to be used in the analysis are as follows: HRR gene status (BRCA2 altered vs CDK12 altered vs all other pathogenic alterations), prior docetaxel use (yes vs no), and volume of disease (high vs low). When performing time-to-event analysis, if any stratum within each stratification factor has a sample size of less than 10% of the total sample size, this particular stratum may be combined with other strata for the stratified analysis.

## 1.7. Analysis Sets

The definitions of analysis sets are presented in Table 3.

**Table 3: Definition of analysis sets**

| **Analysis Sets** | **Definition** | |
|---|---|---|
| Full Analysis Set (FAS) | The FAS includes all randomized participants classified according to their assigned treatment arm, regardless of the actual treatment received. | Demographics and baseline disease characteristics, Disposition, efficacy, and PRO analysis |
| Safety Analysis Set | The safety analysis set includes all randomized participants who received at least 1 dose of study medication | Safety, treatment compliance, and exposure analyses |
| Pharmacokinetics Analysis Set | The PK analysis set is defined as participants who received at least 1 dose of study medication and have at least 1 valid blood sample drawn for PK analysis. | PK/PD analyses |

## 1.8. Definition of Subgroups

Subgroup analyses will be performed as appropriate to evaluate the consistency of treatment benefit for the selected efficacy endpoints and for safety. Table 4 provides the categorical variables that will be used for subgroup analyses whenever appropriate. In addition, subgroup analyses of selected countries may be performed for regional regulatory filing purposes. Subgroup analyses may be performed to explore the association of the duration of prior AAP or docetaxel use with key efficacy endpoints.

**Table 4: Categorical Variables for Subgroup Analysis**

| **Subgroup** | **Definition of Group** | **Analysis Type** |
|---|---|---|
| Age | Age <65 years, ≥65 to <75 years, ≥75 years | E, S |
| Race | White, Asian, Other | E, S |
| Baseline ECOG performance status | 0, ≥1 | E, S |
| Baseline Brief Pain Inventory-Short Form (BPI-SF) Question 3 (worst pain in the last 24 hours) score | 0, 1 to 3, >3 | E, S |
| Gleason total score at initial diagnosis | ≤7, >7 | E |
| Region | North America, Europe, Asia, rest of the world (ROW) | E, S |

**Table 4: Categorical Variables for Subgroup Analysis**

| Subgroup | Definition of Group | Analysis Type |
|---|---|---|
| Prior docetaxel use | Yes, no | E |
| Prior AAP use | Yes, no | E |
| Presence of visceral metastases at baseline | Yes, no | E |
| Bone metastasis only at baseline | Yes, no | E |
| Number of bone lesions at baseline | ≤10, >10 | E |
| Gene mutation type at baseline | BRCA mutation present (regardless of others), non-BRCA | E |
| Volume of disease at baseline | high, low | E |
| Metastasis stage at diagnosis | M0, M1 | E |
| Duration of prior ADT | <3 months, ≥3 months | E |
| Baseline PSA above median | yes, no | E |
| Baseline lactate dehydrogenase above upper limit normal | yes, no | E |
| Baseline alkaline phosphatase above upper limit normal | yes, no | E |

E=efficacy; S=Safety
Note: Analyses will be performed for each subgroup as appropriate.

## 1.9. Study Day and Relative Day

Study Day 1 refers to the start of the first study medication administration. Study day will be calculated in reference to the date of randomization for randomized but untreated participants. All efficacy and safety assessments at all visits will be assigned a day relative to this date. Efficacy analyses on time-to-event endpoints will use the date of randomization as the start date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Study Day 1
- Visit date - date of Study Day 1, if visit date <date of Study Day 1

There is no 'Day 0'.

## 1.10. Baseline

Baseline is defined as the last observation prior to the start of the first study medication administration (randomization date for randomized untreated participants).

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study drug administration (including time if time is available). If the first administration date is missing or the administration is not done, then the baseline measurement is the closest non-missing measurement taken on or prior to the randomization date.

## 1.11. Imputation Rules for Missing AE Date of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
    - If month/year of the onset of AE is different than that month/year of Study Day 1: first day of the month that the AE occurred

  - If month/year of the onset of AE, resolution of AE, and Study Day 1 are the same: The day of Study Day 1 or day of AE resolution date, whichever is earliest
  - If month/year of the onset of AE and Study Day 1 are the same, but month/year of the resolution of AE is different: The day of Study Day 1

- If the onset date of an AE is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the Day 1, or
  - Month and day of the Day 1, if this date is the same year that the AE occurred, or
  - Last day of the year if the year of the AE onset is prior to the year of the Day 1, or
  - The AE resolution date.
- Completely missing AE onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an AE is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

# 2. INTERIM ANALYSIS AND INDEPENDENT DATA MONITORING COMMITTEE REVIEW

## 2.1. Interim Analysis

There is no interim analysis for the primary endpoint of rPFS.

Two interim analyses and a final analysis for the secondary endpoint of OS are planned according to Table 5, based on number of OS events in the All HRR population. The first interim analysis (IA1) will coincide with the primary analysis of rPFS (hereafter referred to as 'PA-IA1').

Formal analyses for TSP will be performed at IA1 and IA2 only.

The group-sequential design according to the Kim-DeMets alpha spending function with parameters of 2 and 2.5 will be used for TSP and OS, respectively. The corresponding alpha spending function is $\alpha t^{\rho}$, with t denoting the information fraction. The overall family-wise Type-1 error will be controlled at 0.05. Details of the testing procedure for controlling family-wise type I error are described in Section 4.1.1.1.

**Table 5: Operating Characteristics of OS and TSP Analysis with a Maximum Overall Alpha of 0.05***

| | | IA1 | IA2 | FA |
|---|---|---|---|---|
| OS | Number of events expected in HRR full analysis set (info fraction) | ~170 (~43.7%) | ~255 (65.6%) | 389 (100%) |
| | Efficacy exit boundary** | HR<0.658 | HR<0.736 | HR<0.814 |
| | P value boundary | 0.0063 | 0.0144 | 0.0424 |
| TSP | Number of events expected in HRR full analysis set (info fraction) | ~133 (66.8%) | ~199 (100%) | |
| | Efficacy exit boundary** | HR<0.672 | HR<0.747 | |
| | P value boundary | 0.0219 | 0.0392 | |

*If the overall alpha is less than 0.05 (see Section 4.1.1.1, for details), cumulative alpha spent at IAs and the final analysis will be reduced, and the efficacy boundary will be adjusted accordingly.
**HR exit boundary values are approximate; the testing results will be based on the corresponding p-value boundary values

## 2.2. Independent Data Monitoring Committee

An IDMC will be commissioned to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in the study and to review efficacy information. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC charter.

The IDMC will be composed of members not associated with the conduct of the study, except in their role on the IDMC. The sponsor will also designate an independent biostatistician not affiliated with the project to prepare and provide study data to the IDMC. Complete details regarding the composition and governance of the IDMC is outlined in the IDMC Charter.

# 3. PARTICIPANT INFORMATION

The number of participants in each analysis set will be summarized and listed by treatment arm and overall. In addition, the distribution of participants by region, country, and site ID will be presented unless otherwise noted.

## 3.1. Demographics and Baseline Characteristics

Table 6 presents a list of the demographic and baseline characteristics variables that will be summarized by treatment arm and overall, for the full analysis set.

**Table 6: Demographic and Baseline Characteristics Variables**

| **Continuous Variables:** | **Summary Type** |
|---|---|
| • Age (years)<br>• Weight (kg), Height (cm)<br>• Baseline PSA, hemoglobin, lactate dehydrogenase, alkaline phosphatase<br>• Baseline pain score (BPI-SF Item 3)<br>• Time from initial diagnosis with prostate cancer to randomization<br>• Time from metastatic diagnosis to randomization | Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]) |
| **Categorical Variables** | **Summary Type** |
| • Age <65 years, ≥65 to <75 years, ≥75 years)<br>• Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Multiple)<br>• Ethnicity (Hispanic or Latino, not Hispanic or Latino) | Frequency distribution with the number and percentage of participants in each category |

**Table 6: Demographic and Baseline Characteristics Variables**

| | |
|---|---|
| • Baseline ECOG performance status (0, 1, 2)<br>• Tumor stage at diagnosis, lymph node stage at diagnosis, metastasis stage at diagnosis<br>• Gleason score at diagnosis<br>• Extent of disease at baseline (bone, lymph node, visceral, soft tissue)<br>• Baseline pain score (BPI-SF Item 3) (0, 1 to 3, >3)<br>• Prior prostate cancer therapy<br>• Number of bone lesions at study entry (≤10, >10) | |

[a] If multiple race categories are indicated, the race is recorded as 'Multiple'

## 3.2. Disposition Information

The number of participants randomized, the number of participants receiving study treatment, the number of participants with treatment ongoing, and the number of participants who have discontinued the study treatments, as well as the reasons for treatment discontinuation (including COVID-19) as documented in the CRF will be summarized. Similarly, the number of participants ongoing and who discontinued the study as well as the reasons for study discontinuation (including COVID-19) will be summarized.

Listings of participants who discontinued study treatment, participants who terminated the study prematurely, participants who were unblinded during the study period, and participants who were randomized but did not receive study medication will also be provided.

## 3.3. Treatment Compliance

Study medication compliance will be summarized descriptively and will be calculated as follows:

Study medication compliance (%) = (actual number of tablets taken / total number of tablets expected to be taken) x 100.

## 3.4. Extent of Exposure

Treatment duration is defined as the time between the date of the first dose and the date of the last dose of study medication. Descriptive summaries include total treatment duration in months, total dose administered, dose intensity, and dose interruption/modification and reasons (including COVID-19).

## 3.5. Protocol Deviations

Protocol deviations will be summarized by treatment arm. Protocol deviations will be reviewed based on protocol deviation guidance to assess if they are major deviations for this study. The final list will be compiled prior to database lock. Examples of major protocol deviations may include, but are not limited to, the following:

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy eligibility criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose

- Other

Protocol deviations related to COVID-19 and to major regional disruptions (ie, Ukraine, Russia, and Israel) will be summarized.

## 3.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose of study medication. Concomitant medications are defined as any medication used on or after the same day as the first dose of study medication, including those that started before and those that continue through 30 days after the last dose of study medication.

Summaries of concomitant medications will be presented by ATC term, generic medication name, and treatment arm. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least one concomitant medication. Prior medications will be summarized by treatment arm, ATC term, and generic medication name. Prior anticancer therapy including radiotherapy, surgery, chemotherapy, hormonal therapy, and other systemic therapy will be summarized.

## 3.7. Subsequent Anti-cancer Therapies

Subsequent therapies received after discontinuation of study treatment, including systemic therapy, radiation and surgical interventions will be summarized by treatment arm as well as by geographic region. Medications will be coded using WHO-DD.

The following imputation rule will be used for missing start dates for subsequent therapies:

a. If all parts of the start date are missing, the date will be imputed with the date after the discontinuation date.
b. In the case where only the start day of therapy is missing, it will be replaced by the day after the discontinuation date if the therapy starts in the same month and year as the discontinuation date. Otherwise, it will be replaced by the first of the month.

If both the start day and month of therapy are missing, the start day and month will be replaced by the day and month of the date after the discontinuation date if the therapy and the discontinuation occur in the same year; otherwise, it will be replaced by 1st of January.

# 4. EFFICACY

## 4.1. Analysis Specifications

### 4.1.1. Level of Significance

The family wise type 1 error will be controlled at 5% (2-sided). All tests will be conducted at a 2-sided alpha level of 0.05 and 95% confidence intervals (CIs) will be provided, unless stated otherwise.

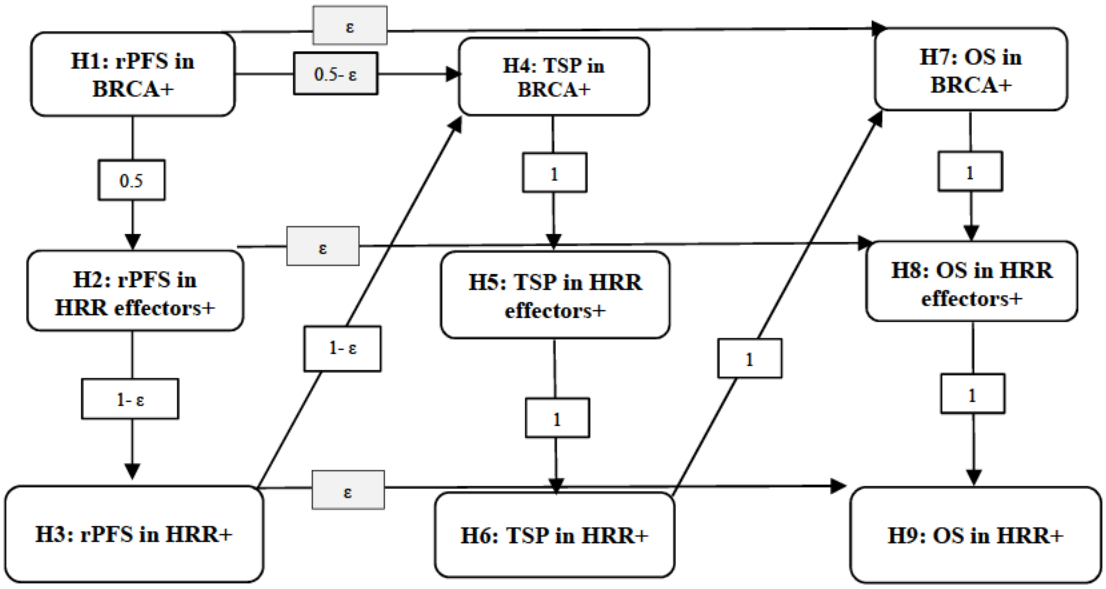
#### 4.1.1.1. Multiplicity Adjustment for Testing of Primary and Key Secondary Endpoints

To preserve the overall family-wise type I error rate at the 2-sided 0.05 level, the multiple comparison testing procedure in a group sequential design using the graphical approach will be applied. The procedure takes into account both sources of multiplicity, multiple hypothesis tests (eg, across primary and secondary endpoints) and multiple analyses planned for the study (eg, two interim analyses and a final analysis for OS).

There are two key components that define this approach, testing algorithm for multiple hypotheses specified by the graphical representation and repeated testing of some hypotheses using the alpha-spending function methodology. The testing algorithm codes a series of graph transformations which happen at each successful clearing of a hypothesis as described in Maurer (2013). During execution of the procedure, different scenarios for local significance levels emerge in an iterative manner.

Figure 1 defines the graphical procedure where the hypotheses of interest are represented by the nodes. A given transition weight, written to the directed edge on the graph, specifies the fraction of the local significance level transferred from the initial node to the connected edge terminal node, if the null hypothesis corresponding to the initial node is successfully rejected.

**Figure 1: Graphical Approach for Testing Key Efficacy Endpoints**




The hypothesis testing starts with H1 at 2-sided alpha=0.05. If rPFS meets statistical significance in BRCA, then half of the alpha (0.025) will be passed to H2 and the other half will be split between H4 and H7, with 0.5-ε and ε weights, respectively. The overall family-wise type I error rate is preserved at the pre-specified 2-sided 0.05 level. Following the planned testing procedure, the values of local significance levels (2-sided) for rPFS, TSP and OS in each subgroup are presented in Table 7 (listing scenarios for the alpha available for each hypothesis incorporating recycling of alpha per the procedure).

**Table 7: Operating Characteristics for rPFS, TSP, and OS Analysis with Planned Graphical Procedure**

| Endpoint | | Alpha Level Available | Significance Level (2-sided) at Each IA and FA* | | |
|---|---|---|---|---|---|
| | | | IA1 | IA2 | FA |
| rPFS | H1: BRCA | 0.05 | 0.05 | - | - |
| | H2: HRR effectors | 0.025 | 0.025 | - | - |
| | H3: All HRR | 0.0247 | 0.0247 | - | - |
| TSP | H4: BRCA (only H1 meets statistical significance) | 0.0245 | 0.0108 | 0.0190 | |
| | H4: BRCA (H1, H2, and H3 meet statistical significance) | 0.049 | 0.0216 | 0.0393 | - |
| | H5: HRR effectors (H1 and H4 meet statistical significance) | 0.0245 | 0.0110 | 0.0189 | - |
| | H5: HRR effectors (H1, H2, H3, H4 meet statistical significance) | 0.049 | 0.0219 | 0.0392 | - |
| | H6: All HRR (H1, H4, and H5 meet statistical significance) | 0.0245 | 0.0109 | 0.0189 | - |
| | H6: All HRR (H1, H2, H3, H4, and H5 meet statistical significance) | 0.049 | 0.0219 | 0.0392 | - |
| OS | H7: BRCA (H1, H4, H5, and H6 meet statistical significance) | 0.025 | 0.0031 | 0.0069 | 0.0207 |
| | H7: BRCA (H1 to H6 meet statistical significance) | 0.0495 | 0.0061 | 0.0139 | 0.0421 |
| | H8: HRR effectors (H1, H4, H5, H6, and H7 meet statistical significance) | 0.025 | 0.0031 | 0.0069 | 0.0207 |
| | H8: HRR effectors (H1, H2, H4, H5, H6, and H7 meet statistical significance) | 0.0253 | 0.0031 | 0.0070 | 0.0209 |
| | H8: HRR effectors (H1 to H7 meet statistical significance) | 0.0498 | 0.0061 | 0.0141 | 0.0423 |
| | H9: All HRR (H1, H4, H5, H6, H7, and H8 meet statistical significance) | 0.025 | 0.0032 | 0.0070 | 0.0206 |
| | H9: All HRR (H1, H2, H4, H5, H6, H7, and H8 meet statistical significance) | 0.0253 | 0.0032 | 0.0071 | 0.0208 |
| | H9: All HRR (H1 to H8 meet statistical significance) | 0.05 | 0.0063 | 0.0144 | 0.0424 |

* The significance level for TSP and OS might change depending on the number of events that are observed at the time of the analysis.
Note: ε is set to 0.01. The OS operating characteristics are only presented for scenarios where the available alpha is at least 0.025.

### 4.1.2. Data Handling Rules

In general, no imputation method is planned for handling missing or incomplete data unless specified otherwise for a specific endpoint.

### 4.1.3. General Analysis Considerations

All continuous variables will be summarized using number of participants (N), mean, standard deviation (SD), median, minimum, and maximum. Discrete variables will be summarized with

number and percent. The full analysis set of all randomized participants will be used for the formal analysis of primary and secondary endpoints following an intention to treat principle. The Kaplan-Meier product limit method and a stratified Cox model will be used to estimate the time-to-event variables and to obtain the HR along with the associated confidence intervals. Unless otherwise specified, stratified log-rank tests will be used to test the treatment effect for time-to-event variables. If necessary, data will be pooled for the stratification factors based on the rules defined in Section 1.6.1.

## 4.2. Primary Efficacy Endpoint

### 4.2.1. Definition

The primary endpoint, rPFS, is defined as the time interval from the date of randomization to the first date of radiographic progression as assessed by investigator or death due to any cause, whichever occurs first. Radiographic progression is determined by the first occurrence of progression by bone scan (according to PCWG3 criteria) or progression of soft tissue lesions by CT or MRI (according to RECIST 1.1 criteria).

Radiographic progression should be evaluated as follows:

Progression of soft tissue lesions measured by CT or MRI as defined by RECIST 1.1.

Progression by bone lesions observed by bone scan and based on PCWG3. Under these criteria, any bone progression must be confirmed by a subsequent scan ≥6 weeks later. The Week 8 scan (first post-treatment scan) should be used as the baseline to which all subsequent scans are compared to determine progression. Bone progression is defined as one of the following:

1. Participant whose Week 8 scan is observed to have ≥2 new bone lesions that would fall into one of the 2 categories below:
    a. Participant whose confirmatory scan (which is performed ≥6 weeks later) shows ≥2 new lesions compared to the Week 8 scan (ie, a total of ≥4 new lesions compared to baseline scan) will be considered to have bone scan progression at Week 8.
    b. Participant whose confirmatory scan did not show ≥2 new lesions compared to the Week 8 scan will not be considered to have bone scan progression. The Week 8 scan will be considered as the baseline scan to which subsequent scans are compared. The FIRST scan timepoint that shows ≥2 new lesions compared with the Week 8 scan will be considered as the bone scan progression timepoint if these new lesions are confirmed by a subsequent scan ≥6 weeks later.
2. For a participant whose Week 8 scan does not have ≥2 new bone lesions compared to baseline scan, the first scan timepoint that shows ≥2 new lesions compared with the Week 8 scan will be considered as the bone scan progression timepoint if these new lesions are confirmed by a subsequent scan ≥6 weeks later.

rPFS for the participants without radiographic progression or death will be censored at the last disease assessment date if subsequent anti-cancer therapy is never received or censored at the last disease assessment date prior to the start of the subsequent anti-cancer therapy if the participant started subsequent anti-cancer therapy. Key censoring rules are summarized in Table 8.

**Table 8: rPFS censoring rules**

| Scenario | Censoring Rule |
|---|---|
| No disease assessment at baseline<br>or<br>No disease assessment after baseline and no death | Censored on the date of randomization |
| Participants who are lost to follow-up or withdraw from study | Censored on the date of the last disease assessment |
| Participants who receive new systemic anti-cancer therapy known or intended for the treatment of mPC during the study prior to documented disease progression or death | Censored on the date of the last disease assessment prior to the start of the new systemic anti-cancer therapy |
| Participants with no evidence of radiographic progressive disease or death | Censored on the date of the last disease assessment |
| Participants with progression or death immediately following ≥2 consecutive missed or unevaluable planned radiographic scans | Censored on the date of the last disease assessment before the missed/unevaluable scans. |

### 4.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in this study, is defined by the following four components [ICH E9 (R1) 2017]:

- Population: Men >18 years of age with deleterious germline or somatic HRR gene-mutated mCSPC as defined by the inclusion/exclusion criteria to reflect the targeted patient population for treatment
- Variable: rPFS by investigator
- Intercurrent event (described in Table 9): use of subsequent anti-cancer therapy, treatment discontinuation due to AE or other reasons than AE or worsening of disease
- Population-level summary: hazard ratio (niraparib + AAP compared with AAP), median rPFS and its 95% CI, rPFS rates at selected time points for each treatment arm.

**Table 9: Intercurrent Events and The Corresponding Strategies**

| Intercurrent Events | Strategy for Addressing Intercurrent Events and Its Description |
|---|---|
| Treatment discontinuation due to AE or other reasons than AE or worsening of disease | **Treatment Policy Strategy:** Use time to PD or death, regardless of whether or not this intercurrent event had occurred. |
| Initiation of subsequent anti-cancer therapy prior to the documented disease progression or death | **Hypothetical strategy:** subjects are censored at the last disease assessment showing no evidence of PD before the use of subsequent anti-cancer therapy. |

### 4.2.3. Analysis Methods

The primary analysis of rPFS will be performed after approximately CCI [redacted] events are observed in the All HRR population and will be tested using stratified log-rank test at the overall 2-sided significance level of 0.05.

The Kaplan-Meier product limit method and a stratified Cox model will be used to estimate the median rPFS and to obtain the HR estimate along with the associated 95% confidence intervals, respectively.

Sensitivity analysis using non-stratified log rank test will also be performed as supportive analyses.

The proportional hazard assumption will be assessed graphically by plotting log (-log [estimated survival distribution function]) against log (survival time). The resulting graphs should have approximately parallel lines when the assumption holds. If the proportional hazards assumption is reasonably met, then the HR will be used as an estimate of treatment effect. If the proportional hazards assumption is violated, then the inference remains statistically valid for testing equality in survival distributions, but treatment effect will only be estimated using the median time to event in each treatment arm. Sensitivity analysis such as piecewise constant hazards model may be performed as appropriate.

To assess the consistency of treatment benefit across important subgroups, forest plots will be provided for subgroups as defined in Section 1.8. The comparison between the two treatment arms will be evaluated using the hazard ratio with its 95% CI from a univariate non-stratified Cox regression model in each subgroup.

Multivariate Cox regression analysis, adjusting for important selected prognostic factors, will also be performed as supportive analysis, if appropriate. The adjusted HR and its 95% confidence interval for treatment and each factor will be provided. The following baseline covariates will be considered for inclusion in the model for as needed:

- PSA (continuous, log transformed)
- Lactate dehydrogenase (continuous, log transformed)
- Alkaline phosphatase (continuous, log transformed)
- Age (continuous)
- Pain score (BPI-SF Item 3, continuous)
- ECOG PS grade (0 vs. ≥1)
- Number of bone lesions at baseline (<=10 vs. >10)
- Presence of visceral disease (yes vs. no)
- Geographic region (NA/EU vs. Asia/ROW)
- Gleason score (<=7 vs. >7)
- Prior docetaxel use (yes vs. no)
- Volume of disease (low vs high)
- Gene mutation group (BRCA vs non-BRCA) (only for All HRR population)

Each factor will be assessed individually for prognostic value ($p<0.05$) using univariate Cox regression model. Factors that are deemed to have prognostic value will be included as covariates in a multivariate Cox regression model to assess their significance in the presence of the other

factors. Backward selection methods will be used to identify the final set of prognostic factors (exit p-value set to be 0.10). Treatment will then be added to this final model to assess the effect of treatment when adjusted for these prognostic factors. The multivariate analysis will be performed for the BRCA and HRR Effectors subgroups.

Sensitivity analysis will be performed using all progression or death events, whichever occurs first, regardless of change of therapy or missed/unevaluable scans for 2 or more consecutive visits.

The symmetry of disease assessment schedules between treatment arms will also be examined. Reasons for censoring will be summarized by treatment arm to check for informative censoring.

Stratified log-rank test and Cox proportional-hazard model by excluding subjects with major protocol (MPD) deviations (including COVID-19 or/and regional crisis Ukraine/Russia/Israel MPD) will be performed as sensitivity analysis if MPD>20%.

Missing disease assessment due to COVID-19 will be summarized to evaluate COVID-19 impact on disease assessment. Sensitivity analysis will be performed as needed by censoring death event due to COVID- 19 at last disease assessment date.

#### 4.2.4. Blinded Independent Central Review (BICR)

Blinded independent central review (BICR) will be conducted for confirmation of radiographic progression. Sensitivity analysis using BICR assessed radiographic progression will also be performed. The concordance rate between the BICR-determined rPFS and investigator-determined rPFS will be evaluated.

### 4.3. Secondary Efficacy Endpoints

#### 4.3.1. Definition

The secondary efficacy endpoints are:

- **OS**: defined as the time from the date of randomization to the date of death from any cause. Participants alive at the time of analysis will be censored on the last date the participant was known to be alive.

- **Time to symptomatic progression**: defined as the time from the date of randomization to the date of any of the following (whichever occurs first):
    - The use of external beam radiation for skeletal or pelvic symptoms. Note: radiation planned prior to randomization will not be considered as symptomatic progression.
    - The need for tumor-related orthopedic surgical intervention
    - Other cancer-related procedures (eg, nephrostomy insertion, bladder catheter insertion, or surgery for tumor symptoms).
    - Cancer-related morbid events (ie, fracture [symptomatic and/or pathologic], cord compression, urinary obstructive events).
    - Initiation of a new systemic anti-cancer therapy because of cancer symptoms.

If no event was observed, the participant will be censored at the last known alive date.

- **Time to Subsequent Therapy**: defined as the time from the date of randomization to the date of initiation of subsequent therapy for prostate cancer. Participants who did not initiate subsequent therapy at the time of the analysis will be censored at the last known alive date.

For all these time-to-event endpoints, participants with no on-study assessment or no baseline assessment will be censored on the date of randomization.

### 4.3.2. Analysis Methods

The testing of these secondary efficacy endpoints will be based on the stratified log rank test. Multiplicity adjustment will be performed as described in Section 4.1.1.1, Secondary efficacy endpoints will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Cox proportional hazard models will be used to estimate the HR and its 95% confidence interval. Sensitivity analysis using non-stratified log rank test may be performed as supportive analyses.

The proportional hazard assumption will be assessed graphically by plotting log (-log [estimated survival distribution function]) against log (survival time).

The strength of association between rPFS and OS will be evaluated using Spearman's correlation coefficient taking censoring into account.

The following sensitivity analyses for OS may be carried out as appropriate if it is deemed useful to aid interpretation of the results.

- Forest plots will be provided for subgroups as defined in Section 1.8. The comparison between the two treatment arms will be evaluated using the hazard ratio with its 95% CI from a univariate non-stratified Cox regression model in each subgroup.

- Multivariate Cox regression analysis, adjusting for important selected prognostic factors, will also be performed as supportive analysis, if appropriate. The adjusted hazard ratio and its 95% confidence interval for treatment and each factor will be provided.

- To assess the impact of the use of subsequent therapies on the treatment effect on the OS, a time-dependent analysis using Cox regression will be performed. A stratified Cox model will include treatment variable and a time-dependent covariate for the status change with respect to receiving subsequent therapy. Stratified hazard ratio and its 95% confidence interval for treatment will be provided. This analysis may be conducted if a significant number of participants receive subsequent therapies.

- Sensitivity analysis for OS will be performed by censoring deaths due to COVID-19 if sufficient data is available.

- In the event that a large number of participants in the placebo group crossover to a medication that is in the same class as niraparib, at least one of the following analyses may be performed, if appropriate, in estimating the true treatment effect on OS:
  - The rank preserving failure time model as described by (Robins 1991)
  - Inverse Probability Censoring Weighted (IPCW) log-rank test as described by (Cole 2004)
  - Iterative Parameter Estimate (IPE) method as described by (Branson 2002) and (Robins 1991)

## 4.4. Other Efficacy Variables

### 4.4.1. Definition

Other efficacy endpoints are defined in Table 10.

**Table 10: Definition of other efficacy endpoints**

| Endpoint | Description | Analysis Population |
|---|---|---|
| Time-to-pain progression | Defined as the time from the date of randomization to the date of the first observation of pain progression. Pain progression is defined as an increase of at least 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive evaluations ≥3 weeks apart. Participants with no pain progression at the time of analysis will be censored at last date of BPI-SF pain score collection | FAS |
| Objective response rate | Defined as the proportion of participants with measurable disease at baseline achieving a complete (CR) or partial response (PR) according to modified RECIST 1.1. with no evidence of bone progression according to the PCWG3 criteria. | Participants with measurable disease at Baseline |
| Duration of response | Duration of response in participants with measurable disease at baseline (based on modified RECIST 1.1) is defined from the time of documented response to the first date of documented disease progression.<br>This endpoint considers only the participants who (1) had a measurable lesion at baseline according to RECIST 1.1 (ie, having a record in the Target dataset) and (2) had a tumor response of CR or PR (whichever occurred first) post baseline and before PD identified by RECIST.<br>For RECIST lesions, as the scan dates associated with a given visit may span more than a single date, PD date will be the earliest scan date for the visit; all other responses will be linked to the latest scan date for the visit.<br>Definition of PD and rule for censoring are the same as that for the rPFS by investigator | Participants with CR or PR |

**Table 10: Definition of other efficacy endpoints**

| Endpoint | Description | Analysis Population |
|---|---|---|
| Time to PSA progression | Time to PSA progression is defined as the time from randomization to the first date of documented PSA progression per PCWG3 criteria.<br><br>Definition of PSA progression:<br>- After a decline from baseline, PSA increases ≥ 25% and ≥ 2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later (ie, a confirmed rising trend), or<br>- If there is no decline from baseline, PSA increases ≥25% and ≥ 2 ng/mL from baseline after 12 weeks.<br><br>Participants with no PSA progression at the time of analysis will be censored on the last known date with no progression.<br><br>Participants without a baseline PSA or without any post baseline values will be censored at the randomization date. | FAS |
| PSA response rate | Proportion of participants achieving a PSA decline of ≥50% according to PCWG3 criteria.<br><br>Proportion of participants achieving a PSA decline of ≥90% at any time.<br><br>Proportion of participants achieving a PSA decline to level ≤ 0.2ng/mL at any time. | FAS |
| Progression-free survival on first subsequent therapy (PFS2) | PFS2 is defined as time from randomization to the date of progression (radiographic, clinical, or PSA progression) on the first subsequent therapy or death from any cause, whichever occurs first.<br><br><u>General rules for PFS2 event and censoring:</u><br><br>1. For participants who initiated a subsequent anti-cancer therapy:<br>a. If there is a disease progression on 1st subsequent anti-cancer therapy or death, this is a PFS2 event, date of PFS2 = minimum of disease progression date and death date.<br>b. If no disease progression on 1st subsequent anti-cancer therapy and no death prior to start of 2nd subsequent anti-cancer therapy, this is not a PFS2 event, the participant will be censored at start date of 2nd subsequent anti-cancer therapy - 1 day.<br>c. If no disease progression on 1st subsequent anti-cancer therapy and no death and no start of 2nd subsequent anti-cancer therapy, this is not a PFS2 event, the participant will be censored at last known alive date. | FAS |

**Table 10: Definition of other efficacy endpoints**

| Endpoint | Description | Analysis Population |
|---|---|---|
| | 2. For participants who did not receive any subsequent anti-cancer therapy:<br>a. If a participant died, this is a PFS2 event with death date as date of PFS2.<br>b. If a participant did not die, this is not a PFS2 event, the participant will be censored at last known alive date. | |
| Time to initiation of cytotoxic chemotherapy | The time from the date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer. Subjects who did not initiate cytotoxic chemotherapy at the time of the analysis will be censored on the last known date. | FAS |

Other exploratory endpoints may be analyzed if appropriate.

### 4.4.2. Analysis Methods

Estimates of the time-to-event endpoints will be obtained using the Kaplan-Meier estimates of the survival distributions. A stratified Cox model will be used to obtain the HR along with the associated 95% confidence intervals, except duration of response which will be analyzed by unstratified Cox model. The testing of these other efficacy endpoints will be based on the stratified log rank test.

ORR and PSA response rate will be summarized by treatment arm using descriptive statistics (count and percentage). The relative risk will be reported along with the corresponding two-sided 95% CI. The two treatment arms will be compared by using the chi-square test; Fisher's exact test may be used if the expected counts in some of the cells are less than 5.

## 4.5. Efficacy Analysis by HRR Genes

HRR gene mutations that are included in the HRR gene panel include:

| HRR Genes | Definition |
|---|---|
| BRCA1 | Breast Cancer gene 1 |
| BRCA2 | Breast Cancer gene 2 |
| BRIP1 | BRCA1 Interacting Protein C-terminal Helicase 1 gene |
| CDK12 | Cyclin-Dependent Kinase 12 |
| CHEK2 | Checkpoint Kinase 2 gene |
| FANCA | Fanconi Anemia Complementation Group A gene |
| PALB2 | Partner and Localizer of BRCA2 gene |
| RAD51B | RAD51 paralog B |
| RAD54L | RAD54-Like |

Frequency of gene alterations will be summarized by treatment arm.

Primary and secondary endpoints will be analyzed by single gene alteration and by unique gene groups where multiple gene alterations occurred. A subject will only be counted once in a gene group. Only gene alterations with at least 5 events will be analyzed.

A Forest plot will be provided for efficacy analysis by HRR gene groups.

In addition, sensitivity analysis on primary and secondary endpoints for the following subgroups of subjects with HRR alterations will be performed:

1. Subjects with BRCA (BRCA 1 or BRCA 2) gene alteration regardless of other co-occurring gene alterations.
2. HRR effectors: Subjects carrying the following single or co-occurring gene alterations: BRCA1, BRCA2, BRIP1, PALB2, RAD51B, and RAD54L.
3. Subjects with non-BRCA HRR gene alterations
4. Non-BRCA HRR Effectors (BRIP1, PALB2, RAD51B, RAD54L)
5. Non-HRR effectors: Subjects with HRR gene alterations minus HRR effectors (CDK12, CHEK2, FANCA)
6. Subjects with All HRR gene alterations excluding:
   a) Subjects with a single CHEK2 alteration identified by a liquid biopsy (i.e. cfDNA+) and negative for HRR gene alterations by paired tissue testing.
   b) Subjects with a single CHEK2 alteration identified by a liquid biopsy (i.e. cfDNA+) and with either negative HRR gene alteration by paired tissue testing or no available paired tissue testing.
7. Subjects with non-BRCA HRR gene alterations excluding subjects in a and b above.
8. Subjects with a single CHEK2 alterations excluding subjects in a and b above.

In the event that the Sponsor is notified by a vendor that the pathogenicity of a variant(s) is reclassified to non-pathogenic, sensitivity analysis excluding the variant(s) may be performed.

# 5. SAFETY

Safety data will be analyzed using the Safety Analysis Set. Additionally, safety analysis will be performed on the target subgroups to ensure the safety profile is consistent across all subgroups.

## 5.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any new or worsening AE occurring at or after the initial administration of study treatment through the day of last dose plus [30] days or prior to the start of subsequent anticancer therapy, whichever is earlier, or the follow-up AE (linked to an existing TEAE) with onset date and time beyond [30] days after the last dose of study treatment but prior to the start of subsequent therapy is considered to be treatment emergent. If any event is considered drug-related, then this event will be assumed to be treatment emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the number and

percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment arm.

For each treatment arm, AE incidence rates will be summarized with frequency and percentage by SOC and preferred term, with all participants treated in that treatment arm as the denominator, unless otherwise specified. In addition, AE incidence rates will also be summarized by severity and relationship to study medication. Treatment-related AEs are those judged by the Investigator to be at least possibly related to the blinded study medication. Participants with multiple occurrences of events will only be counted once at the maximum severity for each preferred team, SOC, and overall. Deaths that occur within 30 days after the last dose of study medication are defined as on-study deaths.

Summary tables of the following AEs will be provided:

- Overall summary of AEs: the number and percentage of participants who experienced any AE, Grade 3/4 AEs, any serious adverse event (SAE), any treatment-related AE, treatment related Grade 3/4 AE, any treatment-related SAE, AE leading to treatment discontinuation, AE leading to death, related AE leading to death
- All AEs by SOC and preferred term (for all AEs and for most frequent AEs [reported in ≥ 5% of participants])
- All AEs by SOC, preferred term, and toxicity grade
- All AEs by decreasing frequency of preferred term
- Grades 3 or 4 AEs by SOC and preferred term
- Treatment-related AEs by SOC and preferred term
- Treatment-related AEs by SOC, preferred term, and toxicity grade
- Treatment-related Grades 3 or 4 AEs by SOC and preferred term (for all Grades 3 and 4 AEs and for Grades 3 and 4 most frequent AEs [reported ≥ 1% of participants])
- AEs that led to study medication discontinuation by SOC and preferred term. Study medication discontinuation will be determined from the End of Treatment CRF (where reason for termination is “Adverse Event”) and the specific AE will be determined from the AE CRF page (where action taken is “Withdrawn from Study”)
- AEs that led to study medication discontinuation by SOC, preferred term, and toxicity grade
- All SAEs by SOC and preferred term
- All SAEs by SOC, preferred term, and toxicity grade
- Deaths will be summarized by time period (on-study vs. during follow-up) and cause of death.

The incidence of AEs of special interest will be summarized by category and preferred term. Adverse Events of Special Interest for niraparib and AA, plus prednisone include following categories:

- MDS/AML
- Grade 3 or higher anemia, thrombocytopenia, and/or neutropenia.

- Hypertension (including hypertensive crisis; excluding subjects with single BP elevations)
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Hypokalemia
- Fluid retention/edema
- Hepatotoxicity
- Osteoporosis (including osteoporosis-related fracture)
- Rhabdomyolysis/myopathy
- Allergic alveolitis
- CYP2D and CYP2C8 drug interactions and food effect
- Major Adverse Cardiovascular Events (MACE)

Participant listings of all Grades 3 or 4 AEs, all SAEs, AEs that led to study medication discontinuation, and all deaths will also be provided.

The study was on-going during the COVID-19 pandemic (March 11, 2020 to May 11, 2023). Subjects who reported COVID-19 infection during the study will be summarized and listed.

Narratives will be written for the following participants in the final clinical study report:

1. Patients who died within 30 days of the last dose of study drug
2. Patients who had a serious treatment-emergent adverse event
3. Grade 3 or higher treatment-emergent adverse events of special interest
4. Any TEAEs that lead to treatment discontinuation.

## 5.2. Death

Deaths within 30 days of the last dose of study medication will be displayed by actual treatment received. Frequencies for the following parameters will be included in the summary table:

- Number of participants who died
- Cause of death
- A listing of participants who died

## 5.3. Clinical Laboratory Tests

Clinical laboratory test results will be summarized. Normal ranges will be used to identify values that are outside the normal ranges and abnormal laboratory results will be graded according to the NCI CTCAE Version 5.0.

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point as appropriate. Parameters with predefined toxicity grades

will be summarized. Change from baseline to the worst grade experienced by the participant during the study treatment will be provided as shift tables.

Participants meeting lab criteria for eDISH (Evaluation of Drug Induced Serious Hepatotoxicity) will be listed. eDISH is defined as 1) Elevated ALT or AST at any time; that is, max (ALT/ULN) >3 or max (AST /ULN) >3 and 2) Elevated TBL at any time; that is, max (TBL/ULN) ≥2.

Subjects meeting lab criteria for Hy's law will be listed. Criteria for Hy's law is defined as 1) (ALT or AST) of >= 3x ULN at any time; 2) bilirubin >= 2x ULN at any time; and 3) excluding subjects with ALP>=2x ULN prior to or on the same date of the 1 st bilirubin >=2x ULN.

## 5.4. Vital Signs and Physical Examination Findings

Baseline weight and vital signs (blood pressure (systolic and diastolic) and heart rate) will be summarized by treatment arm. Only blood pressure and heart rate are reported during the treatment phase. Participants with marked abnormalities in blood pressure as compared to baseline will be summarized according to the following categories defined below.

| Parameter | Criteria for Markedly Abnormality |
|---|---|
| Systolic Blood Pressure | Absolute result < 90 mmHg and decrease from baseline > 20 mmHg |
| | Absolute result > 160 mmHg and increase from baseline > 20 mmHg |
| Diastolic Blood Pressure | Absolute result < 50 mmHg and decrease from baseline > 10 mmHg |
| | Absolute result > 100 mmHg and increase from baseline > 10 mmHg |

All other abnormal findings in physical examination will be recorded and summarized as AEs.

## 5.5. Other Safety Parameters

### 5.5.1. ECOG Performance Status

Frequencies of ECOG performance status will be summarized over time by treatment arm.

# 6. PHARMACOKINETICS/PHARMACODYNAMICS

## 6.1. Pharmacokinetics

PK analyses will be conducted and reported separately.

Plasma concentrations for niraparib, its M1 metabolite will be listed and summarized using descriptive statistics. Population PK analysis of plasma concentration-time data of niraparib will be performed using nonlinear mixed-effects modeling. Previously developed population PK model for niraparib will be used as prior information to obtain individual estimates of exposure. If deemed necessary, the plasma concentration data obtained in this study may be pooled with data from previous studies, used to develop the population PK model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) may be explored as

potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis may be presented as a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for niraparib or abiraterone. PK samples collected after the snapshot date may be halted if PK objectives have been met. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all participants with available plasma concentrations. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of niraparib and its M1 metabolite (if applicable).

### 6.2. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between niraparib measures of exposure (eg, derived AUC or trough concentrations) and key efficacy (eg, rPFS by investigator) and safety parameters, will be explored graphically, as data allow. In addition, the relationship may be characterized using an appropriate PK/pharmacodynamics or logistic regression model. Details will be provided in a separate analysis plan and results will be reported separately from the CSR.

## 7. BIOMARKER

The association of biomarker positivity with clinical response or time-to-event endpoints will be assessed using appropriate statistical methods, (such as analysis of variance, categorical, or survival models), depending on the endpoints. Correlation of biomarkers (eg, DNA alterations, gene expression) with clinical response or relevant time-to-event endpoints may be performed to identify responsive (or resistant) subgroups.

## 8. PATIENT REPORTED OUTCOME

A separate and more detailed statistical analysis plan will be provided for PRO data.

## 9. MEDICAL RESOURCE UTILIZATION

Medical resource utilization will be descriptively summarized by treatment arm. Additional analyses may be conducted; details and results of any additional analyses will be presented in a separate report and will not be a part of the clinical study report.

# 10. REFERENCES

1. Jaleh Fallah et al., Efficacy of Poly(ADP-ribose) Polymerase Inhibitors by Individual Genes in Homologous Recombination Repair Gene-Mutated Metastatic Castration-Resistant Prostate Cancer: A US Food and Drug Administration Pooled Analysis. JCO 0, JCO.23.02105; DOI:10.1200/JCO.23.02105
2. Branson M and Whitehead J. Estimating a treatment effect in survival studies in which patients switch treatment. Statistical Medicine 2002; 21, 2449-2463.
3. Cole SR and Hernán MA Adjusted survival curves with inverse probability weights. Computer Methods and Programs in Biomedicine 2004; 75:45-49.
4. ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, August 2017.
5. Robins JM and Tsiatis AA. Correcting for non-compliance in randomized trials using Rank Preserving Structural Failure Time models. Commun Statist Theory Meth 1991; 20:2609-2631.
6. Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Statistics in Biopharmaceutical Research. 2013;5(4):311-320.
7. Chowdhury S. et al, Deep, rapid, and durable prostate-specific antigen decline with apalutamide plus androgen deprivation therapy is associated with longer survival and improved clinical outcomes in TITAN patients with metastatic castration-sensitive prostate cancer; Annals of Oncology, February 2023.
8. Fizazi K et al. Final analysis of phase III LATITUDE study in patients (pts) with newly diagnosed high-risk metastatic castration-naïve prostate cancer (NDx-HR mCNPC) treated with abiraterone acetate + prednisone (AA+P) added to androgen deprivation therapy (ADT). Journal of Clinical Oncology, April 2019.
9. Chi KN et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. Journal of Clinical Oncology, April 2021.
10. Armstrong A et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. Journal of Clinical Oncology, May 2022.
11. Castro E 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):1748-1757.