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 Treatment of Subjects with Metastatic Prostate Cancer

Protocol 64091742PCR3001; Phase 3
Amendment 4

JNJ-64091742 (niraparib)

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AMENDMENT HISTORY

SAP Version	Issue Date
Original	07 May 2019
Amendment 1	29 October 2019
Amendment 2	07 July 2020
Amendment 3	01 October 2021
Amendment 4	02 June 2022

The overall reason for SAP amendment #4:

Analysis of the primary endpoint of radiographic progression-free survival (rPFS) by Blinded Independent Central Review (BICR) in Cohort 1 was performed per protocol and SAP on 02Nov2021, using a CCO date of 08Oct 2021. The study met its primary endpoint, with statistical significance being shown in rPFS by BICR in the ALL HRR and BRCA populations. The first interim analysis (IA1) for the secondary endpoints of overall survival (OS), time to the initiation of cytotoxic chemotherapy (TCC), and time to symptomatic progression (TSP) was also performed at time of the final rPFS analysis. As none of these three secondary endpoints crossed the very conservative boundary for significance at this IA1 using the OBF spending function, the secondary endpoints of OS, TCC, and TSP will be further tested according to the pre-specified testing schema, at interim analysis 2 (IA2) and the final analysis to occur when approximately CC and CC death events are observed respectively.

Based on the result of the primary analysis, and in conjunction with the IDMC, the sponsor is now unblinded to support regulatory submissions. However, the study remains blinded to the BICR, investigators and patients. Per protocol, when a subject reaches radiographic progression, as determined by BICR, the investigator may request unblinding of the treatment assignment for that subject to aid in choosing appropriate subsequent therapy. As the MAGNITUDE study results were presented publicly at the ASCO GU meeting, the Sponsor anticipates a substantial increase in requests for unblinding of subject treatment assignments after documented disease progression, particularly for patients known to have a BRCA1/2 alteration, where olaparib is approved in the second-line setting in several regions globally, including the US and EU.

While additional requests for subject level unblinding will not impact determination of rPFS, knowledge of mutational status coupled with positive study results being made public may impact physicians' choice of subsequent therapy and may alter the use of cytotoxic chemotherapy based on the practice pattern in place at the inception of the study. Cytotoxic chemotherapy is associated with significant morbidity including neutropenic fever/infections, painful and potentially permanent neuropathy, significant gastrointestinal distress, and alopecia. As chemotherapy is typically one of the subsequent treatment options for patients with mCRPC, it is critical that this patient and prescriber relevant endpoint is fully interpretable. Currently, in the MAGNITUDE study, less than 50% of subjects with progressive disease received subsequent chemotherapy. An alteration in type of subsequent therapy and, likely, increased use of PARP inhibitors as next subsequent therapy (which is essentially a type of cross-over) could impact not only the operating characteristics of the TCC endpoint but could potentially confound TSP and even OS.

The pre-planned IA2 may provide an optimal timepoint for a more mature TCC/TSP analysis with less confounded effect compared with the final analysis and is more likely to accurately characterize the treatment benefit. However, the statistical hypothesis testing, as an important tool to help physicians, patients, and scientists to evaluate the treatment benefit, was designed with a low power to detect the treatment benefit of TCC and TSP at the time of IA1 and IA2 because of the current OBF conservative spending function with majority of alpha allocated for the final analysis. This would delay the readout and the accurate assessment of these two clinically relevant endpoints substantially (final analysis is expected in 2Q2024). The Sponsor will maintain the current testing schema, but has CCI CCI . The pre-planned analysis of OS including the alpha spending for OS would remain unchanged from the currently planned OBF for IA2 and the final analysis. . The overall study-wise Type-1 error rate

will still be adequately controlled at the 2-sided level of 0.05 with this revised alpha spending function for TCC/TSP and the original for alpha-spending function for OS. East software will be used to derive the corresponding efficacy boundary for the statistical hypothesis testing procedure for TCC, TSP, and OS at IA2 and the final analysis.

Of note, the timing for IA2 is still driven by OS events as previously planned and is currently projected for 3Q2022.

CCI [redacted]

CCI [redacted]

Table 3b in Section 3.2 shows the updated CCI [redacted] for TCC and TSP for IA2 and the final analysis per comments from FDA.

Amendment 3 (01 October 2021)

The overall reason for SAP amendment #3:

(a) To align with protocol amendment 5 and clarify the testing strategy for secondary endpoints in Cohort 1 after futility was met for Cohort 2: There is no change in the testing for the primary endpoint rPFS in Cohort 1. Had futility not been met in Cohort 2, and if statistical significance for rPFS in Cohort 1 had been reached, the SAP Amendment 2 outlined the subsequent analysis for the combined population of Cohort 1 and Cohort 2 (Intent-to-Treat [ITT] population) using an initial alpha of 0.025 with the remaining 0.025 pre-allocated to secondary endpoints in Cohort 1. Cohort 2 was determined to be futile after 247/600 subjects were randomized using an alternative composite endpoint of either rPFS or time to PSA progression (as shared with the agency on 26 August 2020). Subjects in Cohort 2 (excluding the 14 subjects with CDK12 mutation who were not included in the futility analysis) were unblinded and allowed to continue on AAP with or without niraparib at the discretion of the investigator, and no further subjects were randomized to this cohort. Therefore, the analysis of rPFS in the ITT population (combination of Cohort 1 and 2) and allotment of alpha to that analysis is no longer applicable and the total alpha of 0.05 is now allocated to secondary endpoints for Cohort 1 after testing for the primary endpoint of rPFS for BRCA subgroup and Cohort 1.

To provide an early assessment of treatment benefit on the secondary endpoints with more mature data and to ensure the integrity of the study with respect to longer term outcomes is not compromised, the analysis plan is updated to utilize a group sequential method for testing secondary endpoints (OS, TCC and TSP) in Cohort 1 with 2 interim analyses and final analysis. The updated testing scheme is outlined in SAP amendment 3.

(b) Add a more detailed analysis plan for gene-by-gene efficacy analysis.

(c) Add an analysis plan for COVID-19 related data.

Amendment 2 (07 July 2020)

The overall reason for the SAP amendment is to align with protocol amendment 4:

(a) to update the statistical analysis of the study to allow evaluation of results for all subjects enrolled in the study combined. For the primary endpoint, subjects with breast cancer gene (BRCA)1 or 2 gene alterations (the BRCA subgroup) of Cohort 1 will be analyzed first. If statistical significance is reached in the BRCA subgroup, then subjects with homologous recombination repair (HRR) gene alterations (Cohort 1) will be tested. If statistical significance in Cohort 1 is reached and futility has not been met in Cohort 2, then the combined population of Cohort 1 and Cohort 2 (Intent-to-Treat [ITT] population) will be tested.

(b) to add statistical analysis plan for the newly added FDC cohort (Cohort 3) under the protocol amendment 4. Subjects in Cohort 3 will receive a fixed-dose combination (FDC) tablet formulation of niraparib and abiraterone acetate (AA). The objective is to provide descriptive summary statistics for the clinical efficacy and safety data with the FDC obtained within this ongoing study.

(c) The futility analysis plan in Cohort 2 is updated to exclude the CDK12 patients in this futility analysis and to modify the statistical boundary in futility evaluation.

Amendment 1 (29 October 2019)

The overall reason for the amendment: To update the secondary endpoints of the study per protocol amendment 2; To specify initial type 1 error (alpha) and weight for CCI among the 3 secondary endpoints within the CCI.

Applicable Section(s)	Description of Change(s)
Section 5.1.1.2 Multiplicity Adjustment for Secondary Endpoints in Each Cohort	The CCI for multiplicity adjustment for secondary endpoints was updated based on the secondary endpoints per protocol amendment 2. Initial alpha and weight for recycling were specified.
Section 5.3.1 Definition for secondary endpoints definition Section 5.4.1 Definition for other Analysis	Per protocol amendment 2, time to symptomatic progression with a modified definition is moved from other endpoint category to a secondary endpoint. Time to pain progression with an updated definition was moved from secondary endpoint category to other endpoint category. Time to chronic opioid use endpoint was removed from secondary endpoint category.

ABBREVIATIONS

AAP	abiraterone acetate plus prednisone
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BPI-SF	brief pain inventory-short form
BRCA	breast cancer gene
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EBRT	external beam radiation therapy
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
HRR	homologous recombination 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
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
TBL	total bilirubin
TCC	time to initiation of cytotoxic chemotherapy
TEAE	treatment-emergent adverse event
TSP	time to symptomatic progression
ULN	upper limit of normal
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 64091742PCR3001: A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Subjects with Metastatic Prostate Cancer. The study will begin with niraparib in combination with abiraterone acetate plus prednisone (AAP) for subjects with first line (L1) metastatic castration-resistant prostate cancer (mCRPC; defined as subjects who have not been treated with any therapy in the metastatic castrate-resistant setting, except for androgen deprivation therapy [ADT] and a limited exposure to AAP). 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. Trial Objectives

The overall objectives and endpoints/assessments for Cohort 1 and the BRCA subgroup are provided in Table 1. In accordance with SAP Amendment 2, the pre-planned futility analysis for Cohort 2 was performed and futility was met. Therefore, the combined Cohort 1 and 2 population is no longer applicable and will not be tested.

Table 1: Objectives and Endpoints/Assessments

Objectives	Endpoints/Assessments
Primary	
• To evaluate the effectiveness of niraparib plus AAP compared to AAP plus placebo	• Radiographic progression-free survival (rPFS) by blinded independent central review (BICR).
Secondary	
• To assess the clinical benefit of niraparib plus AAP compared to AAP plus placebo	• Overall survival (OS) • Time to symptomatic progression (TSP) • Time to initiation of cytotoxic chemotherapy (TCC)
• To characterize the pharmacokinetics (PK) of niraparib when given with AAP and abiraterone trough levels	• Observed plasma concentrations of niraparib and abiraterone and estimated population PK and exposure parameters for niraparib
• To characterize the safety profile of niraparib when given with AAP compared to AAP with placebo	• Incidence and severity of AEs • Clinical laboratory test results
Other	
• To evaluate other efficacy assessments and determine the clinical benefit of niraparib plus AAP compared to AAP plus placebo	• Time to PSA progression based on PCWG3 criteria • PFS on first subsequent therapy (PFS2) • Time to pain progression
• To evaluate subject experience with disease-related symptoms • To evaluate overall health-related quality of life • To evaluate subject experience regarding treatment-related symptoms and tolerability	• Patient-reported outcomes (PROs) as assessed by the Brief Pain Inventory-Short Form (BPI-SF), the Functional Assessment of Cancer Therapy-Prostate (FACT-P), the EQ-5D-5L and PRO-CTCAE[a]

Table 1: Objectives and Endpoints/Assessments

Objectives	Endpoints/Assessments
• To characterize the medical resource utilization profile of subjects treated with niraparib plus AAP compared to AAP plus placebo	• Medical resource utilization data associated with medical encounters
• To evaluate relationship between niraparib exposure, efficacy and safety measures, and exploratory response biomarkers	• Parameters describing exposure-response with efficacy (eg, rPFS by BICR), safety (eg, AEs), and response biomarker (eg, PSA) endpoints

AAP=abiraterone acetate plus prednisone; AE=adverse event; PCWG3=Prostate Cancer Working Group 3; PFS=progression-free survival; PRO-CTCAE=patient-reported outcome(s) Common Terminology Criteria for Adverse Events; PSA=prostate-specific antigen

[a] PRO-CTCAE assessments will only be done in the United States and in English.

As Cohort 3 was added to provide descriptive data on the clinical experience of the FDC in subjects with mCRPC and HRR gene alterations, there is no hypothesis for Cohort 3.

1.2. Trial Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of niraparib 200 mg once daily in combination with AA 1,000 mg once daily and prednisone 10 mg daily compared to placebo plus AAP in subjects with metastatic prostate cancer. Subjects will be assigned to two cohorts (with HRR gene alteration - Cohort 1, and with no-HRR gene alteration - Cohort 2) based on their biomarker status, where HRR gene alteration refers to genes involved in homologous recombination repair. Subjects in each cohort will be randomized in a 1:1 ratio to receive either niraparib plus AAP or placebo plus AAP.

The study will consist of 5 phases: a Prescreening Phase for biomarker evaluation only, a Screening Phase, a Treatment Phase, a Follow-up Phase, and an Extension Phase (either Open-label or Long-term, depending on Cohort assignment). The biomarker status for all subjects will be assessed using the sponsor's required assays during the Prescreening Phase. Subjects may also provide a result from a local Clinical Laboratory Improvement Amendments (CLIA)-certified (or equivalent) laboratory demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel. Subjects will be assigned to a cohort based on their biomarker status and stage of disease. A treatment cycle is defined as 28 days. Imaging will be performed at Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, and then every 12 weeks. All subjects will be monitored for safety as documented in the protocol. Treatment will be administered daily and is planned to be continuous until disease progression, unacceptable toxicity, death, or the sponsor terminates the study.

Radiographic progression will be assessed by both investigator and blinded independent central review (BICR).

Under protocol amendment 4, after enrollment into Cohorts 1 and 2 is completed, an open-label cohort (Cohort 3) will be initiated to gain clinical experience with the FDC tablet formulation of niraparib/AA.

1.2.1. Cohort 1: Subjects with Metastatic Castration-resistant Prostate Cancer and HRR Gene Alteration

Cohort 1 will evaluate the combination of niraparib and AAP versus placebo and AAP in subjects with L1 mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AAP as specified in protocol Section 4) and HRR gene alteration. The cohort will enroll approximately 400 subjects with L1 mCRPC and HRR gene alteration (see protocol Section 9.4 for description of biomarkers to be investigated and definition of biomarker-positivity). Randomization within Cohort 1 was stratified by BRCA (BRCA 1 or 2 versus all other HRR gene alteration) status, so an evaluation of the combination of niraparib and AAP vs. placebo and AAP will also be done within the BRCA subgroup. This subgroup is to comprise at least 50% of Cohort 1.

1.2.2. Cohort 2: Subjects with Metastatic Castration-resistant Prostate Cancer and No HRR Gene Alteration

Cohort 2 was planned to evaluate the combination of niraparib and AAP versus placebo and AAP in subjects with L1 mCRPC and who do not have a HRR gene alteration (see protocol Section 9.4 for description of biomarkers to be investigated and definition of biomarker-negativity). The cohort was planned to enroll approximately 600 subjects.

As there was limited information on the efficacy of adding niraparib to AAP in subjects without HRR gene alterations, a futility analysis was performed after approximately 200 subjects were enrolled and approximately 125 composite progression events (PSA progression events or rPFS events, whichever occurred first) had occurred in Cohort 2.

As part of protocol amendment 3 it was confirmed that subjects with CDK 12 alterations would be included in the definition of HRR gene alterations and would be prospectively enrolled to Cohort 1. The futility analysis did not include the 14 subjects with CDK12 alteration who were enrolled to Cohort 2, and PSA or rPFS events from these subjects were not counted as a composite progression event. The prespecified futility analysis for Cohort 2 was performed and reviewed by the IDMC on 13 August 2020 based on the prespecified required number of events for the futility analysis. The futility criteria was met and Cohort 2 was declared futile per IDMC recommendations. The 14 subjects with CDK 12 alterations from Cohort 2 remain blinded and will be included in sensitivity analysis with Cohort 1.

1.2.3. Cohort 3: Subjects with Metastatic Castration-resistant Prostate Cancer Receiving the Fixed-dose Combination of Niraparib+Abiraterone Acetate

To gain experience with the clinical efficacy and safety of the FDC tablet formulation of niraparib plus AA, a separate open-label cohort has been added to the study (Cohort 3) in protocol amendment 4.

Up to approximately 100 subjects with HRR gene alterations (approximately half of whom should have BRCA alterations) may be enrolled into Cohort 3.

Cohort 3 will be enrolled under the same inclusion/exclusion criteria and undergo the same study procedures as Cohort 1, except that subjects in Cohort 3 will receive open-label niraparib/AA FDC tablet formulation plus prednisone instead of as single agents to gain clinical experience with the FDC tablet formulation. Efficacy and safety of Cohort 3 data will be described separately.

1.3. Statistical Hypotheses for Trial Objectives

Niraparib plus AAP will demonstrate improved rPFS compared to placebo plus AAP in subjects with L1 mCRPC and homologous recombination repair (HRR) gene alterations or in subjects with a prespecified subset of HRR gene alterations (BRCA subgroup).

As Cohort 3 was added to provide descriptive data on the clinical experience of the FDC in subjects with mCRPC and HRR gene alterations, there is no hypothesis for Cohort 3.

1.4. Sample Size Justification

Approximately 400 subjects with mCRPC and HRR gene alterations in Cohort 1 will be randomized in a 1:1 ratio to receive niraparib plus AAP or placebo plus AAP. A target subgroup within Cohort 1 will be comprised of subjects with BRCA1 or BRCA2 mutations (BRCA subgroup); this subgroup is expected to be at least 50% of Cohort 1. It is assumed that the primary endpoint of rPFS follows an exponential distribution with a constant hazard rate. It is estimated that approximately 220 rPFS events will be required to provide 87% power in detecting a HR of 0.65 in subjects with mCRPC and HRR gene alterations (median rPFS of 13 months[6] for the placebo plus AAP treatment arm versus 20 months for the niraparib plus AAP treatment arm) at a 2-tailed level of significance of 0.05. With a 21-month accrual period and an additional 7 months of follow-up, the study duration to reach the required number of rPFS events will be approximately 28 months. Assuming approximately 50% of subjects in Cohort 1 belong to the BRCA subgroup, with the planned sample size and study duration, approximately 102 rPFS events are expected to be observed in the BRCA subgroup to provide 93% power to detect a HR of 0.5 (median 13 versus 26 months) at a 2-tailed level of significance of 0.05.

Cohort 2 sample size was planned to be approximately 600 subjects with mCRPC and no HRR gene alteration with randomization in a 1:1 ratio to receive niraparib plus AAP or placebo plus AAP if futility is not met (Section 1.2.2). The pre-planned futility analysis was performed with 247 subjects enrolled (except for the 14 subjects with CDK 12 alterations). Enrollment was stopped as futility was met. Subjects were unblinded (except for the 14 subjects with CDK 12 alterations) and given the opportunity to either continue niraparib and AAP or discontinue niraparib and AAP and receive AAP alone, per PI's discretion based on benefit and risk assessment. Additional efficacy assessments were not performed, and subjects entered a long-term extension.

The study was originally designed with a long-term survival follow-up until approximately CCI deaths would have been observed for the ITT population (combination of Cohort 1 and 2) if futility was not met for Cohort 2. Assuming a median survival of CC months for the placebo and AAP arm, the study duration to observe CCI deaths would have been approximately CC months, at which time CCI deaths (assuming HR=CCI) would be expected in Cohort 1. Given the outcome of the

futility analysis for Cohort 2, the analysis of Cohort 1 will proceed as planned. The OS data from Cohort 1 will be analyzed at 2 pre-planned interim analyses and a final analysis, which will occur when approximately CCI, CCI and CCI death events are observed respectively.

Approximately 100 subjects with HRR gene alterations will be enrolled into Cohort 3, 50% of whom should have BRCA alterations.

1.5. Randomization and Blinding

1.5.1. Randomization

For Cohorts 1 and 2, subjects 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 in combination with AAP or matching placebo and AAP using permuted block randomization. Subjects will be stratified by past taxane-based chemotherapy exposure (yes versus no), past AR-targeted therapy exposure (enzalutamide or apalutamide versus no exposure) in mHSPC or nmCRPC, and prior AAP use (yes versus no) in mCRPC. In addition, for Cohort 1, stratification by gene mutation group (ie, BRCA1 or BRCA2 versus all other HRR gene alteration) will also be performed. Randomization will take place across all study sites using a centralized Interactive Web Response System (IWRS).

Cohort 3 is open label, which will begin enrollment after Cohort 1 and Cohort 2 enrollment has completed. Randomization is not applicable.

1.5.2. Blinding

Cohort 1 is conducted in double-blind fashion. All subjects, investigator personnel, and study team members associated with the study conduct are to remain blinded to treatment arm assignment until completion of the study, or the IDMC recommendation for unblinding is accepted by the sponsor, or the sponsor decides to unblind after the primary endpoint analysis is completed.

Cohort 2 was conducted in a double-blind fashion. The pre-planned futility analysis was performed on 13 August 2020. Per IDMC recommendation this cohort was declared futile and was unblinded on 03 September 2020 (except for subjects with CDK12 alterations as described in Section 3.1). Communications regarding unblinding of Cohort 2 except for subjects with CDK 12 alterations were sent to HAs.

Cohort 3 is open label, although the independent central imaging reviewers remain blinded to which cohort the subjects are assigned.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, rules might be applied to assign actual visits to analysis visits. These rules will be defined upon further assessment of study data.

2.2. Pooling Algorithm

2.2.1. Pooling Algorithm for Stratification Factors

The stratification factors to be used in the analysis are as follows: past taxane-based chemotherapy exposure (yes versus no), past AR-targeted therapy exposure (enzalutamide or apalutamide versus no exposure) in mHSPC or nmCRPC, and prior AAP use (yes versus no) in mCRPC , and in addition for Cohort 1 gene mutation group (ie, BRCA1 or BRCA2 versus all other HRR gene alteration). For time-to-event related analysis, if any stratum has less than 10 corresponding events for any treatment arm, then the subjects will be pooled together by dropping stratification factors until there are at least 10 events in each stratum for each treatment arm.

2.3. Analysis Sets

2.3.1. Randomized Analysis Set for Cohort 1

Randomized subjects in Cohort 1 will be used for efficacy analysis for Cohort 1. The 14 CDK12 subjects from Cohort 2 remained blinded and will be included in a sensitivity analysis with Cohort 1 on primary and secondary endpoints (please see Section 1.2.2 for details).

2.3.2. Safety Analysis Set

The safety analysis set for Cohort 1 includes all randomized subjects who received at least 1 dose of study medication in Cohort 1. The safety analysis set for Cohort 2 includes all randomized subjects who received at least 1 dose of study medication in Cohort 2 It will be used for evaluating safety and treatment compliance.

2.3.3. FDC Analysis Set

All subjects who signed informed consent form and were enrolled in Cohort 3 will be used for baseline, demographic and efficacy data analysis.

All subjects who received at least 1 dose of study medication in Cohort 3 will be evaluated for safety.

2.4. Definition of Subgroups in Cohort 1 and the BRCA Subgroup

Subgroup analyses will be performed as appropriate to evaluate the consistency of treatment benefit for the selected efficacy endpoints in the BRCA subgroup within Cohort 1 and in Cohort 1 as a whole. Table 2 provides the categorical variables that will be used for subgroup analysis whenever appropriate. In addition, subgroup analysis of selected countries will be performed for regional regulatory filling purpose.

Table 2: Categorical Variables for Subgroup Analysis

Subgroup	Definition of Group	Applicable population	Analysis Type
Age	Age <65 years, ≥65 to <75 years, ≥75 years	BRCA subgroup, and Cohort 1	E, S
Race[a]	White, not white	BRCA subgroup, and Cohort 1	E, S
Baseline ECOG performance status	0, 1	BRCA subgroup, and Cohort 1	E
Baseline Brief Pain Inventory-Short Form (BPI-SF) Question 3 (worst pain in the last 24 hours) score	0, 1 to 3, >3	BRCA subgroup, and Cohort 1	E
Region	North America and South America, Europe, Asia-Pacific	BRCA subgroup, and Cohort 1	E, S
Past taxane-based chemotherapy exposure	Yes, no	BRCA subgroup, and Cohort 1	E
Past AR-targeted therapy exposure (enzalutamide or apalutamide or darolutamide)	Yes, no	BRCA subgroup, and Cohort 1	E
Prior AAP use	Yes, no	BRCA subgroup, and Cohort 1	E
Presence of visceral metastases	Yes, no	BRCA subgroup, and Cohort 1	E
Bone metastasis only at entry	Yes, no	BRCA subgroup, and Cohort 1	E
Number of bone lesions at baseline	≤10, >10	BRCA subgroup, and Cohort 1	E
Baseline PSA above median	Yes, no	BRCA subgroup, and Cohort 1	E
BRCA status	BRCA, non-BRCA	Cohort 1	E
Gene mutation type	individual gene alternation	Cohort 1	E

AAP=abiraterone acetate plus prednisone; AR=androgen receptor; BRCA=breast cancer gene; E= efficacy; ECOG=Eastern Cooperative Oncology Group; S= Safety
a: Race categories will be expanded to white, black, Asian, and other if sufficient numbers of black and Asian subjects are randomized.
Note: Analyses will be performed for each subgroup as appropriate.

2.5. 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 subjects. 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 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 Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'.

2.6. Baseline

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

2.7. 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:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the Day 1
  - The day of Day 1, if the month/year of the onset of AE is the same as month/year of the Day 1 and month/year of the AE resolution date is different
  - The day of Day 1 or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the Day 1 and month/year of the AE resolution date are same
- 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
  - Month and day of the Day 1, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the Day 1,
  - The AE resolution date.
- Completely missing 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.

3. INTERIM ANALYSIS AND INDEPENDENT DATA MONITORING COMMITTEE REVIEW

3.1. Futility Analysis for Cohort 2 (no HRR gene alteration)

A non-binding futility analysis was planned for Cohort 2 for a go/no-go decision after approximately 200 subjects were enrolled and followed for approximately 8 months in the no HRR gene alteration cohort. Enrollment in this cohort was halted after these subjects had been enrolled. The futility analysis was performed after approximately 125 composite progression events (PSA progression events or rPFS by BICR events, whichever occurred first) had been observed with 247

subjects enrolled. Under protocol amendment 3 (issued on 12 February 2020) prior to the futility analysis for Cohort 2, new subjects with a CDK12 alteration were from then onwards enrolled into Cohort 1 and will be included in the Cohort 1 analysis. Subjects with a CDK12 alteration previously enrolled into Cohort 2 were excluded from the futility analysis and will be included in sensitivity analysis for Cohort 1 (see Section 5.2.3and 5.3.2).

The quantitative decision criterion for evaluating futility was derived based on the estimated hazard ratio (HR) using the composite progression events through Cox proportional-hazard model. The Cohort 2 would be considered futile if the observed HR for time to composite progression events is greater than or equal to 1. Note the statistical criterion is non-binding.

After completion of the Cohort 2 futility analysis on 13 August 2020, showing the pre-specified criteria for futility was met, the IDMC recommended that "therapy/registration for this cohort of subjects may be discontinued". The decision was made by Sponsor committee to stop enrollment into Cohort 2 and to unblind the cohort, except for the 14 CDK12 subjects who remain blinded. These 14 subjects will be included with Cohort 1 for sensitivity analysis on primary and secondary endpoints.

3.2. Interim Analysis for Secondary Endpoints for Cohort 1

There are no interim analyses for the primary endpoint rPFS in this study. Two interim analyses and one final analysis for the secondary endpoints (TSP, TCC and OS in Cohort 1) are planned according to the time when approximately CCI, CCI and CCI OS events are observed respectively. The first interim analysis (IA1) was performed at the time of rPFS final analysis for Cohort 1 on 02Nov2021. Analyses of TCC and TSP were to be performed at the same time as OS at IA1, IA2 and FA unless they have been declared significant at a previous analysis. The O'Brien-Fleming (OBF) boundaries as implemented by the Lan-DeMets alpha spending method will be utilized for OS (refer to table 3a), and interim boundary cut-offs will be calculated using the information fraction for OS endpoint. As the study has met the primary endpoint of rPFS by BICR, the secondary endpoints were also tested at the time of IA1 with an alpha of 0.0001 for TCC and TSP separately based on OBF boundaries. An updated alpha spending function will be implemented for TCC and TSP at the IA2 (refer to table 3b). CCI East software (Cytel Inc., 2020)[7] will be used to determine the corresponding efficacy boundary for TCC and TSP. An CCI will be utilized among the three endpoints at IA2 and final analysis. The overall family-wise Type-1 error will be controlled at 0.05. The details of the testing procedure for controlling family-wise type I error are described in Section 5.1.1.1.

The operating characteristics of the OS analyses based on maximum overall alpha of 0.05 (2-sided) are provided in Table 3a.

Table 3a: Operating Characteristics of OS Analysis with a Maximum Overall Alpha=0.05*

	IA1	IA2	FA
Number of OS events expected	CCI	CCI	CCI
Significance level (2-sided)	CCI	CCI	CCI
HR boundary for significance	CCI	CCI	CCI

* If the overall alpha is less than 0.05 (see Section 5.1.1.1for details), cumulative alpha spent at each IA and the final analysis will be reduced proportionally, and the HR boundary will be adjusted accordingly

FA=final analysis; HR=hazard ratio; IA=interim analysis; OS=overall survival.

Table 3b: Operating Characteristics for OS, TCC and TSP Analysis with Planned CCI [redacted]

Endpoint	Alpha Level Available [a]	Significance Level (2-sided) at Each IAs and FA		
		IA1	IA2	FA
OS[b]	CCI [redacted]			
TCC				
TSP				

FA=final analysis; IA=interim analysis; TCC= time to the initiation of cytotoxic chemotherapy; TSP= time to symptomatic progression; OS=overall survival.
[a] Except for the initially assigned alpha, all other alphas are conditional on the outcomes of other endpoint tests from the multiplicity control.
[b] Significant levels at IA1, IA2 and FA for OS with full alpha of 0.05 refer to table 3a.

3.3. Independent Data Monitoring Committee

An IDMC will be commissioned to monitor data on an ongoing basis to ensure the continuing safety of the subjects 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, except for the final primary rPFS analysis where the Sponsor will provide the study data to the IDMC directly. Complete details regarding the composition and governance of the IDMC will be outlined in the IDMC Charter.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment arm and overall for Cohort 1 and Cohort 2 separately. Cohort 3 will be summarized separately as well. In addition, the distribution of subjects by region, country, and site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 4 presents a list of the demographic and baseline characteristics variables that will be summarized by treatment arm and overall.

Table 4: Demographic and Baseline Characteristics Variables

Continuous Variables:	**Summary Type**
• Age (years) • Weight (kg), Height (cm) • Baseline PSA, hemoglobin, lactate dehydrogenase, alkaline phosphatase, testosterone value • Baseline pain score (BPI-SF Item 3) • Time from initial diagnosis to randomization date	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum])
Categorical Variables	
• Age <65 years, ≥65 to <75 years, ≥75 years) • Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Multiple) • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Baseline ECOG performance status (0, 1) • Tumor stage at diagnosis, Lymph node stage at diagnosis, Metastasis stage at diagnosis • Gleason score at diagnosis • Extent of disease • Baseline pain score (BPI-SF Item 3) (0, 1 to 3, >3)	Frequency distribution with the number and percentage of subjects in each category

BPI-SF=brief pain inventory-short form; ECOG=Eastern Cooperative Oncology Group; PSA=prostate-specific antigen

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

4.2. Disposition Information

The number of subjects randomized, the number of subjects receiving study treatment, the number of subjects with treatment ongoing, and the number of subjects 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 subjects ongoing and discontinued the study as well as the reasons for study discontinuation (including COVID-19) will be summarized.

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

4.3. Treatment Compliance

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

Study medication compliance (%) = (actual number of tablets/capsules taken/total number of tablets supposed to be taken) x100.

4.4. Extent of Exposure

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

4.5. Protocol Deviations

Protocol deviations will be summarized by treatment group. Protocol deviations will be reviewed to assess based on protocol deviation guidance 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 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

Number and percentage of COVID-19 related deviations will be summarized.

4.6. 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 continue on after the first dose of study medication through 30 days after the last dose.

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

4.7. Subsequent Anti-cancer Therapies

Subsequent anti-cancer therapies received after discontinuation of study treatment 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.

c. 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.

5. EFFICACY

Efficacy analysis will begin by testing rPFS in the BRCA subgroup of Cohort 1 using a 2-sided alpha level of 0.05. If significance is met in the BRCA subgroup, then rPFS in all of Cohort 1 will be tested, also at a 2-sided alpha level of 0.05. If rPFS in Cohort 1 is significant, then the secondary endpoints will be tested using a group sequential method with 2 interim analyses and the final analysis. The analyses in the ITT population, inclusive of Cohort 1 and Cohort 2, that were to be performed if the futility was not met in Cohort 2 alone (outlined in the SAP Amendment 2), are no longer valid since futility was met in Cohort 2, and subsequently the analyses in the ITT population are removed from all formal statistical assessment for efficacy. The remainder of the SAP is pertinent to Cohort 1 analysis only and the order of testing is depicted in CCI below.

5.1. Analysis Specifications

One analysis is planned for rPFS in the BRCA subgroup and in Cohort 1 as a whole. The rPFS analysis will take place when approximately 102 and 220 rPFS events are observed in the BRCA subgroup and Cohort 1, respectively.

5.1.1. Level of Significance

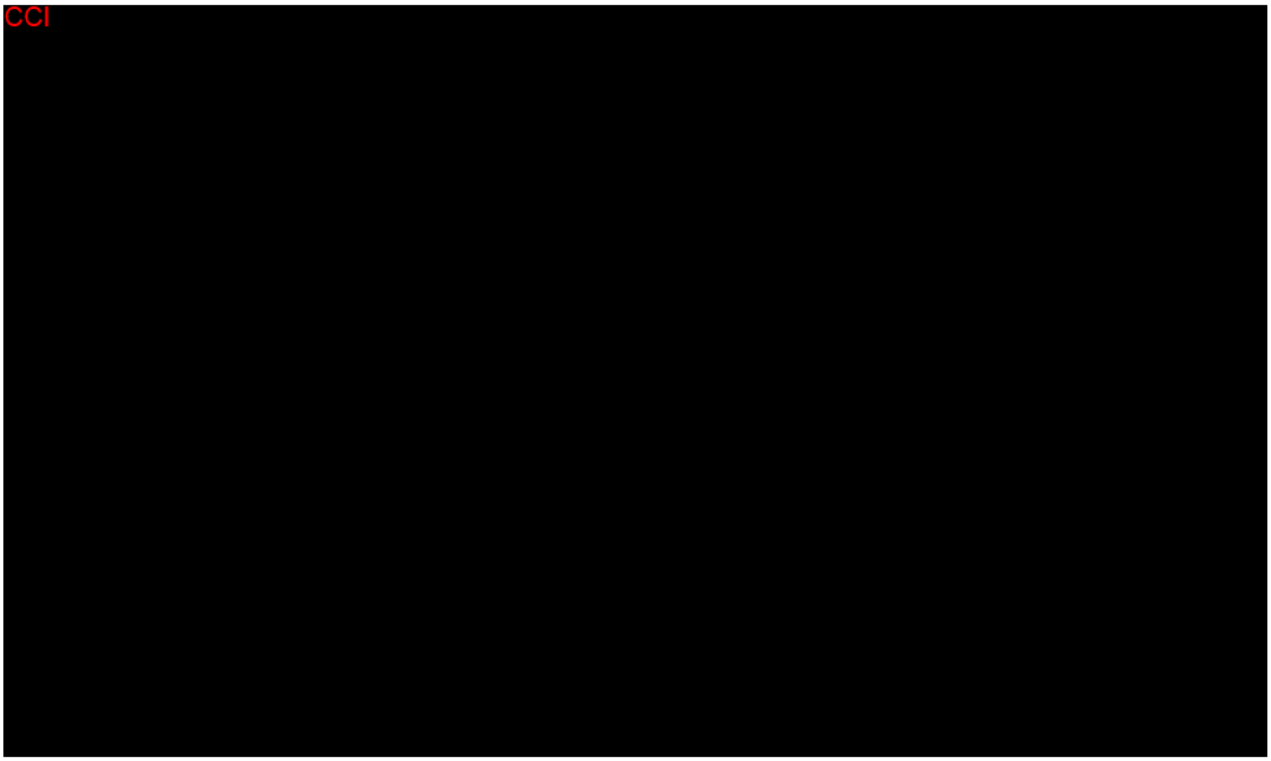
All tests will be conducted at a 2-sided alpha level of 0.05 and 95% confidence intervals (CIs) will be provided, unless stated otherwise.

5.1.1.1. Multiplicity Adjustment for Testing of Primary and Key Secondary Endpoints

To preserve an overall family-wise type I error rate at the 2-sided 0.05 level, the multiple comparison testing procedure in a group sequential design CCI will be applied [2]. The procedure can account for both sources of testing multiplicity: multiple tests (e.g. across primary and secondary endpoints) and multiple analyses (e.g. two interim and final analyses for secondary endpoints).

There are two key components that specify this approach for the repeated testing of multiple hypotheses: (i) testing algorithm for multiple hypotheses CCI (ii) repeated testing of a hypothesis CCI.

CCI defines the CCI where the hypotheses of interest are represented by the nodes. Nodes' weights (written inside nodes) correspond to the local significance levels assigned to the hypotheses. The initial weight for the rPFS in BRCA is 1, and the nodes corresponding to rPFS in Cohort 1 and secondary endpoints have zero initial weights. Also, a given CCI written to the directed edge on the graph, specifies the fraction of the local significance level transferred from the initial node to the connected by the edge terminal node, if the null hypothesis corresponding to the initial node is successfully rejected.



Specifically, the overall approach for this testing scheme is to test rPFS in the BRCA subgroup of Cohort 1 first at alpha=0.05 (2-sided). If this meets statistical significance, then the unspent alpha (0.05) will be passed to rPFS in Cohort 1 for testing. If rPFS in Cohort 1 shows statistical significance at alpha=0.05 (2-sided), then the unspent alpha (0.05) will be passed to the secondary endpoints, TCC, TSP and OS in Cohort 1 for testing.

Two interim analyses and one final analysis for the secondary endpoints (TSP, TCC and OS in Cohort 1) are planned as defined in Section 3.2. CCI will be utilized among the three endpoints at each IA and final analysis per the CCI as presented in CCI This means that if an endpoint reaches significance at its local alpha level then its alpha weight can be re-allocated to other endpoints according to CCI An actual z-value boundary for each endpoint will be calculated according to alpha weight available to that endpoint and the corresponding information fraction at a given analysis (interim or final). If the null hypothesis for an endpoint is rejected at any interim analysis, it will remain being rejected and will not be re-tested at any subsequent time points.

5.1.2. Data Handling Rules

In general, no imputation method is planned for handling missing or incomplete data unless specified otherwise for a specific endpoint. Data for which quality issues may have been detected will be excluded, when deemed necessary, from the sensitivity analysis for efficacy and safety.

5.1.3. General Analysis Considerations

All continuous variables will be summarized using number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum. Discrete variables will be summarized with number and percent. 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 2.2.1.

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary endpoint rPFS by BICR is defined as the time interval from the date of randomization to the first date of radiographic progression as assessed by BICR or death due to any cause, whichever occurs first. Radiographic progression is determined by 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), both assessed by BICR.

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. Subject whose Week 8 scan is observed to have ≥2 new bone lesions would fall into one of the 2 categories below:
    a. Subject 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. Subject 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 subject 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.

Subjects without radiographic progression or death will be censored at the last disease assessment date if they never start subsequent anti-cancer therapy or censored at the last disease assessment date prior to the start of the subsequent anti-cancer therapy if they started subsequent anti-cancer therapy. Key censoring rules are summarized below.

Scenario	Censoring Rule
No disease assessment at baseline or No disease assessment after baseline	Censored on the date of randomization
Subjects who are lost to follow-up or withdraw from study	Censored on the date of the last disease assessment
Subjects who receive new systemic anti-cancer therapy known or intended for the treatment of mCRPC 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
Subjects with no evidence of radiographic progressive disease or death	Censored on the date of the last disease assessment
Subjects who miss ≥2 consecutive planned radiographic scans or has ≥2 consecutive unevaluable scans before progression or death	Censored on the date of the last disease assessment before the missed/unevaluable scans
No postbaseline assessment and death occurred after missed 2 or more planned disease assessments	Censored on the date of randomization

5.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in this study, is defined by the following four components [5]:

- Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval.
- Variable: rPFS by BICR.
- Intercurrent event: use of subsequent anti-cancer therapy, missing ≥2 planned disease assessment visits.
- Population-level summary: hazard ratio, median rPFS by BICR and its 95% CI, rPFS by BICR rates at selected time points for each treatment group.

5.2.3. Analysis Methods

rPFS will be tested using stratified log-rank test at the overall 2-tailed 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 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 group. Sensitivity analysis such as piecewise constant hazards model may be performed as appropriate.

Sensitivity analysis such as piecewise constant hazards model may be performed as appropriate if the assumption of constant hazards is violated.

To assess the consistency of treatment benefit across important subgroups, forest plots will be provided for subgroups as defined in Section 2.4. 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 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. other countries)
- Gleason score (<=7 vs. >7)
- BRCA status (BRCA vs. non-BRCA)
- Prior taxane-based chemotherapy use (yes vs. no)
- Past AR-targeted therapy exposure (enzalutamide or apalutamide vs. no exposure)
- Prior AAP use (yes vs. no)

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.

Sensitivity analysis will be performed by adding the 14 subjects with CDK12 alterations from Cohort 2 to Cohort 1 for rPFS by BICR.

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

In addition, sensitivity analysis using investigator assessed radiographic progression will also be performed. The concordance rate between the BICR-determined rPFS and investigator-determined rPFS will be evaluated.

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

Missingness of 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.

5.3. Secondary Efficacy Endpoints

5.3.1. Definition

The secondary efficacy endpoints are:

- OS: defined as the time from date of randomization to date of death from any cause. Subjects alive at time of analysis will be censored on the last date the subject was known to be alive.
- Time to symptomatic progression is defined as the need to initiate/record any of the following:
  - The use of EBRT for skeletal symptoms
  - The need for tumor-related orthopedic surgical intervention
  - Other cancer-related procedures (for example: nephrostomy insertion, bladder catheter insertion, EBRT, or surgery for tumor symptoms other than skeletal)
  - Cancer-related morbid events (for example: fracture [symptomatic and/or pathologic, cord compression, urinary obstructive events)
  - Initiation of a new systemic anti-cancer therapy because of cancer pain.

  If no event was observed, subject will be censored at last known date without event
- Time to initiation of cytotoxic chemotherapy: defined as the time from 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 last known date.

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

5.3.2. 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 5.1.1.1. 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 a 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 estimated through the Clayton copula, which takes censoring into account.

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

- Forest plots will be provided for subgroups as defined in Section 2.4. 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 subjects receive subsequent therapies.
- In the event that a large number of subjects 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 and Tsiatis[6]
    - Inverse Probability Censoring Weighted (IPCW) log-rank test as described by Cole and Hernan[3]
    - Iterative Parameter Estimate (IPE) method as described by Branson and Whitehead[1]
- Sensitivity analysis will be performed by adding the 14 CDK12 + subjects from Cohort 2 to Cohort 1 to evaluate all secondary endpoints.
- Sensitivity analysis for OS will be performed by censoring the death due to COVID-19.

5.4. Other Efficacy Variables

5.4.1. Definition

Other efficacy endpoints are defined in following table.

Endpoint	Description	Analysis Population
Time-to-pain progression	Time-to-pain progression: defined as the time from date of randomization to the date of the first observation of pain progression. Pain progression is defined as an average increase by 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive evaluations ≥3 weeks apart. Subjects with no pain progression at the time of analysis will be censored at last date of BPI-SF pain score collection.	BRCA /non-BRCA subgroup, Cohort 1
Time to initiation of subsequent therapy	Time to initiation of subsequent therapy is defined as the time from the date of randomization to the date of initiation of subsequent anticancer therapy for prostate cancer. Subjects who did not initiate subsequent anticancer therapy at the time of the analysis will be censored on last visit date prior to or on last known alive date. Subsequent anticancer therapy for prostate cancer will include categories of chemotherapy, hormone therapy, PARPi and any other kind of therapy for prostate cancer.	Subjects with measurable disease at baseline in BRCA/non-BRCA subgroup, Cohort 1
Objective response rate	Objective response rate (ORR) is defined as the proportion of subjects with measurable disease whose best response is either complete response (CR) or partial response (PR) by BICR as defined by RECIST 1.1 with no evidence of bone progression according to the PCWG3 criteria.	Subjects with measurable disease at baseline in BRCA /non-BRCA subgroup, Cohort 1
Duration of response	Duration of response in subjects with measurable disease (based on modified RECIST 1.1) is defined from the time of documented response to the first date of documented disease progression. This endpoint considers only the subjects 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 post baseline and before PD identified by RECIST. 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	Subjects with CR or PR in BRCA/non-BRCA subgroup, Cohort 1

	response will be linked to the latest scan date for the visit. Definition of PD and rule for censoring are the same as that for the rPFS by BICR	
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. There will be a PSA progression when after decline from baseline: PSA increase ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend); And when no decline from baseline: PSA increase ≥25% and ≥ 2 ng/mL from baseline beyond 12 weeks. Subjects with no PSA progression at the time of analysis will be censored on the last known date with no progression. Subjects without a baseline PSA or without any post baseline values will be censored at randomization date.	BRCA /non-BRCA subgroup, Cohort 1
PSA response rate	Proportion of subjects achieving a PSA decline of ≥50% and confirmed at 3-4 weeks later according to PCWG3 criteria by Week 12 and during treatment period Waterfall plot will be presented for PSA maximum change from baseline (rise or fall) at any time.	BRCA /non-BRCA subgroup, Cohort 1
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. General rules for PFS2 event and censoring: 1. For subjects who initiated a subsequent anti-cancer therapy: 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. 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 subject will be censored at start date of 2nd subsequent anti-cancer therapy - 1 day. c. If no disease progression on 1st subsequent anti-cancer therapy and no death and no start of 2nd	BRCA /non-BRCA subgroup, Cohort 1

subsequent anti-cancer therapy, this is not a PFS2 event, the subject will be censored at last known alive date.

2. For subjects who did not receive any subsequent anti-cancer therapy:
   a. If a subject died, this is a PFS2 event with death date as date of PFS2.

   b. If a subject did not die, this is not a PFS2 event, the subject will be censored at last known alive date.

5.4.2. Analysis Methods

Estimates of the time-to-event endpoints will be obtained using the Kaplan-Meier estimates of the survival distributions and a stratified Cox model will be used to obtain the HR along with the associated 95% confidence intervals. 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 descriptive statistics (count and percentage) by the treatment group. The relative risk will be reported along with the corresponding two-sided 95% CI. The two treatment groups 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.

5.5. Efficacy Analysis by HRR Genes

HRR individual gene alterations that are included in HRR Cohort:

HRR Genes	Definition
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
CDK12	Cyclin-Dependent Kinase 12
FANCA	Fanconi Anemia Complementation Group A gene
PALB2	Partner and Localizer of BRCA2 gene
CHEK2	Checkpoint Kinase 2 gene
BRIP1	BRCA1 Interacting Protein C-terminal Helicase 1 gene
HDAC2	Histone Deacetylase 2 gene
ATM	Ataxia Telangiectasia Mutated gene

Frequency of gene alterations will be summarized by treatment group.

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

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

In addition, sensitivity analysis on primary and secondary endpoints for the following 3 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. Subjects with single ATM gene alteration or single CDK12 gene alteration (including the 14 subjects with CDK12 gene alteration from Cohort 2) or ATM/CDK12 co-occurring gene alterations.
3. Subjects with non-BRCA gene alterations minus subjects in group 2.

6. SAFETY

Safety data will be analyzed using the Safety Analysis Set. Safety data from Cohort 1 and Cohort 2 will be presented separately.

6.1. 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 AE occurring at or after the initial administration of study medication through the day of last dose plus 30 days is considered to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study medication based on partial onset date or resolution date. All reported treatment-emergent AEs will be included in the analysis. For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment arm.

For each treatment group, AE incidence rates will be summarized with frequency and percentage by SOC and preferred term, with all subjects treated in that treatment group 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. Subjects with multiple occurrences of events will only be counted once at the maximum severity to study medication 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 subjects 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, related AE leading to treatment discontinuation, AE leading to death, related AE leading to death, and all deaths within 30 days of last dose
- All AEs by SOC and preferred term (for all AEs and for most frequent AEs [reported in $\geq$ 5% of subjects])
- All AEs by SOC, preferred term, and toxicity grade
- Serious 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 Grade 3 and 4 AEs and for Grades 3 and 4 most frequent AEs [reported ≥ 1% of subjects])
- AEs leading 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 AAP include following categories:

Anemia
Hypertension (including hypertensive crisis)
Posterior Reversible Encephalopathy Syndrome (PRES)
Neutropenia
Thrombocytopenia
Myelodysplastic syndrome
Acute myeloid leukemia
Hypokalemia
Fluid retention/edema
Hepatotoxicity
Osteoporosis (including Osteoporosis-related fracture)
Rhabdomyolysis/myopathy
Allergic alveolitis
CYP2D/CYP2C8 drug interactions and food effect
Major adverse cardiovascular events (MACE): Ischemic heart disease including MI, Cardiac failure, Arrhythmias and Cerebrovascular accidents.

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

Subjects who reported COVID-19 infection during the study will be summarized and listed as well.

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

1. Subjects who died within 30 days of the last dose of study drug
2. Subjects who had a serious treatment-emergent adverse event
3. Grade 3 or higher treatment-emergent adverse events of special interest
4. Subjects who discontinued study drug due to treatment-emergent adverse events

6.2. Death

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

- Number of subjects who died
- Cause of death

A listing of subjects who died will be provided.

6.3. Clinical Laboratory Tests

Only data collected by the central laboratory will be summarized if local labs collected on the same date.

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 subject during the study treatment will be provided as shift tables.

Subjects 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. 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 1st bilirubin >=2x ULN.

6.4. Vital Signs and Physical Examination Findings

Baseline vital signs (blood pressure (systolic and diastolic) and heart rate) will be summarized by treatment group. Only blood pressure and heart rate are reported during the treatment phase. Subjects with markedly 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

Abnormal findings in physical examination will be recorded and summarized as AEs.

6.5. Other Safety Parameters

6.5.1. ECOG Performance Status

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

7. ANALYSIS OF COHORT 3 (FDC)

The goal of Cohort 3 is to describe the clinical experience with the FDC formulation. Descriptive statistics for key endpoints (such as rPFS, TSP, TCC, and OS) along with safety data will be summarized.

8. PHARMACOKINETICS/PHARMACODYNAMICS

8.1. Pharmacokinetics

PK analyses will be conducted and reported separately.

Plasma concentrations for niraparib, M1 and abiraterone 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 subject 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 subjects with available plasma concentrations. Subjects 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 subjects 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).

8.2. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between niraparib measures of exposure (e.g. derived AUC or trough concentrations) and key efficacy (e.g. rPFS by BICR) 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.

9. BIOMARKER

The concordance of HRR gene alteration between tumor tissue DNA and plasma ctDNA will be evaluated.

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 baseline biomarker expression levels with clinical response or relevant time to-event endpoints will be performed to identify responsive (or resistant) subgroups. A separate biomarker statistical analysis plan will be provided for exploratory biomarker evaluations including estimates of concordance and relationship of biomarker subgroups and time to event endpoints and will be reported separately.

10. PATIENT REPORTED OUTCOME

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

11. 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.

REFERENCES

1. Branson M and Whitehead J. Estimating a treatment effect in survival studies in which patients switch treatment. Statistical Medicine 2002; 21, 2449-2463.
2. Willi Maurer and Frank Bretz. Multiple Testing in Group Sequential Trials Using Graphical Approaches. Journal Statistics in Biopharmaceutical Research, 2013, Vol. 5, No. 4.
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. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138-148.
7. East 6 (2020). Statistical software for the design, simulation and monitoring clinical trials. Cytel Inc., Cambridge MA