Janssen Research & Development *

Statistical Analysis Plan

A Phase 2 Efficacy and Safety Study of Niraparib in Men with Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies

Protocol 64091742PCR2001; Phase 2

JNJ-64091742 (Niraparib)

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Status:	Approved
Date:	22 February 2021
Prepared by:	Janssen Research & Development, LLC

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

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ABBREVIATIONS

AE	adverse event
AR	androgen receptor
ANCOVA	analysis of covariance
BCF	biochemical failure
BICR	blinded independent central review
CI	confidence interval
CRF	case report form
CRPC	castration-resistant prostate cancer
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
IDMC	Independent Data Monitoring Committee
RT	external-beam radiation therapy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EPIC	Prostate Index Composite
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
GnRH	gonadotropin releasing hormone
HR	hazard ratio
ICH	International Conference on Harmonization
IHC	immunohistochemistry
ITT	Intent-to-Treat
IWRS	interactive web response system
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
MRU	medical resource utilization
OS	overall survival
PD	pharmacodynamic
PK	pharmacokinetic(s)
PRO	patient reported outcome
PSA	prostate specific antigen
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class

1. INTRODUCTION

This statistical analysis plan (SAP) describes the definitions of analysis sets, derived variables, and statistical methods for all planned statistical analyses for protocol 64091742PCR2001. The SAP is intended to supplement the study protocol. Any deviations from this SAP will be described in the clinical study report (CSR).

1.1. Trial Objectives

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

Table 1: Study Objectives and Endpoints/Assessments

Objectives	Endpoints/Assessments
Primary	
• To assess the efficacy of niraparib in subjects with measurable mCRPC and BRCA mutation	• Objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with no evidence of bone progression according to the PCWG3 criteria
Secondary	
• To assess the efficacy of niraparib in subjects with measurable mCRPC and non-BRCA mutation	• ORR of soft tissue (visceral or nodal disease) as defined by RECIST 1.1 with no evidence of bone progression according to the PCWG3 criteria
• To assess the efficacy of niraparib in subjects with mCRPC and DNA-repair anomalies	• CTC response defined as CTC=0 per 7.5 mL blood at 8 weeks post-baseline in subjects with baseline CTC >0
• To evaluate response outcomes of niraparib in subjects with mCRPC and DNA-repair anomalies (BRCA, non-BRCA)	• OS: time from enrollment to death from any cause • As defined by PCWG3 – rPFS: time from enrollment to radiographic progression or death from any cause, whichever occurs first – Time to radiographic progression – Time to PSA progression – Time to symptomatic skeletal event (SSE)
• To evaluate the safety and tolerability of niraparib	• Incidence of adverse events • Clinical laboratory test results
• To evaluate duration of tumor response (BRCA, non-BRCA)	• Duration of objective response: time from complete response (CR) or partial response (PR) to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurs first
Exploratory	
• To assess the efficacy of niraparib in subjects with mCRPC and DNA-repair anomalies	• Composite Response rate (CRR), where composite response is defined as 1 of the following by PCWG3: – Objective response (as defined by RECIST 1.1), or – Conversion of CTC from ≥5 cells per 7.5 mL blood at baseline to <5 cells per 7.5 mL blood nadir, confirmed by a second consecutive value obtained 4 or more weeks later, or

Objectives	Endpoints/Assessments
	– PSA decline of ≥50% from baseline, measured twice 3 to 4 weeks apart • Time to unequivocal clinical progression (defined in section 5.4.1)
• To evaluate the population PK of niraparib and exposure-response relationships	• Analysis of niraparib oral clearance (CL/F), oral volume of distribution (V/F), and derived measures of exposure (e.g., area under the curve [AUC]) • Effect of demographic and physio-pathological covariates on niraparib PK parameters • Analysis of relationships between exposure and safety or efficacy endpoints.
• To evaluate the steady-state PK of niraparib and its metabolite M1	• C_{max}, T_{max}, C_{trough}, AUC_{0-24} of niraparib and its metabolite M1 in a subset of subjects
• To evaluate the concordance between tissue-based and blood-based methodologies for detection of genomic alterations	• Comparison of gene alterations in DNA from tissue and in circulating tumor DNA (ctDNA) from plasma
• To evaluate potential DNA and RNA biomarkers predictive of response and resistance	• Changes in the levels or types of DNA and RNA biomarkers observed over time
• To evaluate the effect of niraparib on circulating tumor cells (CTCs)	• Changes in CTC counts observed over time
• To evaluate subject-relevant experiences (disease-related symptoms, treatment-related symptoms, and health-related quality of life)	• Assessment of subject-relevant experience data including BPI-SF, FACT-P and EQ-5D-5L • Time to deterioration in subject-relevant experiences

Abbreviations: ATM=Ataxia Telangiectasia Mutated gene; AUC=area under the curve; BRCA1=Breast Cancer gene 1; BRCA2= Breast Cancer gene 2; BRIP1=BRCA1 Interacting Protein C-terminal Helicase 1 gene; CHEK2=Checkpoint Kinase 2 gene; CR=complete response; CTC=circulating tumor cell; ctDNA=circulating tumor DNA; DNA=deoxyribonucleic acid; FANCA=Fanconi Anemia Complementation Group A gene; HDAC2=Histone Deacetylase 2 gene; mCRPC=metastatic castration-resistant prostate cancer; ORR=objective response rate; OS=overall survival; PALB2=Partner and Localizer of BRCA2 gene; PCWG3=Prostate Cancer Working Group 3; PD=progressive disease; PK=pharmacokinetics; PR=partial response; PSA=prostate specific antigen; RECIST= Response Evaluation Criteria in Solid Tumors; rPFS=radiographic progression-free survival; RNA=ribonucleic acid; RR=response rate; SSE=symptomatic skeletal event.

Summary tables of subject study disposition, treatment disposition, study compliance, TEAE, and death will include COVID-19 related information to assess impact on data.

1.2. Trial Design

This is a Phase 2, multicenter, open-label study to assess the efficacy and safety of once daily dosing of 300 mg niraparib in male subjects over the age of 18 years with mCRPC and DNA-repair anomalies who have received prior taxane-based chemotherapy and AR-targeted therapy. The study will assess up to approximately 120 subjects with measurable disease who are biomarker-positive, as defined in Section 9.7 of the protocol (approximately 75 subjects with a BRCA anomaly (defined as either biallelic DNA-repair anomaly in BRCA [BRCA1 or BRCA2] or germline BRCA DNA-repair anomaly) and approximately 45 subjects with non-BRCA anomaly

(defined as biallelic DNA-repair anomalies in ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2). In addition, at least 90 subjects with non-measurable mCRPC (i.e., bone disease only) and DNA-repair anomalies (both BRCA and non-BRCA) will be included to evaluate the activity of niraparib in this population. All subjects will be monitored for safety during the study period, and up to 30 days after the last dose of study drug. Treatment will continue until disease progression, unacceptable toxicity, death, or the sponsor terminates the study.

The study will consist of 4 phases; a Prescreening Phase, a Screening Phase, a Treatment Phase, and a Follow-up Phase. After approximately 30 subjects have been enrolled and observed for 8 weeks or more, a preliminary review of the efficacy and safety data will be performed by a Data Review Committee (DRC). Enrollment will not be suspended while the DRC reviews these data.

To be eligible for the study, subjects must have a DNA-repair anomaly by either: a) a sponsor-validated blood or tissue assay or b) a germline pathogenic BRCA1/BRCA2 DNA-repair anomaly by any test. A subject's results indicating a somatic DNA-repair anomaly must be confirmed as positive by a sponsor-validated assay before enrollment (defined as Cycle 1 Day 1).

1.3. Statistical Hypothesis for Trial Primary Objective

Niraparib will demonstrate a >15% objective response rate (ORR, per RECIST 1.1) in subjects with mCRPC and DNA-repair anomalies who have measurable disease.

1.4. Sample Size Justification

For the primary objective using the ORR endpoint in subjects with measurable disease, mCRPC and BRCA anomaly, efficacy of niraparib will be declared if the lower bound of the 2-sided 95% exact CI for ORR is >15%. With approximately 75 such subjects, the study will have over 90% power to determine if the lower limit of the 95% CI for ORR exceeds 16%.

For the secondary objective evaluating the ORR endpoint in subjects with measurable disease, mCRPC and non-BRCA anomaly, the null hypothesis that the ORR is ≤15% will be tested against the alternate hypothesis that the ORR is ≥32%. With a 1-sided α of 0.05 and power of 80%, up to 45 such subjects are to be enrolled based on Simon's two-stage design. At end of Stage 1, approximately 14 subjects will be evaluated for ORR after at least 1 post-treatment scan and a confirmatory scan. Future enrollment in this group may be terminated if 2 or fewer responses are observed in the first stage. Otherwise, enrollment may proceed to the second stage with a total of approximately 45 subjects combined for the 2 stages, and the null hypothesis will be rejected if 10 or more responses are observed.

Assuming a historical CTC response rate (CTC RR) of CCI [redacted] and a target CTC RR of 40%, approximately 60 subjects with non-measurable disease (BRCA and non-BRCA) will be required to provide a lower bound of the 2-sided 95% CI greater than 20%, with a probability of 0.9.

1.5. Randomization and Blinding

This is an open-label, single-treatment study; therefore, blinding and randomization procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

The date of enrollment is the date of the first dose of study medication and is also Cycle 1 Day 1. Study Day is calculated based on this date. Positive study days will count forward from Study Day 1. Study Day -1 will be the day before Study Day 1, and all subsequent negative study days will be measured backward from Study Day -1. There will be no Study Day 0. The first dose starts on Day 1 of Cycle 1. Unless otherwise specified, baseline value is defined as the closest measurement prior to or on the date of the first dose of study drug. Change from baseline will be defined as (post-baseline value – baseline value).

Treatment Duration is calculated as the duration of time from the date of the first dose of study drug to the date of last dose of the study drug, i.e., date of last dose – date of first dose + 1.

Time to Event is calculated as the number of days from the date of enrollment to the date of the event of interest, i.e., date of event of interest – date of enrollment + 1. Time to event or duration of event endpoints will be based on the actual date of the event, not visit number or visit date.

Continuous/numerical variables will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using count and percentage.

Missing data will be handled using a data as observed approach, no imputation will be implemented unless specified.

2.1. Pooling Algorithm for Analysis Centers

There is no plan to pool data across centers (study sites) for analyses.

2.2. Analysis Sets

Multiple analysis sets will be defined for analysis purposes.

Enrolled Analysis Set: All subjects who are enrolled into the study.

Efficacy Analysis Set: All subjects who received at least 1 dose of study drug and have BRCA (biallelic or germline DNA-repair anomalies) or non-BRCA (biallelic DNA-repair anomaly).

- BRCA analysis set (Primary Efficacy Analysis): a subset of efficacy analysis set with BRCA subjects (biallelic or germline DNA-repair anomalies).
- Non-BRCA analysis set: a subset of efficacy analysis set with non-BRCA subjects (biallelic DNA-repair anomaly).

Safety Analysis Set: All subjects who received at least 1 dose of study drug (same population as the Enrolled Analysis Set).

Patient-report Outcomes Analysis Set (PRO): All subjects who completed the baseline assessment and at least 1 post-baseline assessment of BPI-SF, FACT-P, or EQ-5D-5L questionnaires.

Pharmacokinetics Analysis Set (PK): All subjects who received 1 dose of study drug and have at least 1 blood sample for PK obtained post-baseline.

2.3. Definition of Subgroups

In order to assess the consistency of treatment benefit across different subject subpopulations, the planned analyses may also be carried out using the following subgroups if appropriate:

- Baseline measurable disease status as defined by RECIST 1.1[2] (non-measurable disease is bone disease only)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (0-1 versus 2)
- Baseline Age (<70, ≥70 years)
- Baseline visceral disease (visceral disease versus non-visceral disease for all subjects)
- Biomarker status (BRCA, non-BRCA)

3. INTERIM DATA REVIEW AND DATA REVIEW COMMITTEE

3.1. Data Review Committee (DRC)

A DRC will be established for this study to review the planned analyses. The DRC may include individuals both internal and external to the sponsor who are knowledgeable in the disease area. The DRC responsibilities, authorities, and procedures will be documented in detail in a separate DRC charter.

3.2. Futility Analysis and Safety Review

3.2.1 BRCA Subjects

A futility analysis with a preliminary review of the efficacy and safety data will be performed after approximately 30 subjects with measurable disease as defined by RECIST 1.1[2] who have biallelic DNA-repair BRCA gene anomalies (as defined by the sponsor's blood-based assay) have been enrolled and observed for at least 4 cycles. The objective of this review is to have a preliminary benefit/risk evaluation to continue the trial. Data scope for the preliminary review may include the following information as appropriate:

- Descriptive summary of subject disposition, exposure, and baseline disease characteristics
- Descriptive summary of safety parameters such as treatment emergent adverse events (TEAEs), SAEs, death, and key lab parameters
- Descriptive summary of the following efficacy endpoints will be provided:
    - Objective response rate (ORR) based on investigator assessment
    - Duration of objective response

- CTC response defined as CTC=0 per 7.5 mL blood at 8 weeks post-baseline in subjects with baseline CTC >0
- Composite response rate (CRR), where composite response is defined as 1 or more of the following
  - Objective response (as defined by RECIST 1.1 with no evidence of bone progression according to the PCWG3 criteria) based on investigator assessment
  - Conversion of CTC from ≥5 cells per 7.5 mL blood at baseline to <5 cells per 7.5 mL blood nadir, confirmed by a second consecutive value obtained 4 or more weeks later, or
  - PSA decline of ≥50% from baseline, measured twice 3 to 4 weeks apart

- An early look at the primary endpoint of objective response rate (ORR) may be carried out. Lack of clinical activity may be considered if the observed number of responses is ≤3 out of 30 subjects. Under the assumption that the null hypothesis of true ORR ≤15% vs. alternate hypothesis of true ORR ≥32%, this statistical guideline will control the false negative rate to be <1%, i.e., declaring lack of clinical activity when underlying response rate has treatment benefit. There is no penalty for alpha spending for this analysis.

3.2.2 Non-BRCA Subjects

A futility analysis will be performed after approximately 14 non-BRCA subjects with measurable disease as defined by RECIST 1.1[2] who are enrolled under protocol amendment 4 or later and observed for at least 4 cycles. The objective of the futility analysis is to determine if non-BRCA enrollment continues. Data scope for this futility analysis may include the following information as appropriate:

- Descriptive summary of subject disposition, exposure, and baseline disease characteristics
- Descriptive summary of safety parameters such as treatment emergent adverse events (TEAEs), SAEs, death, and key lab parameters
- Descriptive summary of the following efficacy endpoints will be provided:
  - Objective response rate (ORR) based on investigator assessment
  - Duration of objective response
  - CTC response defined as CTC=0 per 7.5 mL blood at 8 weeks post-baseline baseline in subjects with baseline CTC >0
  - Composite response rate (RR), where composite response is defined as 1 of the following
    - Objective response (confirmed per RECIST 1.1) based on investigator assessment, or

- Conversion of CTC from ≥5 cells per 7.5 mL blood at baseline to <5 cells per 7.5 mL blood nadir, confirmed by a second consecutive value obtained 4 or more weeks later, or
- PSA decline of ≥50% from baseline, measured twice 3 to 4 weeks apart

Lack of clinical activity may be considered if the observed number of responses is ≤2 out of the 14 subjects.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized. In addition, the distribution of subjects by site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

The following parameters in table 1 will be summarized using the enrolled analysis set and the primary efficacy analysis set:

Table 1: Demographic and Baseline Characteristics Variables

Continuous Variables:	**Summary Type**
• Age (years) • Weight (kg), Height (cm) • Baseline PSA, hemoglobin, CTC, platelet, neutrophil, lactate dehydrogenase, Alkaline phosphatase, testosterone value • Time from initial diagnosis to Day1 Cycle 1	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum])
Categorical Variables	
• Age <65 years, ≥65 to 69 years, ≥70 to 74 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, 2) • Gleason score at diagnosis • Extent of disease progression (Bone, Visceral, Lymph Node, Soft Tissue) • Evidence of disease progression at study entry • Number of prior therapies (Number of AR-targeted therapies, taxane-based chemotherapy, cytotoxic chemotherapy, and other therapies)	Frequency distribution with the number and percentage of subjects in each category

• [a] If multiple race categories are indicated, the race is recorded as 'Multiple' Note that collection of race and ethnicity is limited to countries were permitted.

4.2. Disposition Information

The number and percentage of subjects who are enrolled, dosed, who discontinue study treatment and discontinue the study (including reasons) will be summarized using the enrolled analysis set and the primary efficacy analysis set specified in Section 2.2.

4.3. Treatment Compliance

Treatment compliance and dose modifications will be summarized using the safety analysis set.

Subjects should take a total of 3 capsules of niraparib (3 x 100 mg) once daily during the treatment phase, unless subjects experience toxicity resulting in protocol-specified dosing modifications.

Treatment compliance will be summarized descriptively and will be calculated as ratio of

actual dose intensity/planned dose intensity * 100%.

Dose intensity is defined as the total amount of drug given in a fixed unit of time. Subjects with at least one dose reduction or with dose interruption and the reason for the dose modification will be summarized.

4.4. Duration of Exposure

Duration of exposure will be summarized using the safety analysis set and the primary efficacy analysis set, in terms of treatment duration in cycles and in months, which are calculated as the number of days with dosing record divided by 30.4375 (i.e., number of days in a month calculated as 365.25/12).

4.5. Protocol Deviations

Major Protocol deviations will be summarized using the enrolled analysis set. Protocol deviations were reviewed per SOP by a cross functional team during the regularly scheduled protocol deviation meetings and assessed if they are considered major protocol deviations. The final list will be compiled prior to database lock. Examples of major protocol deviations may include, but are not limited to, the following categories:

- Deviation from inclusion/exclusion criteria
- Major study drug dosing errors or dose modifications that are not within the protocol specifications that may compromise subject safety or efficacy assessments
- Administration of prohibited concomitant medication during the study treatment period
- Other deviation that impacts subject safety

4.6. Prior and Concomitant Medications and Subsequent Therapies

Prior and concomitant medications will be summarized by WHO Drug therapeutic class and generic medication name using the enrolled analysis set and the primary efficacy analysis set. Prior medications are those taken (with medication start date) prior to Cycle 1 Day 1. Concomitant medications are those, other than study drug, taken during the Treatment Phase.

Subsequent prostate cancer therapies received after the Treatment Phase will be summarized using the efficacy and the primary efficacy analyses sets. If the therapy is medication, then it will also be summarized by World Health Organization (WHO) Drug therapeutic class and generic medication name.

5. EFFICACY

A summary of the planned analyses for efficacy endpoints are listed in Table 2, more details can be found in subsequent sections. All secondary efficacy endpoints will also be analyzed based on the two populations in terms of biomarker status (BRCA versus non-BRCA DNA-repair anomalies).

Table 2: Planned Analyses for Efficacy Endpoints

Endpoint		Analysis Method
Primary endpoint	Objective response rate (ORR)	• Descriptive summary • Two-sided 95% exact confidence interval
Secondary endpoints	OS	• K-M plot • Descriptive summaries
	CTC response rate	• Descriptive summaries • Two-sided 95% exact confidence interval
	rPFS Time to radiographic progression	• K-M plot • Descriptive summaries
	Time to PSA progression Time to symptomatic skeletal event (SSE) Duration of objective response	• K-M plot • Descriptive summaries • Waterfall plot for PSA
Exploratory endpoints	Response Rate (RR) as defined in Section 1.1	• Descriptive summary • Two-sided 95% exact confidence interval
	Change from baseline in CTC over time	• Descriptive summary over time
	Time to degradation in BPI-SF worst pain intensity score	• K-M plot • Descriptive summary
	Time to FACT-P total score degradation	• K-M plot • Descriptive summary
	BPI-SF Worst Pain Intensity score, FACT-P total score, and EQ-5D-5L VAS score	• Descriptive summary

5.1. Analysis Specifications

5.1.1. Level of Significance

In general, all confidence intervals will be calculated on the two-sided 95% confidence level (CI), unless otherwise specified.

5.1.2. Data Handling Rules

In general, no imputation method is planned for handling missing or incomplete data unless specified otherwise. Sensitivity analyses with censoring rules may be conducted if warranted and will be documented in the clinical study report.

The following imputation rule will be used for missing dates in the assessment of an event:

Partial event onset dates will be imputed as follows:

- If the onset date of an event is missing day only, it will be set to the earliest of:

- First day of the month that the event occurred, if month/year of the onset of event 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 event resolution date is different
- The day of Day 1 or day of event resolution date, whichever is earliest, if month/year of the onset of event and month/year of the Day 1 and month/year of the event resolution date are same

- If the onset date of an event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, if 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 event occurred
  - Last day of the year if the year of the event onset is prior to the year of the Day 1,
  - The event resolution date.
- Completely missing onset dates will not be imputed.

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

- If the resolution date of an event 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 event 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.

5.2. Primary Endpoint

5.2.1. Definition

The primary endpoint is Objective response rate (ORR), defined as the proportion of subjects with BRCA DNA-repair anomalies and measurable disease whose best response is either complete response (CR) or partial response (PR) as defined by RECIST 1.1[2] and who have no evidence of bone progression according to the PCWG3 criteria[3].

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:

- Population: all subjects with measurable disease in the BRCA analysis set.
- Variable: ORR based on investigator assessment.
- Intercurrent events and strategies:

Missing baseline assessment	Assume non-response

No post baseline response assessment	Assume non-response

- Population-level summary: ORR will be summarized for BRCA analysis set along with 95% 2-sided exact CI.

5.2.3. Analysis Methods

ORR final analysis will be performed approximately 6 months from Cycle 1 Day 1 of the last subject with a BRCA DNA-repair anomaly and measurable disease and measurable disease. Objective response as determined by investigator assessment will be considered as the primary analysis.

Additionally, all enrolled subjects with a non- BRCA DNA-repair anomaly and measurable disease as defined by RECIST 1.1[2] will be analyzed for objective response.

Subjects who discontinue the study without a response assessment will be considered as non-responders in the analysis. The objective response rate will be calculated and its 2-sided 95% exact CI will be presented. In addition, the counts and percentage of subjects in each response category (CR, PR, etc.) will be tabulated.

5.3. Secondary Endpoints

5.3.1. Definitions

CTC response rate is defined as the proportion of subjects with baseline CTC>0 whose CTC=0 per 7.5 mL blood at 8 weeks post-baseline.

OS is defined as time from enrollment to 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 radiographic progression is defined as time from enrollment to radiographic progression (as determined by the investigator) or death due to disease progression, whichever occurs first.

Radiographic progression is determined by first occurrence of progression, assessed by investigator. Radiographic progression should be evaluated as follows:

- Progression of lesions measured by CT or MRI as defined by RECIST 1.1.
- Bone progression observed on 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 (i.e., 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 does 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 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 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. Subjects who begin a subsequent anti-cancer therapy will be censored the date of the last assessment prior to starting a new 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 enrollment
Subjects who are lost to follow-up or withdraw from study prior to documented disease progression or death	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 have ≥2 consecutive unevaluable scans immediately followed by 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 enrollment

Time to PSA progression is defined as time from enrollment to the first date of documented PSA progression based on PCWG3 criteria. 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 on enrollment date.

Time to symptomatic skeletal event (SSE) is defined as the time from enrollment to the first occurrence of one of the following symptomatic skeletal events:

- Tumor-related spinal cord compression
- Radiation to bone to relieve skeletal symptoms
- Surgery to bone or need for tumor-related orthopedic surgical intervention
- Symptomatic or pathologic fracture

Subjects with no symptomatic skeletal event at the time of analysis will be censored on the last SSE assessment. Death is not an event for SSE.

Duration of objective response is defined as time from complete response or partial response to radiographic progression of disease, unequivocal clinical progression or death, whichever occurs first.

5.3.2. Analysis Methods

ORR in BRCA and non-BRCA subjects will be analyzed in the same way.

Following analyses on CTC response will be performed for BRCA and non-BRCA analysis sets, measurable and non-measurable subgroups:

- Descriptive summaries
- CTC response rate will be tabulated and its 2-sided 95% exact CI
- Waterfall plots of percent change in CTC will also be presented that show the percentage change in CTC counts from baseline to 8 weeks as well as CTC count declines.

All time-to-event endpoints will be evaluated using Kaplan-Meier method for BRCA and non-BRCA analysis sets. Median time to event and the corresponding 95% CI will be provided. Descriptive summaries will be provided for BRCA and non-BRCA analysis sets. In addition, waterfall plots for PSA will be presented for to demonstrate the percentage of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy), as well as the maximal decline in PSA.

5.4. Other Endpoints

Exploratory endpoints include composite response rate (CRR) as defined in Section 1.1, Time to unequivocal clinical progression, change from baseline in CTC counts over time, Time to degradation in BPI-SF worst pain intensity score, Time to FACT-P total score degradation, and BPI-SF Worst Pain Intensity score, FACT-P total score, and EQ-5D-5L VAS score (see section 9 for definition).

5.4.1. Definition

Composite response rate (CRR), where composite response defined as 1 of the following:

- Objective response (as defined by RECIST 1.1 with no evidence of bone progression according to the PCWG3 criteria), or

- Conversion of CTC from ≥5 cells per 7.5 mL blood at baseline to <5 cells per 7.5 mL blood nadir, confirmed by a second consecutive value obtained 4 or more weeks later, or
- PSA decline of ≥50% from baseline, measured twice 3 to 4 weeks apart.

CTC0 with confirmation is defined as CTC drop to 0 post-baseline (confirmed by a second consecutive value obtained 4 or more weeks later) for subjects with baseline CTC>0.

Time to unequivocal clinical progression is defined as time from enrollment to unequivocal clinical progression or death due to disease progression. Subjects without unequivocal clinical progression or death will be censored at the last disease assessment date if never start of subsequent anti-cancer therapy or censored at the last disease assessment date prior to the start of the subsequent anti-cancer therapy if started subsequent anti-cancer therapy.

Unequivocal clinical progression per protocol is defined as one or more of following:

- Deterioration in ECOG PS to Grade 3 or higher.
- Need to initiate any of the following because of tumor progression (even in the absence of radiographic evidence of disease):
    - Alternative anticancer therapy for prostate cancer.
    - Radiation therapy.
    - Surgical interventions for complications due to tumor progression.

Change from baseline in CTC counts over time is defined as the change from baseline in CTC counts at each CTC assessment time point.

5.4.2. Analysis Methods

Response rate will be tabulated and its 2-sided 95% exact CI will be presented. To calculate CTC conversion, subjects who have CTC< 5 cells per 7.5 mL blood at baseline will be removed from the analysis. In addition, the number and percentage of subjects meeting each response criterion (RR, CTC conversion, and PSA decline of 50%) will be tabulated.

The median time to degradation in BPI-SF worst pain intensity score and Time to FACT-P total score degradation will be estimated using a Kaplan-Meier technique. Subjects who did not experience degradation were censored at last data point collected for the PRO assessment. In cases where median values cannot be computed because less than 50% of subjects experienced degradation, 25th percentiles will be reported and compared instead.

Change from baseline in CTC counts over time, in BPI-SF Worst Pain Intensity score, FACT-P total score, and EQ-5D-5L VAS score will be summarized and longitudinal plots will be provided.

Exploratory analyses of CTC0 and CTC conversion with confirmation will be performed to evaluate their impact on OS, rPFS.

6. Safety

The safety parameters to be evaluated are the incidence, intensity, and type of adverse events (AE), vital signs, ECG, and clinical laboratory results.

Unless otherwise specified, no inferential statistical analyses will be performed in analyzing the safety data.

6.1. Adverse Events

Subjects will be assessed for adverse events at each monthly clinic visit while on the study. Adverse events (AEs) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03[1] or later and coded to preferred term and system organ class (SOC) using the MedDRA version 18.0 or later.

All AEs reported on or after the date of first dose until 30 days (inclusive) after the last dose of study drug will be considered treatment-emergent and will be summarized.

AE incidence rates will be summarized with frequency and percentage by SOC and preferred term, with all subjects treated as the denominator, unless otherwise specified. In addition, AE incidence rates will also be summarized by severity and relationship to study drug. Treatment-related AEs are those judged by the Investigator to be at least possibly related to the study drug. Subjects with multiple occurrences of events will only be counted once at the maximum severity to study drug for each preferred team, SOC, and overall. Deaths that occur within 30 days after the last dose of study drug 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, number of subjects with Grade 3/4 AEs, any serious adverse event (SAE), any treatment-related AE, any treatment-related SAE, AE leading to treatment discontinuation, AE leading to death, and all deaths within 30 days of last dose
- All AEs by SOC and preferred term
- Most frequent AEs by SOC and preferred term (reported in ≥ 5% of subjects)
- All AEs by SOC, preferred term, and toxicity grade
- 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
- Most frequent treatment-related Grades 3 and 4 AEs (reported in ≥ 5% of subjects)

- All AEs that led to death by SOC and preferred term
- All AEs that led to study drug discontinuation by SOC and preferred term. Study drug 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 eCRF page (where action taken is "Withdrawn from Study")
- All AEs that led to study drug discontinuation by SOC, preferred term, and toxicity grade
- All AEs that lead to study drug dose modification by SOC and preferred term
- All SAEs by SOC and preferred term
- All SAEs by SOC, preferred term, and toxicity grade
- Deaths by time period (Treatment Phase, Follow-up Phase) and cause of death

Subject listings of all Grades 3 or 4 AEs, all SAEs, AEs that led to study drug discontinuation, dose modification, and all deaths will be provided as well.

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

- Subjects who die within 30 days of the last dose of study drug
- Subjects who discontinue study drug due to adverse events
- Subjects who have a treatment-related serious adverse event
- Subjects who experience a grade 3 or higher AE of special interest (thrombocytopenia, anemia, neutropenia, MDS and AML)

6.2. Clinical Laboratory Tests

For continuous/numerical measurements, descriptive statistics will be provided at baseline and for observed values and changes from baseline at each scheduled time point. The number and percentage of subjects with abnormal laboratory values will be summarized. The number and percentage of subjects whose NCI-CTCAE (version 4.03 or later) toxicity grades of ≥ 3 will also be summarized. For selected key laboratory measurements, changes in toxicity grade from baseline to the worst grade experienced by the subject during the Treatment Phase and the Study will be summarized using shift tables.

A listing of subjects who develop toxicities of Grade ≥ 3 will be provided for each laboratory parameter.

6.3. Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic) and body weight values and changes from baseline will be summarized at each scheduled time point. Descriptive statistics of other vital signs (body temperature, heart rate, respiratory rate) at baseline will also be summarized.

Baseline vital signs, blood pressure (systolic and diastolic), and heart rate will be summarized. 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
Weight	10 - < 20% weight loss from baseline

6.4. Physical Examination

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

6.5. Electrocardiogram

Electrocardiogram parameters will be summarized using descriptive statistics. The number and percentage of subjects with values beyond clinically important limits will also be summarized.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetic analyses will be performed and summarized in a separate report.

8. BIOMARKERS

Biomarker analyses will be performed and summarized in a separate technical report.

9. PATIENT-REPORTED OUTCOMES

Patient-reported outcome (PRO) assessments include BPI-SF, FACT-P and EQ-5D-5L, which will be analyzed to assess the subjects' perspective of response to treatment.

Missing PRO assessments will be calculated as the expected number of assessments for a particular visit minus the actual number of assessments received for that visit. Compliance (% received and % missing forms) will be tabulated for each visit. Expected number of assessments per visit will be determined by subject-level study completion status. Separate tables will be produced for FACT-P Total, BPI-SF, and EQ-5D-5L.

Descriptive statistics (N, Mean, Standard Deviation, Median, Min, Max for observed and changes from baseline) will be provided for each component of the BPI-SF, FACT-P and EQ-5D-5L. Components are as follows:

- FACT-P Total (PWB + SWB + EWB + FWB + PCS; Range: 0-156)

- FACT-P Physical Wellbeing (PWB) (Items GP1-GP7; Range: 0-28)
- FACT-P Social/Family Wellbeing (SFWB) (Items GS1-GS7; Range: 0-28)
- FACT-P Emotional Wellbeing (EWB) (Items GE1-GE6; Range: 0-24)
- FACT-P Functional Wellbeing (FWB) (Items GF1-GF7; Range: 0-28)
- FACT General (FACT-G) (PWB + SFWB + EWB + FWB; Range: 0-108)
- FACT-P Prostate Cancer Subscale (PCS) (Sum of items C2, C6, P1-P7, BL2, P8, Bl5; Range: 0-48)
- FACT-P Trial Outcome Index (TOI) (PWB + FWB + PCS; Range: 0-104)
- FACT-P Pain-related Scale (PRS) (Sum of items P1-P3, GP4; Range: 0-16)
- FACT Advanced Prostate Symptom Index (FAPSI-8) (Sum of items GP1, GP4, GE6, C2, P2, P3, P7, P8 Range: 0-32)
- EQ-5D-5L VAS
- EQ-5D-5L Health Utility Score
- BPI-SF Pain Severity Index (PSI) (Items 3-6; Range: 0 – 40)
- BPI-SF Pain Interference Index (PII) (Items 9A – 9G; Range: 0 – 70)

Time to degradation in FACT-P Total and BPI-SF worst pain intensity item (#3) will be determined using the meaningful change threshold values:

- FACT-P Total: 10-point reduction from baseline
- BPI-SF worst pain intensity item: 30% reduction from baseline

The median time to degradation in each total score will be estimated using a Kaplan-Meier technique. Subjects who do not experience degradation will be censored at last data point collected for the PRO assessment. In cases where median values cannot be computed because less than 50% of subjects experienced degradation, 25th percentiles will be reported and compared instead.

10. MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Data collected on medical resource utilization (MRU) will be used in the construction of economic model. The modeling and reporting will be provided in a separate report.

REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®) Prostate Cancer. Version 3.2012 (www.NCCN.org).
2. Eisenhauer EA, Therasse P, Bogaerts, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.
3. Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20;34(12):1402-1418.