STATISTICAL ANALYSIS PLAN

TRITON2: A Multicenter, Open-label Phase 2 Study of Rucaparib in Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency

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APPROVAL PAGE

TABLE OF CONENTS

LIST OF IN-TEXT TABLES

LIST OF FIGURES

ABBREVIATIONS AND SPECIALIST TERMS

AE	adverse event
ATC	Anatomical Therapeutical Chemical (coding)
ATM	ataxia telangiectasia mutated serine/threonine kinase
BRCA	breast cancer genes
CI	confidence interval
Cmin	minimum concentration
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HRD	homologous recombination deficiency
HRR	homologous recombination repair
ICH	International Conference on Harmonisation
IRR	independent radiology review
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
ORR	objective response rate
OS	overall survival
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PFS	progression-free survival
PR	partial response
PRO	patient reported outcomes
rPFS	radiographic progression-free survival
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event

1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for Clovis Oncology's protocol CO-338-052 "TRITON2: A Multicenter, Open-label Phase 2 Study of Rucaparib in Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency".

This statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of rucaparib (CO-338) in patients with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination deficiency (HRD).

The purpose of the SAP is to ensure the credibility of the study findings by providing a detailed outline of the statistical analyses that will be presented. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.3 or higher.

2 OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

2.1 Study Objectives and Endpoints

Table 1. Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	Primary Endpoints
To assess the efficacy of rucaparib based on the response rate in mCRPC patients with HRD who progressed on AR-targeted therapy (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent) and taxane-based chemotherapy in the castration-resistant setting	A. Cohort A: Confirmed radiographic ORR (as assessed by central independent radiology review [IRR]) using modified RECIST Version 1.1 (ie, CR or PR by IRR assessment and no confirmed progression in bone per PCWG3 by IRR assessment). Analyzed separately for patients with deleterious BRCA1/2 and ATM mutations. B. Cohort B: Confirmed PSA response (≥ 50% decrease from baseline) as assessed by a local laboratory. Analyzed separately for patients with deleterious BRCA1/2 and ATM mutations. C. Cohort C: Confirmed radiographic ORR (as assessed by central IRR) using either modified RECIST Version 1.1 (if measurable visceral and/or nodal disease is present) or confirmed PSA response (≥ 50% PSA

	decrease from baseline) (if measurable visceral and/or nodal disease is absent).
Secondary Objectives	**Secondary Endpoints**
To assess duration of response (DOR)	Time from the date that a response (modified RECIST Version 1.1/PCWG3 criteria or PSA ≥ 50%, respectively) is first reported to the time that progression (using modified RECIST Version 1.1/PCWG3 criteria or PSA-progression criteria, respectively) is first documented.
To assess radiographic progression-free survival (rPFS)	Time from first dose of rucaparib to the date of first objective evidence of radiographic progression (soft tissue or bone lesion, using modified RECIST Version 1.1/PCWG3 criteria, respectively) or death due to any cause, whichever comes first
To assess overall survival (OS)	Time from first dose of rucaparib to date of death due to any cause.
To assess clinical benefit rate (CBR)	Proportion of patients with CR, PR, or SD as defined by modified RECIST Version 1.1 and no progression in bone by PCWG3 criteria
To assess PSA response	Confirmed PSA response, defined as having 2 consecutive PSA values (at least 3 weeks apart) that are at least 50% lower than baseline and that occur prior to PSA progression. Similarly, a cut off of at least a 90% reduction will be assessed.
To assess time to PSA progression	Time from first dose of rucaparib to the date that a ≥ 25% increase and absolute increase of ≥ 2 ng/mL above the nadir is observed, confirmed by a consecutive measure at least 3 weeks later
To assess the safety and tolerability of rucaparib	The incidence of adverse events (AEs), clinical laboratory abnormalities, dose modifications, vital signs, ECGs, physical examinations, and ECOG performance status
To characterize the steady-state pharmacokinetics (PK) of rucaparib	Trough level plasma rucaparib concentrations (C_{min})

Exploratory Objectives	Exploratory Endpoints
To evaluate patient reported outcomes (PRO) using the EuroQol 5 dimensions questionnaire (EQ-5D-5L), Functional Assessment of Cancer Therapy – Prostate (FACT-P), analgesic drug score, and Brief Pain Inventory – Short Form (BPI-SF) instruments	Change and/or percent change from baseline for the EQ-5D-5L instrument. FACT-P and BPI-SF summarized according to their respective scoring manuals. Analgesic drug score recorded according to the World Health Organization (WHO) scale.
To assess changes in the molecular profile over time of matched pre- and post-treatment tumor and plasma samples	Changes in cancer-related mutations detected in plasma and tissue samples.
To assess concordance in HRR gene mutation status in matched screening biopsy tumor tissue, archival primary and metastatic tumor tissue and plasma ctDNA	Pairwise comparisons of available tissue and plasma HRR testing results.
To assess ctDNA as a molecular marker of response	Target lesion and/or PSA dynamics in relation to available longitudinal ctDNA test results.
To assess time to first subsequent antineoplastic therapy	Kaplan-Meier plot and/or descriptive statistics.
To evaluate loss of heterozygosity (LOH) in metastatic disease site biopsy and archival primary and metastatic tumor tissue samples	Concordance between percentage genomic loss of heterozygosity (%LOH) in available archival primary and metastatic tumor tissue samples.
To evaluate mechanisms of response and resistance in ctDNA and progression tumor tissue samples	Target lesion and/or PSA dynamics in relation to available plasma and tissue test results.

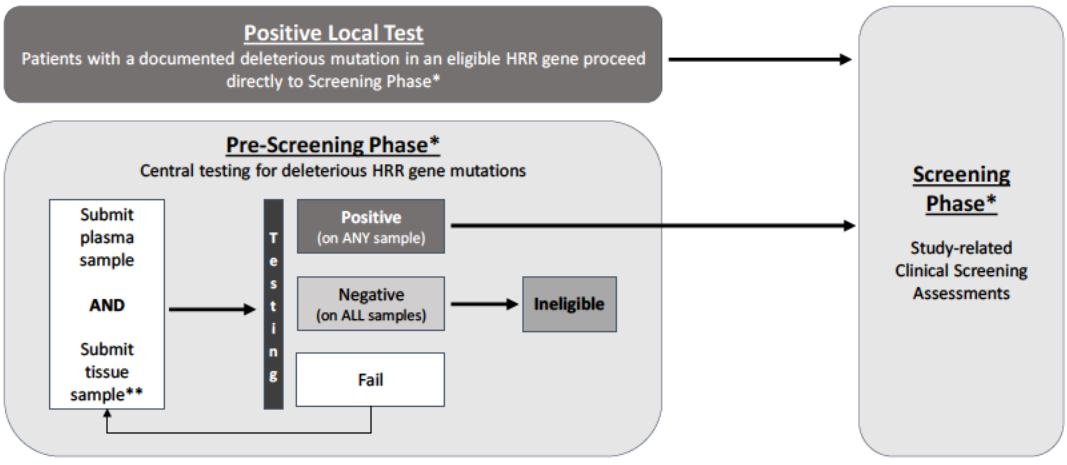
2.2 Trial Design

This is a Phase 2 multicenter study evaluating rucaparib for treatment of patients with mCRPC whose tumors are associated with HRD. This study will enroll mCRPC patients with mutations in BRCA1/2, ATM, or other HRR genes (BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, or RAD54L). Patients will be enrolled in 1 of 3 cohorts based on whether or not they had measurable disease at baseline per investigator, and based on gene mutation. All patients will be required to have progressed following treatment with at least 1, but no more than 2, prior AR-targeted therapy (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent). Patients must also have progressed after 1 prior taxane-based chemotherapy for mCRPC. Patients who received prior PARPi treatment, mitoxantrone, cyclophosphamide or platinum-based chemotherapy will be excluded.

This study consists of Pre-Screening Phase, Screening Phase, Treatment Phase, and Post-Treatment Phase. Patients will receive rucaparib monotherapy in the Treatment Phase, and will undergo procedures and assessments including regular safety and efficacy evaluations during the entire conduct of the study. The study schemas are shown in Figure 1 (Pre-screening Phase) and Figure 2 (all other Phases).

Rucaparib will be administered at a starting dose of 600 mg BID until disease progression as assessed by the investigator based on modified RECIST Version 1.1[1] and/or PCWG3[2] (for bone lesions only) criteria, or other reason for discontinuation. Patients may continue to receive rucaparib beyond progression if agreed upon by the investigator and sponsor. Tumor assessments by CT, MRI, PET/CT, and/or bone scans will be performed during screening, at the end of every 8 calendar weeks (± 7 days) from Study Day 1 (Week 1) up to 24 weeks and every 12 calendar weeks (± 7 days) thereafter, and should be performed at the time of treatment discontinuation, at the 28-day Follow-up visit, or during Long-term Follow-up if the reason was other than radiologically confirmed disease progression and it has been ≥ 8 weeks (≥ 12 weeks if previous scan was after 24 weeks on study) since the last assessment. Tumor assessments should continue on schedule (ie, every 8 or 12 weeks) during Long-term Follow-up until radiographically confirmed disease progression by modified RECIST v1.1 and/or PCWG3 criteria. Copies of all radiographic scans will be collected for central independent radiology review (IRR).

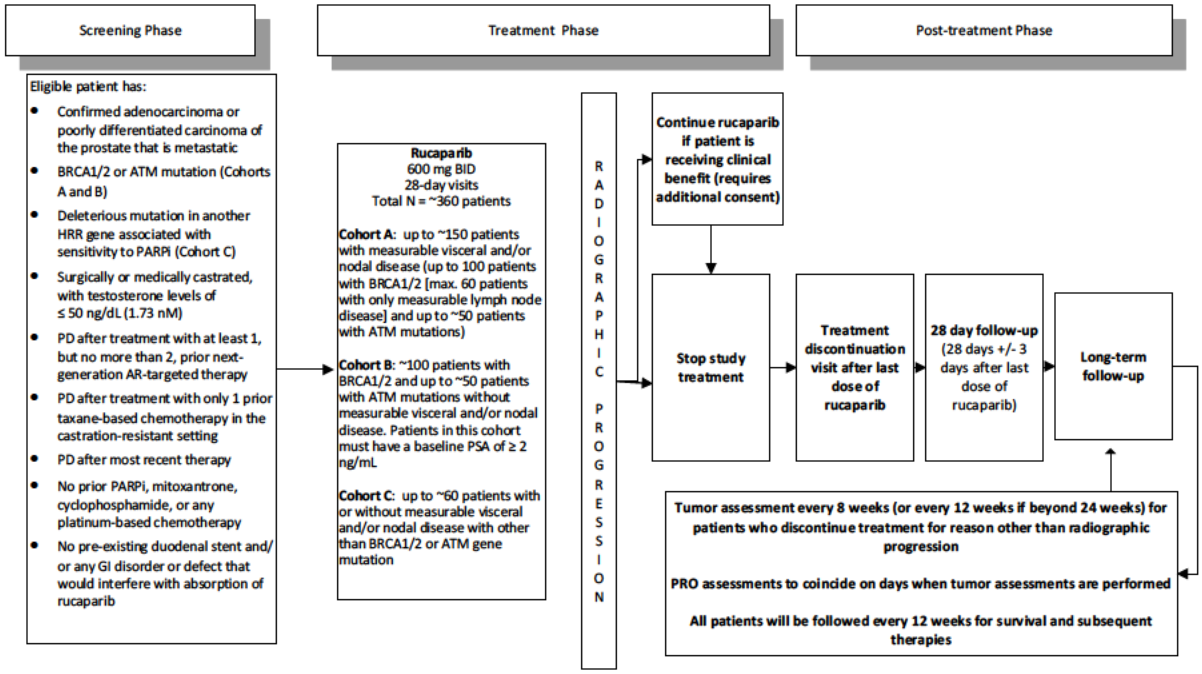
Figure 1: Pre-Screening Study Schema.



* Patients should be demonstrating radiographic or biochemical progression in order to enter the Pre-Screening and Screening Phases

** Metastatic biopsy (preferred) or archival tissue; tissue samples should be < 3 years old

Figure 2: Study Schema - Screening, Treatment, and Post-treatment Phases.



2.3 Sample Size Justification

The enrollment planned for this study is approximately 360 patients, with up to approximately 150 patients with measurable visceral and/or nodal disease in Cohort A (ie, up to 100 patients with a deleterious BRCA1/2 mutation [with a maximum of 60 patients who have only measurable lymph node disease], and up to approximately 50 patients with a deleterious ATM mutation); up to approximately 150 patients without measurable disease in Cohort B (ie, up to approximately 100 patients with a deleterious BRCA1/2 mutation and 50 patients with a deleterious ATM mutation); and up to approximately 60 patients with or without measurable visceral and/or nodal disease who have a deleterious mutation in a HRR gene other than BRCA1/2 or ATM in Cohort C.

Cohort A

Cohort A will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM).

Cohort A (BRCA1/2)

A Simon 2-stage design to evaluate confirmed ORR by modified RECIST Version 1.1 criteria per investigator will be used. With rolling enrollment, after the first 37 patients with a

deleterious BRCA1/2 mutation have either: a) completed 16 weeks of treatment or b) discontinued treatment prior to completing, an analysis will be performed (ie, Stage 1). If ≤ 8/37 patients in Stage 1 have a confirmed objective response (CR or PR per investigator and without progression in bone per PCWG3), the data monitoring committee (DMC) will evaluate the overall benefit/risk for patients with deleterious BRCA1/2 mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 9/37 patients have a confirmed objective response, then enrollment will continue with additional patients in Stage 2. With 83 total patients with a deleterious BRCA1/2 mutation, characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug
- 90% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 35% for an effective drug

If there are at least 23 responses in 83 patients with a deleterious BRCA1/2 mutation, the null hypothesis (ORR = 20%) will be rejected. This design yields a type I error rate of 5% and power of 90% when the true response rate is 35%.

Note: If the study is to proceed to Stage 2, additional patients with a deleterious BRCA1/2 mutation up to 100 total patients will be enrolled in Cohort A (BRCA1/2) if additional clinical data are requested by any Health Authority to support a regulatory filing. If sufficient evidence exists to support a regulatory filing prior to fully enrolling Cohort A (BRCA1/2), enrollment may be discontinued early.

Cohort A (ATM)

Patients in Cohort A (ATM), having a deleterious ATM mutation, will be enrolled concurrently with patients from Cohort A (BRCA1/2). It is expected that about 1/3 of the Cohort A patients will have a deleterious ATM mutation. If 100 patients are enrolled in Cohort A (BRCA1/2), then approximately 50 patients would be expected to enroll into Cohort A (ATM).

A Simon 2-stage design to evaluate confirmed ORR by modified RECIST Version 1.1 criteria per investigator will be used. Characteristics of the Simon 2-stage (minimax) design include:

- 5% probability of accepting a minimally effective drug
- 80% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 35% for an effective drug

In the first stage, 31 patients with a deleterious ATM mutation will be evaluated. If there are 6 or fewer responses, the DMC will consider stopping the sub-cohort for futility. If the sub-cohort proceeds to the second stage (≥ 7/31 responders), additional patients will be accrued for a total of approximately 50. According to the Simon 2-stage parameters, if there are at

least 16 responses in a total of 53 patients, the null hypothesis (ORR = 20%) would be rejected.

Cohort B

Cohort B will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM). Cohort B will be enrolled concurrently with Cohort A and is expected to enroll at approximately the same rate as Cohort A. Enrollment in Cohort B (both sub-cohorts) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort B (BRCA1/2)

A Simon 2-stage type futility rule will be employed in Cohort B (BRCA1/2). The Stage 1 analysis will be performed after the first 19 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this analysis occurs. If ≤ 4/19 patients in Stage 1 have a PSA response (≥ 50% decrease from baseline), the DMC will evaluate the overall benefit/risk for patients with a deleterious BRCA1/2 mutation in this sub-cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 5/19 patients have a PSA response, then enrollment will continue in Stage 2. With 54 total patients with a deleterious BRCA1/2 mutation, characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug
- 90% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 40% for an effective drug

If there are at least 16 responses in 54 patients with a deleterious BRCA1/2 mutation, the null hypothesis (ORR = 20%) will be rejected. This design yields a type I error rate of 5% and power of 90% when the true response rate is 40%. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 100 total, may be enrolled. Enrollment in Cohort B (BRCA1/2) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort B (ATM)

Patients in Cohort B (ATM), having a deleterious ATM mutation, will be enrolled concurrently with patients from Cohort B (BRCA1/2). It is expected that about 1/3 of the Cohort B patients will have a deleterious ATM mutation. If 100 patients are enrolled in Cohort B (BRCA1/2), then approximately 50 patients would be expected to enroll in Cohort B (ATM).

A Simon 2-stage type futility rule will be employed. The Stage 1 analysis will be performed after the first 18 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this analysis occurs. If ≤ 4/18 patients in Stage 1 have a PSA response (≥ 50% decrease from baseline), the DMC will evaluate the overall benefit/risk for patients with a deleterious ATM mutation in this cohort and make a recommendation whether further enrollment should be

discontinued. If ≥ 5/18 patients have a PSA response, then enrollment will continue in Stage 2. With 33 total patients with a deleterious ATM mutation, characteristics of the Simon 2-stage (minimax) design include:

- 5% probability of accepting a minimally effective drug
- 80% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 40% for an effective drug

If there are at least 11 responses in 33 patients with a deleterious ATM mutation, the null hypothesis (ORR = 20%) will be rejected. This design yields a type I error rate of 5% and power of 80% when the true response rate is 40%. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 50 total, may be enrolled. Enrollment in Cohort B (ATM) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort C

Up to approximately 60 patients will be enrolled in Cohort C. Enrollment in Cohort C will be halted when Cohort A (BRCA1/2) is fully enrolled. Since this cohort will enroll patients that have a deleterious mutation in 1 of several different deleterious HRR genes, each gene will be examined separately. It is anticipated that < 6 patients will have a deleterious mutation in the same HRR gene; however, if enrollment of patients with a deleterious mutation in the same gene is higher than anticipated, then enrollment will be held at 6 patients with a deleterious mutation in the same HRR gene and a futility rule will be implemented such that if no responses are observed, then enrollment of patients with a deleterious mutation in that particular gene will be stopped, in consultation with the DMC.

3 GENERAL ANALYSIS CONVENTIONS

The safety analyses will be performed using the safety population. In general, safety analyses will be presented by gene mutation (e.g., BRCA1/2, ATM, CDK12, CHEK2, and Other) and Overall. Safety data may also be presented by subgroups (e.g., measurable disease status at baseline or germline/somatic status for BRCA patients).

In general, efficacy analyses will be presented by gene mutation based on study entry test results (e.g., BRCA1/2, ATM, CDK12, CHEK2, and Other) and Overall. The CRF has several questions regarding gene mutations. The first asks “Does the patient have a deleterious mutation of either BRCA1, BRCA2 or ATM?” and only 1 can be selected. A second question asks “Does the patient have a deleterious mutation of another gene associated with HRD?” and 12 other gene mutations are listed, and more than 1 can be selected. Patients will be categorized into 1 of several gene mutation groups defined as follows:

- BRCA: if BRCA1 or BRCA2 is selected in the first question (regardless of any others being selected in the second question)

- ATM: if ATM is selected in the first question (regardless of any others being selected in the second question)
- CDK12: if the answer to the first question is "No" and only CDK12 is selected in the second question
- CHEK2: if the answer to the first question is "No" and only CHEK2 is selected in the second question
- Other: all others.

Note: Other gene mutation groups may be added depending on the number of patients with a specific gene mutation.

As mentioned in Section 2.2, patients are enrolled in 1 of 3 cohorts based on measurable disease status at baseline per investigator and based on gene mutation. However, patients could be classified in a different cohort based on IRR assessment of measurable disease at baseline. For example, a patient with a deleterious BRCA1/2 mutation who is assessed to have measurable disease by the investigator would be categorized into Cohort A for analysis of endpoints dependent upon measurable disease status per investigator. However, if this patient was determined to not have measurable disease per IRR, he would not be categorized into Cohort A for analysis of endpoints dependent upon measurable disease status per IRR. As a convention in this SAP, cohort labels (i.e., Cohort A, Cohort B, and Cohort C) will refer to the group of patients associated with the specified analysis (i.e., per investigator or per IRR).

Quantitative variables will typically be summarized using frequencies and percentages for appropriate categorizations and may also be summarized using descriptive statistics. For variables summarized with descriptive statistics, the following will be presented: N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be presented using frequencies and percentages.

The Kaplan-Meier methodology will be used to summarize time-to-event endpoints. If estimable, the 50th percentile (median) with the 95% confidence interval and range (minimum, maximum) will be summarized. The number of patients with events and the number of censored patients will also be presented.

All data will be used to their maximum possible extent but without any imputations for missing data. Unless otherwise specified, baseline is defined as the last measurement on or prior to the first day of study drug administration.

4 ANALYSIS POPULATIONS

The following analysis populations are defined for the study:

Safety Population – The safety population will consist of all patients who received at least 1 dose of protocol-specified treatment.

IRR Efficacy Population – The IRR efficacy population will be defined by measurable disease status at baseline using modified RECIST Version 1.1 criteria per independent radiology review.

- For endpoints using radiographic data, all treated patients with measurable disease (per IRR) at baseline will be included.
- For PSA endpoints, all treated patients without measurable disease (per IRR) at baseline and with a baseline PSA value ≥ 2ng/ml will be included.

Investigator Efficacy Population – The Investigator efficacy population will be defined by measurable disease status at baseline using modified RECIST Version 1.1 criteria per the investigator (Inv).

- For endpoints using radiographic data, all treated patients with measurable disease (per Inv) at baseline will be included.
- For PSA endpoints, all treated patients without measurable disease (per Inv) at baseline and with a baseline PSA value ≥ 2ng/ml will be included.

5 PATIENT DISPOSITION

Patient disposition will be summarized using frequency counts and the corresponding percentages. The number of patients in each analysis population, number of patients discontinued, and the primary reason for discontinuation will be summarized.

A protocol deviation review process/committee will determine the importance of various protocol deviations. The number of patients with important protocol deviations (e.g., those considered to potentially impact the integrity of the analysis or thought to be relevant) will be determined prior to data base lock and will be summarized with frequencies and percentages or provided in a patient listing. Patients will not be excluded from efficacy or safety analyses due to protocol violations.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All demographic and baseline characteristics will be summarized for the safety population.

6.1 Demographics

The demographic variables will be summarized with frequency tabulations and descriptive statistics. The demographic variables presented will include the following categorizations:

- Age (years): <65, 65-74, ≥75 and separately ≤ 50, 51-60, 61-70, 71-80, 81-90, > 90;
- Height (cm): ≤ 75, > 75-100, > 100-125, > 125-150, > 150-175, > 175;
- Weight (kg): ≤ 50, > 50-75, > 75-100, > 100-125, > 125-150, > 150;

- Race: American Indian or Alaska Native, Asian, Black, Native Hawaiian or Pacific Islander, White, Other, Not Reported;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown;
- Smoking status: Current Smoker, Former Smoker, Never Smoked;
- Region: North America, Europe, and Other

6.2 Baseline Clinical Characteristics

Baseline characteristics, including the following variables, will be summarized with frequency tabulations:

- Time since diagnosis of primary tumor (years): 0-3, >3-6, >6-9, >9;
- ECOG Performance Status: 0, 1, ≥2;
- Gleason score (< 7, 7, 8, 9, 10, not reported);
- HRR gene mutation;
- Germline status for patients with a BRCA mutation (Germline, Somatic, Unknown);
- Measurable disease status;
- Type of measurable disease (nodal only, visceral +/- nodal);
- Prior anticancer therapies for prostate cancer;
- Number of prior anticancer therapies for CRPC.

Descriptive statistics may also be used to summarize the continuous variables.

6.3 Medical History

Medical history events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system version 20.1 or higher. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

7 PRIOR AND CONCOMITANT MEDICATIONS

All concomitant treatments documented during the study period will be summarized in frequency tabulations. Prior/concomitant medication coding will utilize World Health Organization (WHO) Drug version 2017MAR (Enhanced) or higher.

Separate data summaries of prior medications will be provided. Prior medications will be defined as those medications with both a start and a stop date that is before the day of the first dose of study drug administration. If either the start date and/or the stop date of the medication is missing so that it is unclear whether the medication was stopped prior to first dose of study drug administration, then the medication will be included in the summary of the concomitant medications.

8 STUDY DRUG EXPOSURE AND COMPLIANCE

Duration of treatment will be calculated as 1+ the number of days from study drug start date to date of discontinuation. Descriptive statistics and frequencies/percentages for appropriate categorizations will be used to summarize treatment duration.

9 EFFICACY VARIABLES

9.1 Primary Efficacy Variables

For Cohort A, the primary efficacy endpoint for the study is confirmed radiographic ORR (CR or PR per modified RECIST Version 1.1 criteria and no confirmed bone progression per PCWG3 prior to a CR or PR) by central IRR in patients with measurable visceral and/or nodal disease at baseline per IRR.

For Cohort B, the primary efficacy endpoint is confirmed PSA response (≥ 50% decrease) as assessed by a local laboratory in patients without measurable disease at baseline per IRR.

For Cohort C, the primary endpoint is confirmed radiographic ORR if measurable visceral and/or nodal disease (per IRR) is present at baseline or confirmed PSA response (≥ 50% decrease) if measurable visceral and nodal disease (per IRR) is absent at baseline.

Supportive analyses will also be conducted using measurable disease status at baseline per the Investigator.

9.2 Secondary Efficacy Variables

Secondary variables include:

- Duration of response (DOR) (modified RECIST 1.1 or PSA ≥ 50%, separately)
- Radiographic progression-free survival (rPFS)
- Overall survival (OS)
- Clinical benefit rate (CBR)
- PSA response ≥ 50% (all patients)
- PSA response ≥ 90% (all patients)
- Time to PSA progression
- AEs, clinical lab abnormalities, and dose modifications
- Trough (C_{min}) level plasma rucaparib concentrations

9.3 Exploratory Efficacy Variables

Exploratory variables include:

- Patient reported outcomes (PROs) including
  - EQ-5D-5L instrument and the EQ VAS

  - FACT-P
  - BPI-SF
  - Analgesic drug score
- Plasma and tissue genomic profiling results
- ORR and/or PSA response in relation to germline/somatic status (patients with a BRCA1/2 alteration)
- Time to first subsequent antineoplastic therapy
- Percentage genomic loss of heterozygosity (%LOH)
- Best change from baseline in PSA at any time

10 EFFICACY ANALYSIS

In general, efficacy analyses will be presented by gene mutation (e.g., BRCA1/2, ATM, CDK12, CHEK2, and Other) and Overall.

Efficacy analyses for the endpoints using radiographic data for the Cohort A sub-cohorts (i.e., BRCA1/2 and ATM) will be conducted using the IRR Efficacy Population (patients evaluable for response by modified RECIST/PCWG3 criteria per IRR). Supportive analyses will also be conducted using the Investigator Efficacy Population.

PSA-related efficacy analyses for Cohort B (patients without measurable disease at Baseline) will be conducted using patients evaluable for PSA response.

Cohort C will consist of some patients with measurable disease at Baseline and some patients without measurable disease at Baseline. Efficacy analyses for Cohort C will be conducted similarly to Cohorts A and B, dependent upon measurable disease status. Generally, Cohort C will be divided up by gene mutation (e.g., CDK12, CHEK2, and Other), when warranted by the numbers of patients with a specific mutation. These categories will typically appear on the outputs in columns along with the BRCA and ATM columns.

Some efficacy endpoints can be assessed regardless of measurable disease status (e.g., PSA response, CBR, rPFS). These endpoints may also be summarized for all patients, regardless of measurable disease status at Baseline. Additionally, the primary efficacy endpoint will also be presented by age group (< 65, 65-74, ≥ 75) and race (White, Other).

10.1 Primary Efficacy Analysis

For Cohort A, the primary efficacy endpoint is confirmed radiographic ORR by central IRR (as described in Section 9.1) in patients with measurable visceral and/or nodal disease at baseline. To be considered a responder at a specific time point, a patient must have a CR or PR assessment per modified RECIST and no confirmed bone progression per PCWG3 on or prior to a CR or PR. To be considered a confirmed responder, a patient must have at least 2 responses at least 4 weeks apart prior to a modified RECIST/PCWG3 progression event.

Confirmed radiographic ORR will be summarized with frequencies and percentages along with 95% confidence intervals. The frequency and percentages of patients with a best overall response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) will also be summarized.

An analysis of confirmed radiographic ORR by the investigator will also be conducted as supportive to the primary endpoint and will use the Investigator Efficacy Population (patients evaluable for response by modified RECIST/PCWG3 criteria per investigator).

For Cohort B, the primary efficacy endpoint is confirmed PSA response as assessed by a local laboratory in patients without measurable disease at baseline (by central IRR). Confirmed PSA response is defined as having 2 consecutive PSA values (at least 3 weeks apart) that are at least 50% lower than baseline and that occur prior to PSA progression (as defined in Section 10.2.6). Per PCWG3, early rises (before 12 weeks following first dose of study drug) in PSA should be ignored when determining PSA response. Confirmed PSA response will be calculated for patients with PSA values at baseline.

Confirmed PSA response will be summarized separately, with frequencies and percentages along with 95% confidence intervals, for patients without measurable disease per IRR (primary endpoint) and without measurable disease per Investigator (supportive analysis). PSA response will also be summarized for patients with measurable disease (both IRR and Investigator, separately) and for all patients.

For Cohort C, the primary endpoint is confirmed radiographic ORR (by central IRR) if measurable visceral and/or nodal disease is present at baseline [as described for Cohort A] or confirmed PSA response (≥ 50% decrease from baseline) if visceral and nodal disease is absent at baseline [as described for Cohort B]. This endpoint will be summarized with frequencies and percentages along with 95% confidence intervals.

10.2 Secondary Efficacy Analyses

10.2.1 Duration of Confirmed Response

The duration of confirmed response is defined as the time from the date that a response is first reported (which is subsequently confirmed) to the time that progression is first documented plus 1 day.

- For radiographic response, duration of confirmed response is defined as the time from the date that a response (per modified RECIST Version 1.1/PCWG3) is first reported to the time that progression (per modified RECIST Version 1.1 criteria or confirmed bone progression per PCWG3) is first documented. DOR will be summarized separately for patients with confirmed responses per IRR and Investigator.

- For PSA-response, duration of confirmed response (PSA-DOR) is defined as the time from the date that a response (PSA decrease ≥ 50%) is first reported to the time that PSA progression (as defined in Section 10.2.6) is first documented. PSA-DOR will be

summarized separately for patients without measurable disease per IRR and patients without measurable disease per Investigator. PSA-DOR may also by summarized for patients with measurable disease per IRR, patients with measurable disease per Investigator, and for all patients.

Patients without a progression event will be censored at the time of their last assessment (radiographic or PSA, as applicable). The duration of confirmed response will be summarized using Kaplan-Meier methodology. In the case of a low censoring rate, the duration of response may be summarized with descriptive statistics.

10.2.2 Radiographic PFS

rPFS is defined as the time from first dose of rucaparib to the date of first objective evidence of radiographic progression (soft tissue or bone lesion) or death due to any cause, whichever occurs first, plus 1 day. Radiographic disease progression includes confirmed bone disease progression and soft tissue disease progression adjudicated by IRR using the PCWG3 guidelines for bone disease and modified RECIST Version 1.1 for soft tissue disease. Patients without a documented event of progression will be censored on the date of their last adequate tumor assessment (i.e., radiographic assessment) or date of first dose of study drug if no post-baseline tumor assessments have been performed.

Patients who withdraw from treatment prior to radiographic progression will be followed for disease status and survival whenever possible. Only tumor scans (and deaths, for PFS analyses) prior to start of any subsequent anticancer treatment will be included. If a patient discontinues study drug due to a reason other than radiographic PD and subsequently begins another anticancer therapy (ACT) prior to a PFS event, that patient will be censored at the last scan prior to the start of ACT. However, scans/PFS events occurring more than 24 weeks after DC/stop of study drug and more than 24 weeks after their last previous scan but prior to start of subsequent ACT will not be included in the analysis and such patients will be censored at their last scan prior to the end of the 24-week window.

rPFS will be presented by gene mutation for all patients (separately, using IRR and Investigator assessments) and may also be presented by measurable disease status at Baseline.

A sensitivity analysis will be performed in which patients who have discontinued without radiographic progression, but who have had PSA progression, will be treated as having an event at the time of PSA progression.

rPFS will be summarized using Kaplan-Meier methodology and in the case of a low censoring rate it may be summarized with descriptive statistics.

10.2.3 Overall Survival

OS is defined as the date from first dose of rucaparib to the date of death due to any cause, plus 1 day. OS will be summarized using the Safety Population, by gene mutation and Overall, using Kaplan-Meier methodology. OS may also be summarized for the subgroups of

patients defined by measurable disease status at baseline. In the case of a low censoring rate OS may be summarized with descriptive statistics.

10.2.4 Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the number of patients without radiographic progression (defined by modified RECIST Version 1.1/ PCWG3 criteria) who were continuing with study drug treatment through the given time interval divided by the number of patients who had the given amount of follow-up. Clinical benefit rates will be summarized at several intervals: e.g., 4-, 6-, 9-, and 12-months, with frequencies and percentages along with 95% confidence intervals. For example, the 6-month CBR would be the number of patients who neither discontinued nor had radiographic PD through 6 months divided by the number of patients who were enrolled at least 6 months prior to the visit cut-off.

CBR will be summarized for all patients (separately, using IRR and Investigator assessments) and may also be summarized for the subgroups of patients defined by measurable disease status at baseline.

10.2.5 Confirmed PSA Response

Confirmed PSA response (≥ 50% reduction) will be analyzed for all patients who had PSA values at baseline as described in Section 10.1. Similarly, PSA response will also be analyzed using a ≥ 90% reduction.

10.2.6 Time to PSA progression

Time to PSA progression is defined as the time from first dose of rucaparib to the date that a ≥ 25% increase and absolute increase of ≥ 2 ng/mL above the nadir (or baseline if there was no PSA decline after baseline) in PSA was measured, plus 1 day. The increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later (unless the PSA progression occurred at the last recorded PSA assessment). If confirmed, the date used for time of PSA progression is the earlier of the 2 PSA dates. Additionally, early rises (before 12 weeks following first dose of study drug) are not considered in determining PSA progression.

Time to PSA progression will be summarized for all patients and may also be summarized for the subgroups of patients defined by measurable disease status at baseline.

10.3 Exploratory Efficacy Analyses

10.3.1 Patient-reported Outcome

Patient reported outcome endpoints by FACT-P and BPI-SF will be summarized according to their respective scoring manuals.

Analgesic drug score will be recorded according to the World Health Organization (WHO) scale (0 for no medication, 1 for non-opioid pain medication, 2 for opioids for moderate pain, and 3 for opioids for severe pain).

Analyses of change and/or percent change from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for the EQ-5D-5L VAS.

Patients who do not have both a baseline measurement and at least one post-baseline measurement will not be included.

PRO endpoints will be summarized for all patients and may also be summarized for the subgroups of patients defined by measurable disease status at baseline.

BPI-SF

The primary analysis of change in pain intensity over time will be assessed using BPI-SF Item #3 (pain symptoms at their worst over the last 24 hours). A composite assessment of change in pain intensity (Item #3-6, worst pain, least pain, average pain, and current pain, respectively) will also be analyzed.

BPI item scores, change from baseline, and percentage change from baseline in daily pain intensity will be summarized at each visit and at the final visit using descriptive statistics (N, mean, SD, minimum, median, and maximum).

Longitudinal plots of the mean changes from baseline to each scheduled visit may also be presented. These plots may exclude visits for which only a small percentage (e.g., ≤ 30%) of patients have data.

FACT-P

Scores and post-baseline score changes for the FACT-P global, physical, functional, and prostate-cancer scale scores as well as scores for the FACT-P trial outcome index (TOI) will be summarized at each visit and at the final visit using descriptive statistics (N, mean, SD, minimum, median, and maximum).

Longitudinal plots of the mean changes from baseline to each scheduled visit may also be presented. These plots may exclude visits for which only a small percentage (e.g., ≤ 30%) of patients have data.

EQ-5D-5L

Change and percent change from baseline will be analyzed at each visit and at the final visit for EQ-5D-5L VAS. Patients who do not have both a baseline measurement and at least one post-baseline measurement will not be included.

10.3.2 Changes in Tumor Samples and Changes in Circulating Tumor DNA

The relationship between rucaparib activity and gene mutations identified from testing the available tissue and plasma samples will be evaluated. Additional genomic or transcriptional signatures may also be evaluated. Analyses will be described using graphical plots and descriptive statistics.

10.3.3 Concordance of HRR gene status between Metastatic Disease Site Biopsy, Archival Primary Tissue and Plasma ctDNA

Pairwise comparisons will be performed using available plasma and tissue (including archival and metastatic) test results to explore the concordance in HRR gene alterations.

10.3.4 ORR and/or PSA Response in Relation to Germline/Somatic Status

The ORR and/or PSA response rate will be analyzed for the subgroups of patients with a germline or a somatic BRCA1/2 alteration.

10.3.5 Time to First Subsequent Antineoplastic Therapy

Time from date of last dose of study drug to first subsequent antineoplastic therapy will be summarized using a Kaplan-Meier plot and descriptive statistics.

10.3.6 Genomic Loss of Heterozygosity (%LOH)

The percentage genomic loss of heterozygosity (% LOH) will be determined from all tissue samples with adequate sequencing data. The concordance between % LOH in archival and metastatic samples will be evaluated. The relationship between % LOH and response to rucaparib may also be explored.

10.3.7 Change from Baseline in PSA

Best change from baseline in PSA at any time will be presented using a waterfall plot.

10.4 Exploratory Pharmacokinetic Analyses

In all patients with at least one PK sample collected, the trough plasma rucaparib PK data (C_{min}) and summary statistics (N, mean, SD, minimum, median, max, CV%) will be reported. The PK data and selected safety and efficacy endpoints will be included in exploratory population PK and exposure-response analyses, and the results will be reported separately.

11 STATISTICAL / ANALYTICAL ISSUES

11.1 Handling of Dropouts or Missing Data

All data will be used to their maximum possible extent but without any imputations for missing data. All time to event analyses include censoring and the rules for deriving the censoring value are described in more detail under each one of the time to event endpoints.

11.2 Pooling of Centers in Multi-Center Studies

The centers within a given region (e.g., United States versus Rest of World) will be pooled, if applicable.

11.3 Multiple Comparison / Multiplicity

No adjustments for multiple comparisons will be made.

11.4 Interim Analysis and Data Monitoring

A DMC has been incorporated into the Study conduct to provide review and assessment of the safety and efficacy data, in a systematic manner and to safeguard the interest and the safety of the participating patients in the Study. The DMC is tasked with regularly reviewing the safety and efficacy of the Study to ensure a favorable risk-benefit ratio for the patients. A separate DMC charter contains the details regarding the membership and activities of the DMC.

Simon 2-stage designs have been employed in each sub-cohort to allow futility analyses to be conducted to help assess whether each sub-cohort should proceed to full enrollment. The Sample Size Justification section (Section 2.3) contains additional detail regarding the Simon 2-stage assumptions and parameters.

Cohort A

Cohort A will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM).

Cohort A (BRCA1/2)

A Simon 2-stage design to evaluate confirmed ORR by modified RECIST Version 1.1 criteria per investigator will be used. With rolling enrollment, after the first 37 patients have either: a) completed 16 weeks of treatment, or b) discontinued treatment prior to completing, an analysis will be performed (i.e., Stage 1). If $\leq$ 8/37 patients in Stage 1 have a confirmed objective response (CR or PR per investigator and without progression in bone per PCWG3), the DMC will evaluate the overall risk benefit for study treatment and make a recommendation whether further enrollment should be discontinued. If $\geq$ 9/37 patients have a confirmed objective response, then enrollment will continue with additional patients in Stage 2. The parameters of the Simon 2-stage design would accrue a total of 83 patients in this sub-

cohort. If there were at least 23 responses in 83 patients, the null hypothesis (ORR = 20%) would be rejected.

Note: If the study is to proceed to Stage 2, additional patients with a deleterious BRCA1/2 mutation up to 100 total patients may be enrolled in Cohort A (BRCA1/2) if additional clinical data is requested by the regulatory authorities to support regulatory filing. If sufficient evidence exists to support a regulatory filing prior to fully enrolling Cohort A (BRCA1/2), enrollment may be discontinued early.

Cohort A (ATM)

Patients in Cohort A (ATM), having a deleterious ATM mutation, will be enrolled concurrently with patients from Cohort A (BRCA1/2). It is expected that about 1/3 of the Cohort A patients will have deleterious ATM mutations. If 100 patients are enrolled in Cohort A (BRCA1/2), then approximately 50 patients would be expected to enroll into Cohort A (ATM).

A Simon 2-stage type futility rule will be employed in Cohort A (ATM). The Stage 1 analysis will be performed after the first 31 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this analysis occurs. If $\leq$ 6/31 patients in Stage 1 have a confirmed objective response (CR or PR per investigator and without progression in bone per PCWG3), the DMC will evaluate the overall benefit/risk for patients with deleterious ATM mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If $\geq$ 7/31 patients have a confirmed objective response, then enrollment will continue in Stage 2. If the study is to proceed to the second stage, additional patients with a deleterious ATM mutation may be accrued for a total of approximately 50, dependent upon the enrollment of Cohort A (BRCA1/2). If there are at least 16 responses in 53 patients with a deleterious ATM mutation, the null hypothesis (ORR = 20%) would be rejected.

Cohort B

Cohort B will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM). Cohort B will be enrolled concurrently with Cohort A and is expected to enroll at approximately the same rate as Cohort A. Enrollment in Cohort B will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort B (BRCA1/2)

Up to approximately 100 patients may be enrolled into Cohort B (BRCA1/2), dependent upon enrollment in Cohort A (BRCA1/2). As in Cohort A, a Simon 2-stage type futility rule will be employed. The Stage 1 analysis will be performed after the first 19 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this analysis occurs. If $\leq$ 4/19 patients in Stage 1 have a PSA response ($\geq$ 50% decrease), the DMC will evaluate the overall risk benefit for study treatment. If $\geq$ 5/19 patients have a PSA response, then enrollment will continue in Stage 2.

If the study/cohort proceeds to the second stage, additional patients with a deleterious BRCA1/2 mutation will be accrued for a total of 54. If there are at least 16 responses in 54 patients, the null hypothesis (ORR = 20%) will be rejected. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 100 total, may be enrolled. Enrollment in Cohort B (BRCA1/2) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort B (ATM)

Patients in Cohort B (ATM), having a deleterious ATM mutation, will be enrolled concurrently with patients from Cohort B (BRCA1/2). It is expected that about 1/3 of the Cohort B patients will have deleterious ATM mutations. If 100 patients are enrolled in Cohort B (BRCA1/2), then approximately 50 patients would be expected to enroll into Cohort B (ATM).

A Simon 2-stage type futility rule will be employed in Cohort B (ATM). The Stage 1 analysis will be performed after the first 18 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this analysis occurs. If $\leq 4/18$ patients in Stage 1 have a PSA response ($\geq 50\%$ decrease), the DMC will evaluate the overall benefit/risk for patients with deleterious ATM mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If $\geq 5/18$ patients have a PSA response, then enrollment will continue in Stage 2. If there are at least 11 responses in 33 patients with a deleterious ATM mutation, the null hypothesis (ORR = 20%) will be rejected. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 50 total, may be enrolled. Enrollment in Cohort B (ATM) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort C

Up to approximately 60 patients will be enrolled into Cohort C. Enrollment in Cohort C will be halted when Cohort A (BRCA1/2) is fully enrolled. Since this cohort will enroll patients that have 1 of several different deleterious HRR gene mutations, each gene will be examined separately. It is anticipated that < 6 patients will have a deleterious mutation in the same HRR gene; however, if enrollment of patients with a deleterious mutation in the same gene is higher than anticipated then enrollment will be held at 6 patients with any 1 deleterious gene mutation and a futility rule will be implemented such that if no responses are observed, then enrollment of patients with a deleterious mutation in that particular gene will be stopped, in consultation with the DMC.

12 SAFETY ANALYSIS

The safety analyses will be performed using the safety population. In general, safety analyses will be presented by gene mutation (e.g., BRCA1/2, ATM, CDK12, CHEK2, and Other) and Overall. Safety data may also be presented by measurable disease status at baseline to explore the safety profile between patients with and without measurable disease at baseline. Additionally, safety data will be further explored by age group (< 65, 65-74, ≥ 75) and race (White, Other).

12.1 Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03 or higher whenever possible. Treatment-emergent adverse events (TEAEs) are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days. Adverse events will be considered treatment-emergent if all or part of the date of onset of the adverse event is missing and it cannot be determined if the adverse event meets the definition for treatment-emergent.

The number and percentage of patients who experienced TEAEs for each system organ class and preferred term will be presented. Multiple instances of the TEAE in each system organ class and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one TEAE will also be summarized.

MedDRA preferred terms will also be combined and presented in summaries for the following similar terms:

- Asthenia/Fatigue;
- ALT/AST Increased;
- Anemia and/or Decreased Hemoglobin;
- Thrombocytopenia and/or Decreased Platelets; and
- Neutropenia and/or Decreased ANC.

Separate tables will be presented as follows:

- TEAE Overview;
- All TEAEs;
- Treatment-related TEAEs;
- Grade 3 or higher TEAEs;
- Grade 3 or higher treatment-related TEAEs;
- Serious TEAEs;
- Serious treatment-related TEAEs;
- TEAEs by CTCAE grade;

- Treatment-related TEAEs by CTCAE grade;
- TEAEs with an outcome of death;
- Treatment-related TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study medication;
- Treatment-related TEAEs leading to discontinuation of study medication;
- TEAEs leading to reduction of study medication;
- Treatment-related TEAEs leading to reduction of study medication;
- TEAEs resulting in interruption of study medication;
- Treatment-related TEAEs resulting in interruption of study medication;
- TEAEs resulting in reduction or interruption of study medication;
- Treatment-related TEAEs resulting in reduction or interruption of study medication;
- TEAEs resulting in reduction or interruption or discontinuation of study medication; and
- Treatment-related TEAEs resulting in reduction or interruption or discontinuation of study medication.

The incidence of TEAEs will be summarized by relationship to study drug according to the following categories: "treatment-related," or "not treatment-related". If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once, as a relationship category of treatment related.

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of "Missing." For each toxicity grade, the number and percentage of patients with at least one TEAE of the given grade will be summarized.

Time to the first treatment-related TEAE that resulted in a dose reduction, interruption, or discontinuation of study drug is defined as 1+ the number of days from the first dose of study drug to the start of the first respective AE. The cumulative incidence will be presented in a Kaplan-Meier plot for just the patients with an event, and the median time to onset will be calculated along with the 95% CI. Additionally, the analysis of combined terms for anemia will be presented as a time to first event analysis, as described above.

Non-TEAEs (pre-treatment and post-treatment) will be presented in the by-patient data listings for the safety population.

12.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will generally be presented in SI units. The on-treatment period will be defined as the time from first dose to 28 days after the last dose of study drug. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include tables based on CTCAE grades generally using CTCAE version 5.0. A few assessments (e.g., hyperglycemia, hypophosphatemia, and hyponatremia) may use version 4.03 as quantitative grading is not available in version 5.0. Where available, Baseline, Worst Post-baseline, and Shift to Worst Post-baseline grade during the on-treatment period will be summarized. The baseline value will be defined as the value closest to, but not subsequent to, the date of first dose.

The summary of laboratory data will also include descriptive statistics (N, mean, SD, minimum, median, and maximum) of the maximum, minimum, and last value during the on-treatment period. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given. Longitudinal plots of the mean (and/or percent) changes from baseline to each scheduled visit may also be presented for select laboratory parameters. These plots may exclude visits for which only a small percentage (e.g., ≤ 30%) of patients have data.

Supporting laboratory data including normal ranges and abnormal laboratory flags may be provided using by-patient listings. Separate listings may be produced for laboratory abnormalities that meet Grade 3 or 4 criteria according to CTCAE.

12.3 Vital Signs

The on-treatment period will be defined as the time from first dose to 28 days after the last dose of study drug. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital sign data will include descriptive statistics (N, mean, SD, minimum, median, and maximum) of the maximum, minimum, and last value during the on-treatment period. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given. The data will be presented separately for each sub-cohort and overall.

12.4 ECGs

ECGs are collected at Screening (within 28 days prior to enrollment), at the Treatment Discontinuation Visit, and if clinically indicated, at other times during the study. The following are measured or calculated: heart rate, PR, QRS, QT, and QTc. Descriptive statistics (N, mean, SD, minimum, median, and maximum) will be used to summarize ECG parameters at Screening and at Treatment Discontinuation.

13 CHANGES IN THE PLANNED ANALYSES

The definition of confirmed PSA responder (primary endpoint for Cohort B) in the protocol has been described in more detail in the SAP. The protocol stated:

> Confirmed PSA response is defined as ≥ 50% reduction in PSA from baseline to lowest post-baseline PSA result, with a consecutive assessment conducted at least 3 weeks later. PSA response will be calculated for all patients with PSA values at baseline and at least 1 post-baseline assessment.

This has been updated in the SAP to the following:

> Confirmed PSA response is defined as having 2 consecutive PSA values (at least 3 weeks apart) that are at least 50% lower than baseline and that occur prior to PSA progression (as defined in Section 10.2.6). Per PCWG3, early rises (before 12 weeks following first dose of study drug) in PSA should be ignored when determining PSA response. Confirmed PSA response will be calculated for patients with PSA values at baseline.

The definition of time to PSA progression in the protocol did not contain all the details outlined in the PCWG3 guidelines. The protocol stated:

> Time to PSA progression is defined as the time from first dose of rucaparib to the date that a ≥ 25% increase and absolute increase of ≥ 2 ng/mL above the nadir (or baseline value for patients who did not have a decline in PSA) in PSA was measured. The increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later.

This has been updated in the SAP to the following:

> Time to PSA progression is defined as the time from first dose of rucaparib to the date that a ≥ 25% increase and absolute increase of ≥ 2 ng/mL above the nadir (or baseline if there was no PSA decline after baseline) in PSA was measured, plus 1 day. The increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later (unless the PSA progression occurred at the last recorded PSA assessment). If confirmed, the date used for time of PSA progression is the earlier of the 2 PSA dates. Additionally, early rises (before 12 weeks following first dose of study drug) are not considered in determining PSA progression.

The clinical benefit rate analysis in the protocol has been described in more detail in the SAP. The protocol stated:

> Clinical benefit rate (CBR) is defined as the combination of CR, PR, and SD as defined by modified RECIST Version 1.1 and no progression in bone by PCWG3 criteria. Per RECIST, to be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

This has been updated in the SAP to the following:

> Clinical benefit rate (CBR) is defined as the number of patients without radiographic progression (defined by modified RECIST Version 1.1/ PCWG3 criteria) who were continuing with study drug treatment through the given time interval divided by the number of patients who had the given amount of follow-up. Clinical benefit rates will be summarized at several intervals: e.g., 4-, 6-, 9-, and 12-months, with frequencies and percentages along with 95% confidence intervals. For example, the 6-month CBR would be the number of patients who neither discontinued nor had radiographic PD through 6 months divided by the number of patients who were enrolled at least 6 months prior to the visit cut-off.

The PCWG3 paper suggests analyzing best percent change from baseline in PSA (using a waterfall plot). This analysis has been added in the SAP.

At the time the protocol was initiated, version 4.03 was the current version of CTCAE. It has since been updated to version 5.0 so this more current version will be used to grade the laboratory data.

14 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
2. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, 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.