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Study Title: TRITON3: A Multicenter, Randomized, Open-label Phase 3 Study of Rucaparib versus Physician’s Choice of Therapy for Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency

STATISTICAL ANALYSIS PLAN

TRITON3: A Multicenter, Randomized, Open-label Phase 3 Study of Rucaparib versus Physician's Choice of Therapy for Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency

PROTOCOL: CO-338-063

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ABBREVIATIONS AND SPECIALIST TERMS

AE(s)	adverse event(s)
ANCOVA	analysis of covariance
AR	androgen receptor
ATM	ataxia telangiectasia mutated serine/threonine kinase
BID	twice daily
BPI-SF	Brief Pain Inventory – Short Form
BRCA	breast cancer gene
CBR	clinical benefit rate
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating cell-free tumor DNA
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ER	exposure-response
EQ-5D-5L	EuroQol five-dimension scale (five levels of severity)
FACT-P	Functional Assessment of Cancer Therapy - Prostate
HR	hazard ratio
HRD	homologous recombination deficiency
IDMC	Independent Data Monitoring Committee
IRR	independent radiology review
ITT	intent-to-treat
KM	Kaplan-Meier
LOH	loss of heterozygosity
mCRPC	metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
ORR	overall response rate
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PARPi	PARP inhibitor
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease

PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient reported outcome
PSA	Prostate-specific antigen
PSA50	PSA response rate (≥ 50% Reduction)
PSA90	PSA response rate (≥ 90% Reduction)
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
PFS	Radiographic progression-free survival
rPFSinv	Radiographic progression-free survival, investigator assessed
rPFSirr	Radiographic progression-free survival, independent radiology reviewer assessed
SACT	subsequent anti-cancer therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
StD	standard deviation
SOC	System Organ Class
SOP	standard operating procedure
TEAE(s)	treatment-emergent adverse event(s)
TOI	trial outcome index
ULN	upper limit of normal
VAS	Visual Analogue Scale

1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for the clinical study report (CSR) for Clovis Oncology protocol CO-338-063 "TRITON3: A Multicenter, Randomized, Open-label Phase 3 Study of Rucaparib versus Physician's Choice of Therapy for Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency".

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study findings by prespecifying the statistical approaches to the analysis of study data prior to the snapshot for the primary endpoint in this study. This SAP provides additional details concerning the statistical analyses that are already outlined in the original protocol dated 12 October 2016, protocol amendment 1 (dated 7 December 2017), protocol amendment 2 (dated 19 June 2018), protocol amendment 3 (dated 27 August 2020), and protocol amendment 4 (dated 18 February 2022). TRITON3 SAP Version 3.0 (1 July 2022) replaces Version 2.0 (28 Feb 2022) and Version 1.0 (23 Oct 2019). A brief summary of the key changes is provided in Appendix 5.

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 Outlined in Protocol

Table 1. Primary, Secondary and Exploratory Objectives

Primary Objectives
To assess the efficacy of rucaparib versus physician's choice of treatment based on radiographic progression free survival (rPFS) in mCRPC patients with HRD who progressed on prior AR-directed therapy and have not yet received chemotherapy in the castration-resistant setting
Secondary Objectives
To assess overall survival (OS)
To assess objective response rate (ORR) using modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in patients with measurable (nodal or visceral) disease
To assess duration of response (DOR) using modified RECIST Version 1.1 in patients with measurable (nodal or visceral) disease
To assess time to PSA progression
To assess PSA response ≥ 50% (all patients) To assess PSA response ≥ 90% (all patients)
To evaluate Patient reported Outcome (PRO) using the following instruments: • EuroQol 5 dimensions 5 level questionnaire (EQ-5D-5L) • Functional Assessment of Cancer Therapy–Prostate (FACT-P) • Analgesic drug score • Brief Pain Inventory–Short Form (BPI-SF)
To assess clinical benefit rate (CBR)
To assess sparse pharmacokinetics (PK)
To assess safety and tolerability
Exploratory Objectives
To assess concordance in BRCA/ATM gene mutation status in matched pre-screening biopsy tissue, archival primary and metastatic tumor tissue, and plasma circulating cell-free tumor DNA (ctDNA)
To assess changes in the molecular profile over time of matched pre and post-treatment tumor or plasma samples
To evaluate loss of heterozygosity (LOH) in metastatic disease site biopsy and archival primary and metastatic tumor tissue samples
To evaluate mechanisms of response and resistance in ctDNA and progression tumor tissue samples

2.2 Trial Design

This is an ongoing Phase 3, multicenter, randomized, study of rucaparib versus physician's choice of second-line AR-directed therapy (abiraterone acetate or enzalutamide) or docetaxel as treatment for mCRPC patients who have progressed on one prior AR-directed therapy (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent) and have not yet received chemotherapy in the castration resistant setting. Patients who received prior PARPi treatment will be excluded. This study will enroll mCRPC patients with a deleterious mutation in BRCA (BRCA1 or BRCA2) or ATM.

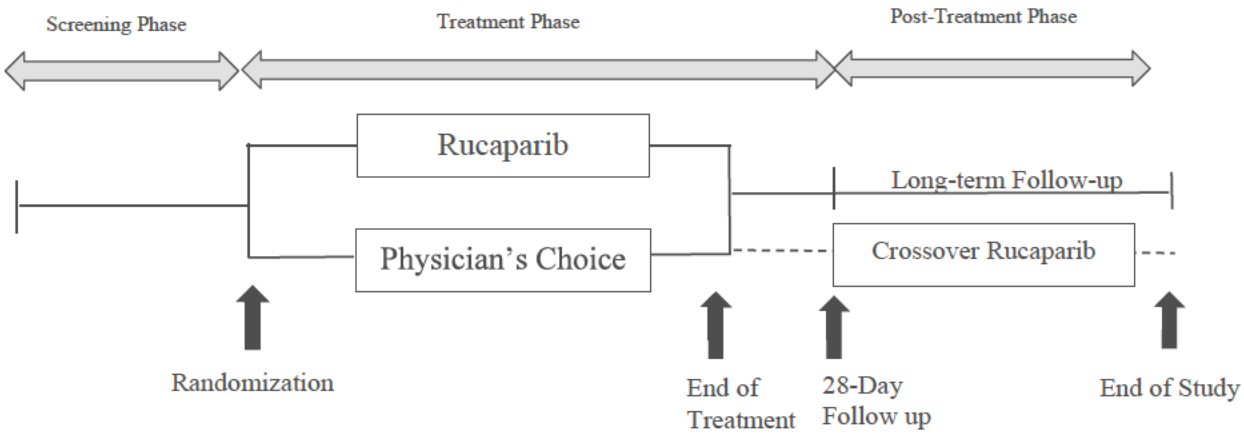
This study consists of a Pre-screening and Screening Phase (denoted as Screening Phase in this document), Randomization, Treatment Phase, Post Treatment Phase, and Cross-over Phase (if applicable). Patients will receive rucaparib monotherapy or physician's choice of comparator therapy (pre-designated prior to randomization) in the Treatment Phase, and will undergo procedures and assessments including regular safety and efficacy evaluations during the entire conduct of the study. Patients randomized to the control arm in the Treatment Phase will have the opportunity to receive treatment with rucaparib in the Cross-over Phase.

Eligible patients will be randomized 2:1 to receive rucaparib (600 mg twice daily [BID]) or physician's choice of either docetaxel or AR-directed therapy (abiraterone acetate or enzalutamide, whichever the patient has not yet received). The physician's choice of agent in the control arm must be prespecified prior to randomization. The randomization assignments are stratified by the patients' ECOG performance status (0 vs 1), presence vs absence of hepatic metastases, and gene (BRCA1 vs BRCA2 vs ATM) to maintain balance between treatment groups.

Patients must have a deleterious mutation in BRCA or ATM in order to be eligible for the study. Mutations may be identified by local testing, or through central testing provided by the sponsor. Patients will be randomized after confirmation that all eligibility criteria in the screening phase have been met.

Patients will receive study drug until radiographic disease progression is confirmed by independent radiology review (IRR) based on modified RECIST Version 1.1[1] (for nodal/visceral lesions only) and PCWG3[2] (for bone lesions only) criteria, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, loss to follow up, or withdrawal of consent. If a patient demonstrates radiographic progression per investigator assessment while receiving treatment with study drug, but continues to derive clinical benefit, then continuation of treatment beyond progression is permitted. In such cases, the patient must consent prior to continuing treatment with study drug. Figure 1 shows the schedule of the study design with the Screening Phase followed by the randomized Treatment Phase and lastly the Post-treatment Phase with an option to cross over for patients randomized to physician's choice.

Figure 1. Schema of Study Design



Disease/tumor assessments will be performed at baseline (screening) and 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 at the Treatment Discontinuation Visit, if applicable. Patients in the docetaxel arm will receive study drug for a maximum of 10 cycles only and so may not be actively on treatment at the time of disease progression.

Patients who cross over to rucaparib treatment after initial disease progression will have tumor assessments every 8 calendar weeks (±7 days) from initiation of rucaparib treatment up to 24 weeks and every 12 calendar weeks (±7 days) thereafter.

Additional assessments and procedures during the study will include: AEs; physical examinations; 12-lead ECGs, vital signs and weight measurements; local laboratory hematology, serum chemistry, urinalysis, and PSA measurements; blood samples for ctDNA and pharmacogenomics analyses; plasma samples for PK analysis; concomitant medications, therapies, and procedures; study drug administration and accountability; and PRO.

Patients randomized to physician's choice have the option to cross over to receive rucaparib upon progression (by IRR) per modified RECIST Version 1.1/PCWG3 in the treatment phase. Once the analysis of the primary endpoint has been performed, radiographic scans will continue to be performed by the investigator as scheduled, but will no longer be read by IRR. Thus, the eligibility for cross over will be determined by radiographic progression as assessed by the investigator based on modified RECIST Version 1.1/PCWG3 assessments.

2.3 Sample Size Determination

The total enrollment planned is approximately 400 patients, with 300 patients in the BRCA subgroup and approximately 100 patients in the ATM subgroup. The median rPFS is assumed to be 6 months for the control arm and 10 months for rucaparib in the BRCA subgroup and 9 months for rucaparib in the total population. A sample size of 300 patients in the BRCA subgroup should result in approximately 200 events of rPFS, which will provide approximately 90% power to detect a hazard ratio (HR) of 0.6 at a one-sided 0.025 significance level (and equivalently at a two-sided 0.05 significance level). A sample size of

approximately 400 total patients should result in approximately 270 events of rPFS, which will provide approximately 90% power to detect a hazard ratio (HR) of 0.67 at a one sided 0.025 significance level (and equivalently at a two-sided 0.05 significance level).

April 2022 – Update on Sample Size per IDMC: Based on discussions with the TRITON3 IDMC, Clovis was informed that the planned number of 200 events in the BRCA subgroup would not be reached in a timely manner congruent with study objectives or may not be reached at all. The IDMC and Clovis further discussed and agreed that it was important to maintain at least 80% power for the rPFSirr analysis in the BRCA subgroup, and thus at least 160 rPFSirr events must be observed, under the original HR assumptions above. Additionally, both Clovis and the IDMC felt that an appropriate amount of follow-up of approximately 6 months should be considered such that all patients would have the opportunity to have at least 3 post baseline scans. The last patient in TRITON3 was randomized on February 28, 2022 allowing for 6 months of follow-up in August 2022. Using prospective IDMC projections and observed monthly rates of events, it was estimated that 160 to 170 events in the BRCA subgroup would be observed by August 2022, after which event accumulation would start to decrease. Therefore, the primary analysis of TRITON3 will occur after at least 160 rPFSirr events in the BRCA Subgroup have occurred and after at least 6 months of follow-up for the last patient has been accrued.

2.4 Independent Data Monitoring Committee (IDMC)

The IDMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The IDMC will provide recommendations about the continuation, revision, or termination of the study. Details regarding the IDMC will be documented in a separate committee charter.

3 GENERAL ANALYSIS CONVENTIONS

All efficacy analyses will be done at a two-sided 0.05 significance level including all data from the randomized portion of the study.

The efficacy data for the patients crossing over from physican's choice to rucaparib will generally be presented separately.

The summary tables will be presented by randomized treatment group (rucaparib vs physican's choice) and may also present each comparator treatment (abiraterone acetate, enzalutamide, or docetaxel) separately. Generally, summary outputs will be presented separately for the BRCA subgroup and for the ITT Population.

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. Months will be calculated as number of days divided by 30.4375.

The Kaplan-Meier (KM) methodology will be used to summarize time-to-event variables. If estimable, 50th percentile (median) with 95% confidence intervals will be presented. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups for the primary endpoint. The number of patients with events and the number of censored patients will also be presented. For stratified analyses, if one or more of the strata contain few patients (eg, < 5 patients) or only patients from a single treatment group, or if the convergence criteria in SAS are not met, strata will be combined to ensure a sufficient number of patients in each stratum by first removing the hepatic metastases variable (which is equivalent to combining the 2 categories) and then combining the BRCA1/BRCA2 categories, if necessary.

For secondary (other than OS), exploratory, and subgroup analyses, statistical testing will not be stratified. Stratified analyses may be performed as sensitivity analyses. For time-to event analyses the log-rank test will be used for treatment group comparisons.

All data will be used to their maximum possible extent without any imputations for missing data.

Unless otherwise indicated, baseline is defined as the last measurement on or prior to the first day of study drug administration or randomization date, if the patient was never treated.

3.1 Analysis Populations

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

Intent-to-Treat Population – The Intent-to-Treat (ITT) Population will consist of all randomized patients (ie, patients with BRCA-mutated mCRPC and patients with ATM-mutated mCRPC) .

BRCA Subgroup – The BRCA subgroup will consist of patients in the ITT Population with BRCA-mutated mCRPC.

IRR Efficacy Population – The IRR Efficacy Population will consist of all patients evaluable for response by modified RECIST Version 1.1/PCWG3 criteria per independent radiology review.

Investigator Efficacy Population – The Investigator Efficacy Population will consist of all patients evaluable for response by modified RECIST Version 1.1/PCWG3 criteria per investigator.

3.2 Statistical Hypothesis

The primary statistical hypothesis for this study is to test for differences in rPFSirr using a stratified log-rank test.

H_0: HR (rucaparib/physician's choice) ≥ 1

H_a: HR (rucaparib/physician's choice) < 1

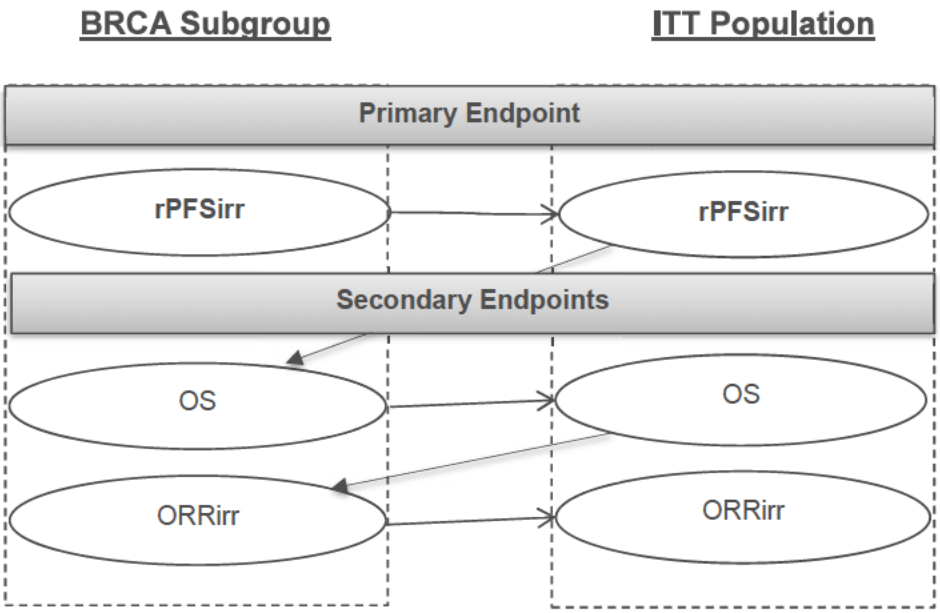
The stratification factors used for randomization are ECOG performance status (0 vs 1), presence vs absence of hepatic metastases, and gene (BRCA1 vs BRCA2 vs ATM). The first test in the step-down procedure is in the subgroup of BRCA patients (thus the stratification for gene will be only 2 levels). The second test is in the ITT Population.

All efficacy analyses will be based on the randomization strata given at randomization, however, a sensitivity analysis of rPFSirr may be performed using the actual strata if patients have been allocated incorrectly.

3.3 Step-down Procedure of Primary and Secondary Endpoints

The primary and key secondary endpoints will first be tested among the BRCA subgroup and then in the ITT Population (ie, BRCA + ATM) using an ordered step-down multiple comparisons procedure. The primary endpoint of rPFSirr (radiographic progression-free survival by independent radiology review) in the BRCA subgroup will be tested first at a two-sided 0.05 significance level. If rPFSirr in the BRCA subgroup is statistically significant, then rPFSirr will be tested in the ITT Population. Continuing in an ordered step-down manner, the key secondary endpoints will be tested at the two-sided 0.05 significance level. To preserve the overall Type 1 error rate, statistical significance will only be declared for a secondary endpoint if the primary endpoints and previous secondary endpoints are also statistically significant. The ordered step-down procedure is illustrated in Figure 2.

Figure 2. Ordered Step-down Procedure



Note: As described in Section 10.2.1, OS will be analyzed at the time of the primary analysis (interim OS analysis) and again for a final OS analysis. If the interim OS results are not statistically significant, p-values for all secondary endpoints will be considered descriptive until the final OS analysis has been performed as part of the step-down procedure.

4 PATIENT DISPOSITION

Patient disposition (analysis population allocation, randomized, discontinued, and primary reason for discontinuation) will be summarized using frequency counts, and the corresponding percentages, by treatment group and overall. Patient disposition will be summarized for the ITT Population and may also be summarized for the prespecified Analysis Populations and/or gene subgroups.

5 PROTOCOL DEVIATIONS

Important protocol deviations will be identified prior to releasing the treatment codes for primary efficacy analysis in accordance with Clovis SOP CR019 (Identification, Documentation, Management and Review of Protocol Deviations). A listing with the important protocol deviations will be presented. No patients will be excluded from the Efficacy Populations due to protocol deviations.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized, by treatment group and overall, for the ITT Population and may also be summarized for the prespecified Analysis Populations and/or gene subgroups.

6.1 Demographics

The demographic variables will be summarized with frequency tabulations that will focus on identifying differences between treatment groups in the extreme values of the distributions. Descriptive statistics may also be used to summarize the quantitative variables. The demographic variables presented will include age, height, weight, race, ethnicity, smoking status, and geographic region using 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 Other 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;
- Geographic Regions: North America, Europe, Other and separately US, Non-US.

These categorizations may be adjusted if the majority of the data lies in only 2 or 3 of the categories.

6.2 Baseline Clinical Characteristics

The following variables will be summarized with frequency tabulations

- Time since diagnosis, years (0 to 3, > 3 to 6, > 6 to 9, > 9);
- Clinical tumor stage at initial prostate cancer diagnosis (Stage I, IIA, IIB, III, IV);
- Clinical regional lymph node stage at initial prostate cancer diagnosis (N0, N1, NX);
- Distant metastasis (M status) at initial prostate cancer diagnosis (M0, M1, MX);
- Gleason score (<7, 7, 8, 9, not reported);
- ECOG performance status (0, 1, ≥2);
- Presence or absence of hepatic metastases;
- Presence or absence of lung metastases;
- HRR gene (BRCA1, BRCA2, or ATM);
- BRCA germline/somatic status;
- ATM germline/somatic status;
- 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 these variables, where appropriate.

6.3 Medical History

The medical history will be summarized for the safety population. 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 (SOC) and Preferred Term (PT).

7 STUDY DRUG EXPOSURE AND COMPLIANCE

Study drug exposure will be summarized for all patients in the Safety Population. The duration of treatment will be calculated as the number of days from the first dose of study drug to the day of the last dose of study drug +1. Descriptive statistics and frequencies/percentages for appropriate categorizations will be used to summarize treatment duration for each treatment arm and also for each of the physician's choice therapies separately.

The number of patients with at least one dose reduction or interruption based on the dosing log will be summarized with frequencies and percentages. In addition, for the patients randomized to rucaparib, the number of patients on each dose level will be summarized (ie, 600 mg BID, 500 mg BID, 400 mg BID, etc.) in order to assess patients with multiple levels of dose reductions.

8 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be summarized for all patients in the Safety Population. All concomitant treatments documented during the study period will be summarized in frequency tabulations for each randomized treatment group and overall. Prior/concomitant medication coding will utilize the World Health Organization (WHO) Drug Dictionary version Global-B3 202003 or later.

Prior medications will only be presented in listings. 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.

9 EFFICACY VARIABLES

9.1 Primary Efficacy Variables

The primary efficacy variable is radiographic PFS by independent radiology review (rPFSirr) in the BRCA subgroup of patients. Following the test in the BRCA subgroup, rPFS by IRR for the ITT Population will be tested in the step-down procedure. Radiographic PFS, as assessed by the investigator (rPFSinv), is defined similarly and will be supportive of the primary endpoint.

9.2 Secondary Efficacy Variables Included in the Step-down Testing

Secondary variables included in the step-down testing procedure:

1. Overall survival (OS), BRCA subgroup → ITT Population
2. Objective response rate (ORR) by IRR, BRCA subgroup → ITT Population

Additional secondary variables:

- Duration of response (DOR) by IRR
- Time to PSA progression
- PSA response (≥ 50% reduction)
- PSA response (≥ 90% reduction)
- Patient-reported outcome endpoints
  - FACT-P
  - BPI-SF
  - EQ-5D-5L
- Clinical benefit rate (CBR)

9.3 Exploratory Efficacy Variables

- To assess concordance in BRCA/ATM gene mutation status in matched screening biopsy tissue, archival primary and metastatic tumor tissue and plasma ctDNA
- To assess changes in the molecular profile over time of matched pre and post-treatment tumor or plasma samples
- To evaluate LOH in metastatic disease site biopsy and archival primary and metastatic tumor tissue samples;
- To evaluate mechanisms of response and resistance in ctDNA and progression tumor tissue samples

10 EFFICACY ANALYSIS

10.1 Primary Efficacy Analysis

The primary efficacy endpoint for the study is rPFSirr, defined as the time from randomization to the first objective evidence of radiographic progression, or death due to any cause (whichever occurs first), +1 day. Radiographic disease progression includes confirmed soft tissue disease progression per modified RECIST Version 1.1 and confirmed bone disease progression per PCWG3 criteria.

Patients who withdraw from treatment prior to progression will be followed for disease status and survival whenever possible.

Scans and deaths occurring after the start of subsequent anticancer treatment (SACT) disallowed per protocol will be excluded from the primary PFS analysis. However, if bone progression started prior to SACT, scans following SACT may be used for the confirmation of bone progression (as the progression date will precede the start of SACT).

A gap in evaluable scans may affect how subsequent scans and events (progression or death) are counted or censored. This gap is defined as two or more missed expected scans resulting

in a duration of greater than 25 weeks (ie, 2 times the 12-week scan interval plus 1 week for protocol visit window allowance) between scans. Any event (death or progression) occurring before the end of this gap may be included in the PFS analysis. If a patient has an event (progression or death) immediately following the gap, the patient will be censored at the last scan date prior to the gap. If a patient has an evaluable non-PD scan immediately following the gap, the gap-clock will reset and subsequent scans and events (progression or death) may be used in the primary PFS assessment (barring intervening SACT, as above).

Patients without a documented event per the rules above will be censored on the date of their last tumor assessment (ie, radiologic assessment), or the date of randomization if no post-baseline tumor assessments have been performed.

Note that patients receiving docetaxel in the Physician's Choice arm only receive up to 10 cycles of study drug. Patients completing their docetaxel treatment without documented disease progression by IRR should continue to be assessed periodically until radiographic progression by IRR is determined. There should not be intervals > 25 weeks between scans for these patients.

The primary endpoint of rPFSirr will be analyzed using Cox proportional hazard methodology. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The stratified log-rank test will be the official test used for the hierarchical testing outlined in Section 3.3. Employing a step-down procedure, a test for significance between the 2 treatment groups will be performed for rPFSirr in the BRCA subgroup of patients. If the result is significant (2-sided, $\alpha = 0.05$), then rPFSirr will be tested for the ITT Population.

Assessment of rPFS by the investigator (rPFSinv) will also be conducted as a supportive analysis for rPFSirr.

10.1.1 Censoring Distribution

Sensitivity analyses for rPFS will be performed to evaluate the impact of censored patients. The following analyses will be performed:

- Patients without radiographic progression who discontinued the study due to clinical progression will be considered to have an event of rPFS on the date of the last dose of study drug.
- Patients who discontinued the study without radiographic progression, but who had confirmed PSA progression, will be treated as having an event of rPFS on the date of PSA progression.
- Patients who initiate subsequent anti-cancer therapy (SACT) prior to an event of rPFS, but who have an event of rPFS at a subsequent radiographic assessment following initiation of SACT, will have this rPFS event counted.

Additional sensitivity analyses may also be performed to evaluate the robustness of the study results. These analyses will be considered exploratory and will likely be motivated by the observed results.

10.2 Secondary Efficacy Analyses

If the primary endpoint is statistically significant, for both the BRCA subgroup and the ITT Population, then key secondary efficacy endpoints will be tested in a step-down order. To preserve the overall Type-1 error rate, statistical significance will only be declared for a secondary endpoint if the primary endpoints and any previous secondary endpoints are also statistically significant. All tests will be performed at the 2-sided 0.05 significance level.

10.2.1 Overall Survival

Overall survival time will be calculated in months as the time from randomization to death (by any cause) +1 day. Patients who have not died will be censored on the date the patient was last known to be alive.

Overall survival will be analyzed using the Cox proportional hazard methodology and a log-rank test. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The stratified log-rank test will be the official test used for the hierarchical testing outlined in Section 3.3.

It is anticipated that the data for overall survival will be heavily censored at the time of the primary endpoint analysis. To adjust for multiple analyses of OS at a later stage, a stopping rule will be applied. The Haybittle-Peto[3, 4] stopping rule will be applied where any interim (early) overall survival with a p-value < 0.001 can be used to claim superiority. This means that a two-sided p-value very close to 0.05 can still be utilized at the final analysis which is projected to be once approximately 70% of the death events has been collected.

For both the interim and final overall survival analyses, the duration of follow-up will be summarized using medians for both the BRCA subgroup and the ITT Population in the following groups of patients:

- In censored patients: Time from randomization date to date of censoring (ie, date last known to be alive) + 1 day
- In all patients (ie, both censored patients and those who have died):
  - For censored patients, treat censored dates as OS event dates and then calculate follow up as time from randomization date to OS event date + 1 day or
  - For patients with OS events, treat OS event dates as censored dates and then calculate follow up as time from randomization date to censoring date + 1 day

Kaplan-Meier methodology will be used to estimate the median duration of follow up for the above patient groups.

To explore the impact of cross over to rucaparib treatment on OS, the following sensitivity analyses may be conducted:

- Censoring the data at time of cross over (ie, patients who crossed over from physician's choice to rucaparib)
- Time-varying covariate for starting rucaparib[5]
- Two-stage estimation[6]

10.2.2 Objective Response Rate by Modified RECIST v1.1/PCWG3

The ORR as assessed by IRR will be analyzed for the IRR Efficacy Population. The confirmed response rate will be summarized. 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 the 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/confirmed PCWG3 progression event. Only tumor scans included for evaluation of the primary endpoint are considered for the ORR endpoint.

ORR will be summarized with frequencies and percentages together with 95% confidence intervals (CI) and compared between treatments by using a Cochran-Mantel-Haenszel (CMH) test. Per the step-down procedure, the BRCA subgroup will be tested followed by the ITT Population.

In addition, the frequency and proportion of patients will be summarized for each of the following best confirmed response categories:

- CR
- PR
- Stable disease (SD)
- Progressive disease (PD)
- Not evaluable (for example discontinuations or deaths before first tumor assessment)

Similar analyses will be performed for ORR as assessed by the investigator for the Investigator Efficacy Population.

10.2.3 Duration of Response

The DOR as assessed by IRR will be analyzed in the IRR Efficacy Population for the subgroup of patients who have a confirmed response. DOR for confirmed response will be measured from the date of the first response (which is subsequently confirmed) until the first date that radiographic progressive disease is documented. DOR will be calculated in months as the time from the first date of the scan showing a response to the first scan with disease progression +1 day. Any patients with an ongoing response will be censored at the date of the last post-baseline scan.

DOR will be analyzed using Cox proportional hazard methodology and a log-rank test. The hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The BRCA subgroup will be tested followed by the ITT Population.

Similar analyses will be performed for DOR as assessed by the investigator for the Investigator Efficacy Population.

10.2.4 Time to PSA Progression

Time to PSA progression is defined as the time from randomization 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 + 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.

This endpoint will be analyzed in patients with both Baseline and at least 1 post-baseline value using Cox proportional hazards methodology. The hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The BRCA subgroup will be tested followed by the ITT Population.

10.2.5 PSA Response Rate (≥ 50% Reduction)

Confirmed PSA response (PSA50) 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 10.2.4). 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 all patients with PSA values at baseline.

PSA response in patients with both Baseline and at least 1 post-Baseline value will be summarized with frequencies and proportion together with 95% CI and compared between treatment groups using a CMH test. The BRCA subgroup will be tested followed by the ITT Population.

10.2.6 PSA Response Rate (≥ 90% Reduction)

Confirmed PSA response (PSA90) is defined as having 2 consecutive PSA values (at least 3 weeks apart) that are at least 90% lower than baseline and that occur prior to PSA progression (as defined in Section 10.2.4). 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 all patients with PSA values at baseline.

PSA90 response in patients with both Baseline and at least 1 post-Baseline value will be summarized with frequencies and proportion together with 95% CI and compared between treatment groups using a CMH test. The BRCA subgroup will be tested followed by the ITT Population.

10.2.7 Patient-Reported Outcomes

The patient reported outcome data will be scored and summarized in accordance with the scoring manuals for the respective questionnaires. Appendix 1 through Appendix 4 include the English version of the questionnaires used. Analysis tables for PROs may be limited to time points with a meaningful amount of patient data. Additionally, patient experience data which includes aspects of healthcare utilization and clinical outcome assessments will be assessed.

For the protocol-specified Treatment Discontinuation visit (which could occur at any time), the PRO assessment will be assigned to the scheduled Cycle to which the assessment date is closest. If multiple assessments are then present at a given Cycle, the scheduled visit assessment will be used.

10.2.7.1 Functional Assessment of Cancer Therapy – Prostate (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, StD, minimum, median, and maximum). Patients who do not have both a baseline measurement and at least 1 post-baseline measurement will not be included.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using analysis of covariance (ANCOVA) with treatment group and baseline measurement for the parameter as a continuous covariate.

Distribution of item level responses and change from baseline in these item levels for the following 5 questions will be summarized by Cycle over the first year of participation in the randomized portion of the study:

<u>From the Physical Well-being questions:</u>

GP1: I have a lack of energy
GP2: I have nausea
GP5: I am bothered by side effects of treatment
GP7: I am forced to spend time in bed

<u>From the Functional Well-being questions:</u>

GF1: I am able to work

Change from baseline will be categorized as: Improved, Stable, Worsening 1 category, Worsening 2 categories, Worsening 3 categories, or Worsening 4 categories. This will be summarized in a table and may be displayed graphically.

10.2.7.2 Brief Pain Index – Short Form (BPI-SF)

The primary assessment of pain from the BPI-SF questionnaire will be taken from item #3 (pain at its worst in the last 24 hours). The other pain severity measures (least, average, and current pain) will be analyzed separately and as a composite (along with item #3, as a mean severity measure) score. BPI pain interference will be scored using the mean of the 7 interference items. For the mean to be calculated, at least 4 of the 7 total interference items must have been completed on a given administration.

Descriptive statistics will be presented for each score, change from baseline, and percent change from baseline at each post-baseline time point for the pain intensity measures and the mean pain interference score.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using ANCOVA with treatment group and baseline measurement for the parameter as a continuous covariate.

10.2.7.3 EQ-5D-5L

Analyses of changes and/or percent changes 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.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an ANCOVA with the treatment group and baseline measurement for the parameter as a continuous covariate.

10.2.7.4 Analgesic Use Questionnaire

The analgesic use questionnaire rates the strength (from 0-3) of pain medication used within the last 24 hours and is completed at the same time points as the other PROs. This questionnaire is designed to be used in conjunction with assessment of pain, so will not be summarized in a stand alone analysis.

10.2.7.5 PRO Patient Disposition and Completion Rate

The following analyses will be summarized to characterize PRO data (eg, FACT-P and EQ-5D) completeness over the first year of participation in the randomized portion of the study.

PRO patient disposition will be displayed in a table (and possibly graphically) with the cumulative patient disposition by treatment per PRO assessment window for each scheduled

post-baseline visit (eg, Cycle 1 Day 1, Cycle 2 Day 1, etc.). The following categories will be summarized:

- PRO assessment expected;
- PRO assessment not expected due to disease progression;
- PRO assessment not expected due to other reasons; and
- Patient ongoing in study, PRO assessment time point not yet reached.

Overall PRO completion rates will be summarized for each PRO assessment window. Overall completion rate is defined as the number of patients having at least 1 response in the PRO instrument, divided by the number of patients expected to have completed a PRO assessment at a given visit.

10.2.7.6 PRO Correlation With Adverse Events

The correlation between EQ-5D and FACT-P will be summarized by tabulating the mean EQ-5D-5L subscale score for the a) mobility, b) self-care, and c) usual activities dimensions at each cycle, within the first 6 months of participation in the randomized portion of the study, broken down by response to FACT-P item GP1 (I have lack of energy) as well as by Grade 1, 2, or 3 CTCAE maximum grade of asthenia/fatigue.

The mean EQ-5D-5L subscale scores of a) self-care and b) usual activities dimensions at each cycle, within the first 6 months of participation in the randomized portion of the study, will be broken down by response to FACT-P item GP2 (I have nausea) as well as by Grade 1, 2, or 3 CTCAE maximum grade of nausea.

10.2.8 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: eg, 4-, 6-, 9-, and 12-months, with frequencies and percentages along with 95% CIs. 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 CBR will be summarized with frequencies and proportions together with 95% CI and compared between treatment groups by using CMH test. The BRCA subgroup will be tested followed by the ITT Population.

10.2.9 Sparse Pharmacokinetics

For patients receiving rucaparib (except those in the Cross-over Phase), plasma samples are to be collected for trough level PK analysis of rucaparib before the morning dose on Study Day 29, Day 57, Day 85, and Day 113 as close as posssible to 12 hours after the

previous dose. Samples are not to be collected in patients receiving comparator therapy or crossing over to rucaparib.

In all patients with at least one PK sample collected, the trough plasma rucaparib PK data (C_{min}) and summary statistics (N, mean, StD, 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 (ER) analyses, and the results will be reported separately.

10.3 Exploratory Efficacy Analyses

10.3.1 Concordance in BRCA1/BRCA2/ATM Gene Mutation Status

Pairwise comparisons will be performed using available plasma and tissue (including archival and contemporaneous samples) test results to explore the concordance in BRCA1, BRCA2, and ATM gene alterations.

10.3.2 Molecular Profile Over Time

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 may be described using graphical plots and/or descriptive statistics.

10.3.3 Loss of Heterozygosity (LOH)

The percentage of 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.

10.3.4 Mechanisms of Response and Resistance

Genomic test results from plasma and tissue samples will be used to evaluate mechanisms of innate and acquired resistance to rucaparib. Due to the exploratory and complex nature of these analyses, analyses are likely to be reported using graphical plots and/or descriptive statistics (or other methods as appropriate).

10.4 Examination of Efficacy in Subgroups

Subgroup analyses of the primary endpoint (rPFSirr) will be presented for the following:

- The stratification factors used for randomization
  - ECOG performance status (0, 1)
  - Presence, absence of hepatic metastases
  - Gene (BRCA1, BRCA2, ATM)
- Age groups (< 65, 65-74, ≥75)

- Race (White, Other, Unknown)
- Region (US, non-US)
- Germline status (germline, somatic) in the BRCA subgroup
- Type of physician's choice of therapy
  - AR-directed therapy (enzalutamide + abiraterone) vs rucaparib
  - Docetaxel vs rucaparib

11 SAFETY ANALYSIS

The safety analyses will be presented for the Safety Population presenting the data for each treatment group separately and overall. All safety data which is considered treatment-emergent will be summarized. Treatment-emergent is defined as safety data with an onset date on or after the date of first dose of study drug until the date of the last study drug plus 28 days, or up to the date of first dose of rucaparib for those patients who cross over from physician's choice.

Safety data will be presented for the Cross-over phase separately, using the safety assessment before or on the date of first dose of rucaparib as the baseline value for the Cross-over phase for the patients who cross over.

11.1 Adverse Events

AEs will be classified using the MedDRA version 23.0 or higher classification system. The severity of the toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) whenever possible.
Treatment--emergent adverse events (TEAEs) are defined as events with an onset date on or after the date of first dose of study drug until the date of the last study drug plus 28 days, or up to the date of first dose of rucaparib for those patients who cross over from physician's choice of therapy. Also AEs 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 AE meets the definition for treatment-emergent.

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

MedDRA PTs will be combined for the following similar terms:

- Asthenia/Fatigue;
- Alanine Aminotransferase (ALT)/ Aspartate Aminotransferase (AST) Increased;
- Anaemia and/or Decreased Haemoglobin;
- Thromobocytopenia and/or Decreased Platelets;
- Neutropenia and/or Decreased Absolute Neutrophil Count (ANC);

- Rash (PTs below):

Blister	Blood blister	Dermatitis	Dermatitis acneiform	Dermatitis allergic
Dermatitis bullous	Dermatitis contact	Eczema	Palmar-plantar erythrodysaesthesia syndrome	Photosensitivity reaction
Pruritus	Pruritus allergic	Pruritus genital	Psoriasis	Rash
Rash erythematous	Rash maculo-papular	Rash papular	Rash pruritic	Scrotal dermatitis
Seborrhoeic keratosis	Skin burning sensation	Skin candida	Skin discolouration	Skin disorder
Skin exfoliation	Skin haemorrhage	Skin hyperpigmentation	Skin induration	Skin lesion
Skin oedema	Skin toxicity	Skin ulcer	Solar dermatitis	Urticaria

Separate tables will be presented as follows:

- TEAE Overview;
- All TEAEs;
- Treatment-related TEAEs;
- Grade 3 or greater TEAEs;
- Grade 3 or greater treatment-related TEAEs;
- Serious TEAEs;
- Serious treatment-related TEAEs;
- TEAEs by PT;
- Treatment-related TEAEs by PT;
- 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 drug;
- Treatment-related TEAEs leading to discontinuation of study drug;
- TEAEs resulting in reduction of study drug;
- Treatment-related TEAEs resulting in reduction of study drug;
- TEAEs resulting in interruption of study drug;
- Treatment-related TEAEs resulting in interruption of study drug;
- TEAEs resulting in reduction or interruption of study drug;

- Treatment-related TEAEs resulting in reduction or interruption of study drug;
- TEAEs resulting in reduction or interruption or discontinuation of study drug;
- Treatment-related TEAEs resulting in reduction or interruption or discontinuation of study drug.

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 maximum grade will be summarized.

The time to certain adverse events will also be explored using KM methodology. The time to event will be defined as 1+ the number of days from the first dose of study drug to the start of the first applicable adverse event. The cumulative incidence will be presented in a 1-KM graph for just the patients with an event and the median time to onset will be calculated together with the 95% CI for the following:

- First TEAE and that led to dose reduction;
- First treatment-related TEAE that led to dose reduction;
- First TEAE and that led to dose interruption;
- First treatment-related TEAE that led to dose interruption;
- First TEAE and that led to discontinuation of study drug;
- First treatment-related TEAE that led to discontinuation of study drug;
- First TEAE of combined terms for anemia;
- First treatment-related TEAE of combined terms for anemia.

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

Transfusions (blood or plasma) and concomitant medications / growth factor support will be provided in patient listings and the number of transfusions will be summarized.

11.2 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 date of the first dose of study drug until the date of the last dose of study drug plus 28 days, or up to the date of first dose of rucaparib for those patients who cross over from physician's choice. Laboratory values collected during the on-

treatment period will be included in the summary tables. The laboratory values collected outside of 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 (eg, 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, StD, 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 presented.

Summary tables and longitudinal plots of the mean (and/or percent) changes from baseline to each scheduled visit may also be presented for select laboratory parameters. These outputs may exclude visits for which only a small percentage (eg, ≤ 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.

11.3 Vital Signs

The on-treatment period will be defined as the time from first dose of study drug to 28 days after the last dose of study drug, or start of first dose of rucaparib for those patients who cross over from physician's choice. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected outside of the on-treatment period will only be presented in the data listings.

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

11.4 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, StD, minimum, median, and maximum) will be used to summarize ECG parameters at Screening and at Treatment Discontinuation.

11.5 Examination of Safety in Subgroups

Safety will be further explored in the following subgroups:

- HRR gene (BRCA1, BRCA2, ATM)
- Germline status (germline, somatic) in the BRCA subgroup
- Age groups (< 65, 65-74, ≥75)
- Race (White, Other, Unknown)
- Region (US, non-US)
- Type of physician's choice therapy
  - AR-directed therapy (enzalutamide + abiraterone) vs rucaparib
  - Docetaxel vs rucaparib

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Appendix 1 FACT-P (Version 4)

A sample form for the FACT-P is below and background for the questionnaire is available at http://www.facit.org/facitorg/questionnaires.

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Appendix 2 Brief Pain Inventory – Short Form

A sample form for the BPI-SF is below and background for the questionnaire is available at https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html.

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

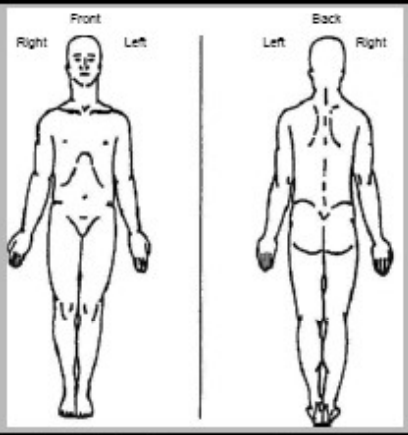
Date: ____/____/____ **Time:** _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ____/____/____ **Time:** _____

Name: _____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

B. Mood

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

C. Walking Ability

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

E. Relations with other people

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

F. Sleep

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

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Appendix 3 Euro-Quality of Life 5 Dimension 5 Level (EQ-5D-5L)

A sample form for the EQ-5D-5L is included on the next page. Background information for the questionnaire is available at https://euroqol.org/.

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

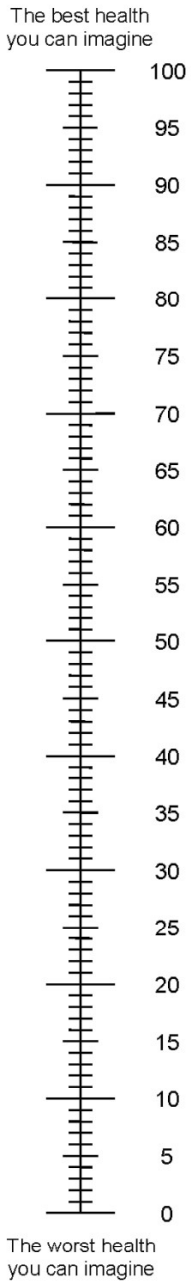
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

Appendix 4 Analgesic Use Questionnaire

A sample form for the Analgesic Use Questionnaire is below:

TRITON3 CLOVIS ONCOLOGY

Study ID #	CO-338-063 (TRITON3)	Site No	
Patient ID:	63-_____-_____	Date	

Analgesic Use Questionnaire

Please indicate the strongest pain medication you have taken within the past 24 hours:

☐ 0 = No pain medication

☐ 1 = Non-opioid pain medication such as aspirin [salicylate], acetaminophen [paracetamol], other non-steroidal anti-inflammatory drug [NSAID], etc.

☐ 2 = Mild opioid pain medication such as codeine, hydrocodone, tramadol, etc.

☐ 3 = Strong opioid pain medication such as morphine, oxycodone, hydromorphone, fentanyl, methadone, etc.

Appendix 5 Amendment History

Brief Description of Notable Changes from SAP version 1.0 (23 Oct 2019) to version 2.0 (28 Feb 2022)

- Overall Survival was elevated to the first secondary endpoint analysis included in the step-down procedure [Section 3.3]
- Added a stopping rule (Haybittle-Peto) to adjust for multiple OS analyses (one at time of primary analysis and a final OS analysis when OS data is more mature) [Section 10.2.1]
- Clarified that the log-rank statistic will be used for the PFS and OS analyses in the step-down procedure [Section 3.3, Section 10.1, Section 10.2.1]
- Removed Duration of Response and PSA-based endpoints from the step-down procedure [Section 3.3]
- Pooling strategy to deal with potential small cell sizes among the stratification variables and/or SAS convergence issues was added [Section 3]
- Specified the use of unstratified analyses for all but the primary endpoints [Section 3]
- Clarified censoring rules for PFS analyses [Section 10.1]
- Clarified that after the analysis of the primary endpoint is completed, for patients remaining on physician's choice treatment, the eligibility to cross over (to rucaparib) will be determined by radiographic progression as assessed by the investigator and scans will no longer be read by IRR [Section 2.2]
- PRO analyses for patient experience data which includes aspects of healthcare utilization and clinical outcome assessments were added [Section 10.2.7]
- Specified a combined term for Rash for use in AE tables [Section 11.1]

Brief Description of Notable Changes from SAP version 2.0 (28 Feb 2022) to version 3.0 (1 July 2022)

- Updated the timing of the primary endpoint analysis [Section 2.3]
- Specified the use of stratified analyses for OS in the step-down procedure [Section 3] and [Section 10.2.1]
- Added potential sensitivity analyses to explore the effect of cross over to rucaparib treatment on OS [Section 10.2.1]
- Minor editorial corrections and format changes for consistency with the Clovis style guide