# STATISTICAL ANALYSIS PLAN

# ARIEL4 (Assessment of Rucaparib In Ovarian CancEr TriaL): A Phase 3 Multicenter, Randomized Study of Rucaparib versus Chemotherapy in Patients with Relapsed, BRCA-Mutant, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

| | |
|---|---|
| **PROTOCOL:** | CO-338-043 |
| **VERSION:** | Primary Efficacy Endpoint Version |
| **DATE FINAL:** | 28 October 2020 |
| **SPONSOR:** | Clovis Oncology |

[redacted]

# APPROVAL PAGE

**This document was reviewed by the following Clovis team members:**

[redacted]

**The document was authored by:**

[redacted]

**The document is hereby approved and signed by:**

[redacted]

# TABLE OF CONTENTS

# LIST OF IN-TEXT TABLES



# LIST OF IN-TEXT FIGURES

# ABBREVIATIONS AND SPECIALIST TERMS

| | |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance |
| ATC | Anatomical Therapeutic Chemical |
| BICR | blinded independent central review |
| BID | twice a day |
| BRCA | breast cancer gene |
| BRCA1/2 | breast cancer gene 1 or breast cancer gene 2 |
| CA-125 | cancer antigen-125 |
| CI | confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CR | complete response |
| 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 |
| EMA | European Medicines Agency |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 |
| EORTC QLQ-OV28 | EORTC ovarian cancer module QLQ-OV28 |
| EQ-5D | Euro-Quality of Life 5D |
| FMI | Foundation Medicine, Inc. |
| gBRCA | germline BRCA1/2 mutation |
| GCIG | Gynecologic Cancer InterGroup |
| HR | hazard ratio |
| IDMC | Independent Data Monitoring Committee |
| invPFS | progression-free survival, investigator assessed |
| ITT | intent-to-treat |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | National Cancer Institute |
| NE | not evaluable |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |

| | |
|---|---|
| PFI | progression-free interval |
| PFS | progression-free survival |
| PFS2 | the second event of PFS, in subsequent line of treatment |
| PK | pharmacokinetic(s) |
| PR | partial response |
| PRO | patient-reported outcome |
| PT | Preferred Term |
| QTcB | QT interval corrected using Bazett's method |
| QTcF | QT interval corrected using Fridericia's method |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAP | statistical analysis plan |
| SD | stable disease |
| SOC | System Organ Class |
| StdD | standard deviation |
| tBRCA | tumor tissue mutation in BRCA1 or BRCA2, includes germline and somatic BRCA |
| TEAE | treatment-emergent adverse event |
| 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 blind break and initial clinical study report (CSR) for Clovis Oncology protocol CO-338-043 "ARIEL4 (**A**ssessment of **R**ucaparib **I**n Ovarian Canc**E**r Tria**L**): A Phase 3 Multicenter, Randomized Study of Rucaparib versus Chemotherapy in Patients with Relapsed, BRCA-Mutant, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer".

This initial CSR is intended to capture the efficacy and safety analyses up to the timing of the snapshot for the blind break and analysis of the primary endpoint. The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to snapshot for the primary endpoint in this study.

The data included and summarized in this SAP is all data up to and including the data cutoff visit date of 30 September 2020.

This SAP provides additional details concerning the statistical analyses that were already outlined in the original protocol, dated 15 June 2016, Protocol Amendment 1 (dated 11 January 2018), and Amendment 2 (dated 23 October 2020). All statistical analyses detailed in this SAP will be conducted using Statistical Analysis Software (SAS)® Version 9.4 or higher.

# 2 OBJECTIVES AND OVERALL STUDY DESIGN

## 2.1 Study Objectives Outlined in Protocol

| Table 1 Primary , Secondary and Exploratory Objectives |
|---|
| **Primary Objectives** |
| To determine investigator-assessed progression-free survival (invPFS) by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 for rucaparib vs chemotherapy |
| **Secondary Objectives** |
| To evaluate progression-free survival (PFS) by RECIST Version 1.1, as assessed by blinded independent central review (BICR; bicrPFS) |
| To compare efficacy of rucaparib vs chemotherapy as measured by overall survival (OS) |
| To compare efficacy of rucaparib vs chemotherapy as measured by overall response rate (ORR) using RECIST Version 1.1 by investigator assessment |
| To compare efficacy of rucaparib vs chemotherapy as measured by duration of response (DOR) by investigator assessment |
| To compare efficacy of rucaparib vs chemotherapy as measured by ORR using RECIST Version 1.1 by investigator assessment and Gynecologic Cancer InterGroup (GCIG) cancer antigen-125 (CA-125) response criteria |
| To evaluate patient-reported outcome (PRO) for rucaparib versus chemotherapy as assessed by the:<br>• European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30<br>• EORTC ovarian cancer module QLQ-OV28 |
| To evaluate the safety and tolerability of rucaparib versus chemotherapy |
| **Exploratory Objectives** |
| To evaluate the second event of PFS, in subsequent line of treatment (PFS2), both by investigator assessment |
| To evaluate disease control rate (RECIST Version 1.1 complete response [CR], partial response [PR], and prolonged stable disease [SD >12 weeks], by investigator assessment) |
| To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D) |
| To assess molecular changes in tumor samples over time in matched pairs |
| To assess circulating cell-free tumor DNA (ctDNA) as a molecular marker of efficacy |
| To evaluate the impact of gene expression molecular subgroups on PFS and OS |
| To assess efficacy in breast cancer gene (BRCA)-mutation subgroups (ie, germline/somatic and BRCA1/BRCA2) |
| To characterize steady-state trough concentrations of rucaparib |
| To explore the relationship between rucaparib exposure and responses (safety and efficacy) |

## 2.2 Overall Study Design

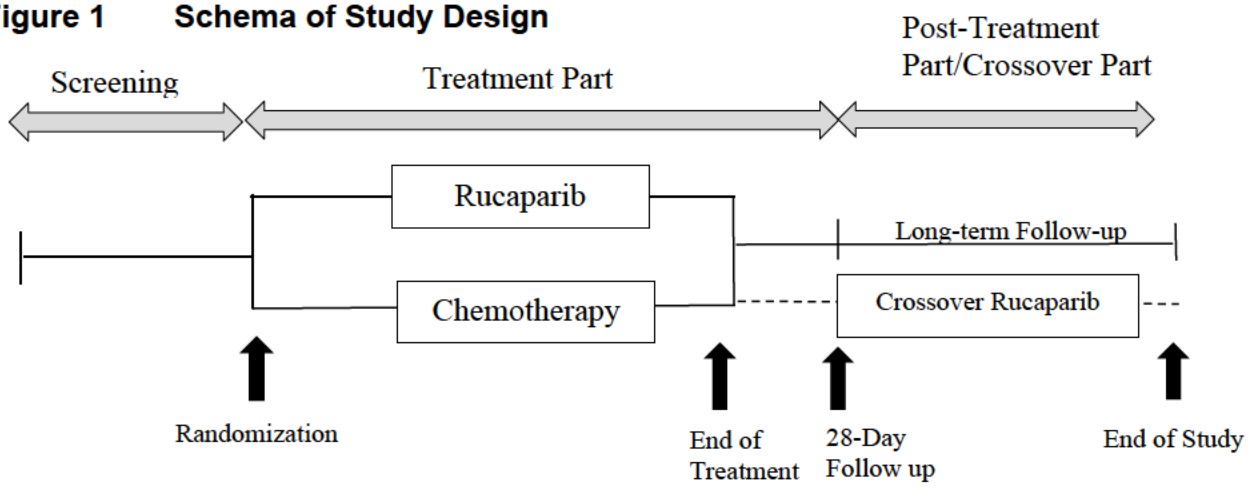
This is a Phase 3 multicenter, randomized study evaluating rucaparib versus chemotherapy for treatment of patients with relapsed, high-grade epithelial serous or Grade 2 or Grade 3 endometrioid ovarian, fallopian tube, or primary peritoneal ovarian cancer. The study will enroll patients with a deleterious BRCA1 or BRCA 2 (BRCA1/2) mutation in their tumor. All patients will be required to have received at least 2 prior chemotherapy regimens. Patients with platinum-refractory disease (ie, disease progression during or within 4 weeks after last dose of the most recent platinum-based chemotherapy) and patients who have received prior poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor (PARPi) treatment will be excluded. Patients with platinum-resistant (ie, disease progression $\geq 1$ to $< 6$ months after the last dose of most recent platinum-based chemotherapy) or partially platinum-sensitive disease (ie, disease progression $\geq 6$ to $< 12$ months after last dose of most recent platinum-based chemotherapy) will be randomized 2:1 to receive either rucaparib or weekly paclitaxel. Patients with platinum-sensitive disease (ie, disease progression $\geq 12$ months after last dose of most recent platinum-based chemotherapy) will be randomized 2:1 to receive either rucaparib or platinum-based chemotherapy consisting of the Investigator's selection of monotherapy platinum (cisplatin or carboplatin) or platinum-based doublet chemotherapy (carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine).

A 2:1 randomization to receive either rucaparib or chemotherapy will allow for statistical comparison of PFS, OS, and ORR between the treatment arms and provide access to rucaparib for a larger number of patients who would otherwise receive standard chemotherapy. The randomization assignments are stratified by the patients' progression-free interval (PFI) after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive) to maintain balance between treatment groups.

Patients will be randomized following classification (ie, deleterious BRCA1/2 mutation) detected by Foundation Medicine Inc. (FMI; central laboratory) analysis or documented local results for deleterious germline or somatic BRCA1/2 mutation, with confirmation of adequate tumor tissue availability for central confirmation testing of a deleterious BRCA1/2 mutation, and confirmation that all other eligibility criteria in the screening phase have been met.

Patients will receive treatment with either rucaparib or chemotherapy until disease progression by RECIST[1] Version 1.1, as assessed by the investigator; unacceptable toxicity or inability to tolerate further treatment, as assessed by the investigator; pregnancy; death; loss to follow-up; withdrawal of consent; or another appropriate clinical reason. Patients receiving platinum-based chemotherapy (monotherapy or doublet therapy) will receive up to a maximum of 8 cycles of treatment and will be followed thereafter until disease progression or other reason for discontinuation. Figure 1 shows the schedule of the study design with the screening phase following by the randomized treatment phase and lastly the post-treatment phase with an option for crossover for patients randomized to chemotherapy.

**Figure 1 Schema of Study Design**




Disease/ tumor assessments will be performed at baseline (screening) and at the end of every 8 calendar weeks relative to Cycle 1 Day 1 after randomization (within 5 days before is permitted). Patients who have been on study at least 18 months may decrease the frequency of tumor assessments to every 16 weeks (within 5 days before is permitted). Disease progression will only be determined by RECIST Version 1.1. Tumor assessments will be performed until investigator-assessed radiologic disease progression by RECIST Version 1.1 for any patient who discontinued from study treatment for reason other than disease progression or death. Patients who cross over to rucaparib treatment after initial disease progression will have tumor assessments every 8 calendar weeks relative to Day 1 of initiation of treatment with rucaparib.

All tumor assessment scans during the treatment part will be submitted to a central imaging vendor to allow for BICR of scans as a secondary objective of the study.

Additional assessments and procedures during the study will include: adverse events (AEs); physical examinations; 12-lead electrocardiograms (ECGs), vital signs and weight measurements; local laboratory hematology, serum chemistry, and CA-125 measurements; blood samples for ctDNA and pharmacogenomics analyses (before dosing in Cycles 1 to 6); plasma samples for pharmacokinetic (PK) analysis; concomitant medications, therapies, and procedures; study drug administration and accountability; and PRO. Urinalysis will be performed as clinically indicated.

Patients randomized to chemotherapy have the option to cross over to receive rucaparib upon radiological progression per RECIST Version 1.1 in the treatment part.

## 2.3 Sample Size Determination

The enrollment planned for this study is approximately 345 patients, with 230 patients randomized to rucaparib and 115 patients to chemotherapy.

The median PFS is assumed to be 12 months for rucaparib and 8 months for the comparator. Assuming an accrual over about 3 years; a dropout rate of 2%; with a hazard ratio (HR) of

0.65; and at least 275 events, a sample size of 345 patients (230 patients randomized to rucaparib and 115 patients randomized to chemotherapy) would yield at least 80% power at a two-sided 0.05 significance level.

## 2.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (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 performed at a two-sided 0.05 significance level for the treatment part. This is a two part study, where all efficacy and safety for the randomized treatment part and the crossover part will be presented separately. All summary tables will be presented by randomized treatment group (rucaparib vs chemotherapy) for the treatment part.

The efficacy data for the patients crossing over from chemotherapy to rucaparib will be presented descriptively in patient listings and as exploratory endpoint as outlined in 10.4.5.

All patients identified retrospectively to have a BRCA reversion mutation will be removed from the Efficacy Population. Efficacy analyses will be performed for both the Efficacy Population and the Intent-to-treat (ITT) Population, which include all randomized patients with or without a BRCA reversion mutation. The methodology used to identify patients with a BRCA reversion mutation will be detailed in a separate document.

It is anticipated that the data for the OS endpoint will be heavily censored at the time of the initial CSR analysis, thus only an interim OS will be presented and described here. Further details around this endpoint is described in Section 10.3.2.

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 (StdD), median, minimum, and maximum. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier (KM) methodology will be used to summarize time-to-event variables. If estimable, 50th (median) with 95% confidence intervals (CIs) will be presented. The number of patients with events and the number of censored patients will also be presented. The stratified HR from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. Months will be calculated as number of days divided by 30.4375.

## 3.1 Analysis Populations

The following patient populations will be summarized for the treatment part:

**Safety Population** – Patients who received at least one dose of protocol-specified treatment.

**Intent-to-treat (ITT) Population** – All randomized patients.

**Efficacy Population** – All randomized patients with a deleterious BRCA mutation, excluding those identified to have a BRCA reversion mutation.

The crossover part will only be summarized both for the Safety Population and Efficacy Population as defined above.

## 3.2 BRCA Subgroups

Patients are required to have a BRCA positive result as part of inclusion criteria to the study protocol from either local labs or centralized tumor tissue test with FMI. Both the local lab and the central lab will read out the BRCA status (BRCA1, BRCA2, or non-BRCA).

In addition, a central blood test of germline BRCA (gBRCA) will be performed by an external vendor in order to assess the BRCA mutation type. The germline and somatic designation for BRCA1/2 mutation in tumor tissue (tBRCA) will be based on the information from local and/or central germline BRCA testing as described in Table 2.

**Table 2 Algorithm for Determination of Germline/Somatic Status**

| Tumor Tissue BRCA Result | Germline Blood Test Result (central[a] and/or local test[b] result[c]) | Designation |
|---|---|---|
| BRCA Positive | BRCA Positive | Germline |
| BRCA Negative | BRCA Positive | Germline |
| BRCA Positive | BRCA Negative | Somatic |
| BRCA Positive | Not tested | Unknown |

Abbreviation: BRCA = breast cancer gene.

[a] Blood sample.

[b] Blood or buccal sample.

[c] If either the central or local test is BRCA positive, then the patient is considered BRCA positive.

All patients randomized to this study will also be tested for BRCA reversion mutation by an external vendor. The Efficacy Population for this study consists of all randomized patients with a deleterious BRCA mutation, excluding those that have BRCA reversion mutation identified. The hypothesis around excluding these patients is that the patients who have a BRCA reversion mutation will not benefit from treatment with rucaparib. The BRCA

reversion status for all patients and identification of the Efficacy Population will be completed prior to any unblinding of treatment assignments for the initial CSR.

# 4 PATIENT DISPOSITION

Patient disposition (analysis population allocation, randomized, discontinued, and primary reason for discontinuation for the treatment part) will be summarized using frequency counts, and the corresponding percentages. In addition, the number of patients who cross over to rucaparib, and their primary reason for discontinuation of the crossover part or ongoing status will be summarized.

## 4.1 Disposition and Summary of COVID-19 Impact

Number of patients who were ongoing and impacted by COVID-19 will be summarized. This is defined as all patients ongoing either in the treatment part, crossover part, or long-term follow up starting with visits dated on and after 01 March 2020. The number of tumor scans missed, visits missed, and the number of telehealth visits will also be summarized. A patient listing summarizing the COVID-19 impacted visits will also be produced.

# 5 PROTOCOL DEVIATIONS

Major protocol deviations will be identified prior to releasing the treatment codes for primary efficacy analysis in accordance with Clovis Standard Operating Procedure (SOP) CR019 (Identification, Documentation, Management and Review of Protocol Deviations). A listing with all the major protocol deviations will be presented. No patients will be excluded from the Efficacy Population due to a major protocol violation.

# 6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All demographic and baseline characteristics variables will be summarized separately for the ITT Population, Efficacy Population, and Safety Population by randomized treatment group and overall for the treatment part. The demographic and baseline characteristics for the treatment part is defined as the last measurement on or prior to treatment start date. For patients randomized but not treated the last measurement on or prior to randomization will be used.

In addition, the demographics and baseline characteristics for the patients who cross over to rucaparib will be summarized for the Safety Population. The demographic and baseline characteristics for patients who cross over to rucaparib is defined the last measurement on or prior to first dose of rucaparib in the crossover part.

## 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, gender, race, and Eastern

Cooperative Oncology Group (ECOG) performance status using the following categorizations:

- Age (years): ≤ 50, 51-60, 61-70, 71-80, 81-90, > 90; and < 65, 65-74, ≥ 75
- Gender: Female
- Race: American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported)
- Country
- Height (cm): ≤ 75, > 75-100, > 100-125, > 125-150, > 150-175, > 175
- Weight (kg): ≤ 50, > 50-75, > 75-100, > 100-125, > 125-150, > 150
- Body mass index
- ECOG performance status: 0, 1
- Smoking status (Current Smoker, Former Smoker, Never Smoked)

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

### 6.2.1 Summary of Disease Characteristics

- Measurable disease per Investigator (Yes, No)
- Number of Target lesions per investigator (0, 1, 2, 3, 4, 5)
- Sum of Diameters of Target Lesions per Investigator

### 6.2.2 Cancer History and Prior Anti-cancer Treatment

The following variables will be summarized with frequency tabulations:

- Time since diagnosis (months): 0-12, > 12-24, > 24
- Type of ovarian cancer: epithelial, primary peritoneal, fallopian tube, other
- Histological classification: serous, endometrioid, mixed, other
- Histological grade: high, low
- FIGO stage at diagnosis
- Number of prior anti-cancer treatment regimens
- Number of prior chemotherapy regimens
- Number of prior platinum-based chemotherapy regimens
- Number of intervening non-platinum regimens prior to enrollment
- The randomization factor of PFI status for the most recent prior platinum-based regimen:

- Platinum resistant: patients who progressed ≥ 1 to < 6 months after the last dose of platinum-based chemotherapy;
- Partially platinum-sensitive: patients who progressed ≥ 6 to < 12 months after last dose of platinum-based chemotherapy; and
- Platinum sensitive: patients who progressed ≥ 12 months after last dose of platinum-based chemotherapy

- Platinum status subgroups based electronic case report form (eCRF) data:
  - Platinum status based on most recent prior platinum-based regimen (resistant, partially-sensitive, sensitive);
  - PFI on most recent prior platinum-based regimen (0-6 months, 6 to < 12 months, 12 to < 24 months, ≥ 24 months)

Descriptive statistics may also be used to summarize these variables.

### 6.2.3 Summary of BRCA mutation Status and Type

The following BRCA mutation characteristics will also be summarized:

- BRCA status by central test: BRCA1, BRCA2, non-BRCA, Unknown
- BRCA status by local test: BRCA1, BRCA2, non-BRCA, Unknown
- BRCA mutation status (germline, somatic, or unknown)
- BRCA mutation gene (BRCA1 or BRCA2)
- BRCA reversion status (detected, not detected, failed)

## 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 23.0 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 for the treatment part. 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. The duration will be summarized with summary statistics and by categories (0 to < 6 months, ≥ 6 to < 12 months, ≥ 12 to < 24 months, ≥ 24 months) for each treatment arm.

For the patients randomized to rucaparib; dose intensity and the number of patients who reduced study drug will be summarized. The dose intensity is defined as time normalized actual dose received divided by the starting dose of 600 mg twice a day (BID), The number of patients with at least 1 dose reduction will be summarized with frequencies and percentages, and the number of patients on each dose level will be summarized

(ie, 500 mg BID, 400 mg BID, and 300 mg BID) in order to assess patients with multiple levels of dose reductions.

For the patients randomized to chemotherapy; the number of cycles received, the type of chemotherapy assigned, and the number of patients who dose reduced will be summarized.

In addition, the exposure for the crossover part will be summarized for the Safety Population as outlined above.

# 8 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be summarized for all patients in the Safety Population for the treatment part and crossover part separately. Prior/concomitant medication coding will utilize the World Health Organization (WHO) Drug Dictionary Version 2019MAR Global B3 or later. All concomitant treatments documented during the treatment part will be summarized in frequency tabulations for each randomized treatment group using Anatomical Therapeutic Chemical (ATC) level 4. All concomitant treatments documented during the crossover part will be summarized in frequency tabulations using ATC level 4. For the crossover part, the prior medications are defined as any medications that has both start and stop date that is after the last dose of randomized treatment in the treatment part. If either the start date and/or the stop date of the medication is missing such that it is unclear whether the medication was stopped, then the medication will be included in the summary of the concomitant medications for that study part.

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 in the treatment part.

# 9 EFFICACY ENDPOINT VARIABLES

## 9.1 Primary Efficacy Endpoint

The primary efficacy variable is invPFS for the treatment part.

## 9.2 Secondary Efficacy Endpoints

### 9.2.1 Hierarchical Step-down Order for Secondary Endpoints

The following secondary endpoints for the treatment part of the study are part of the hierarchical step down model[2, 3] as presented in Section 11.3 for the initial CSR.

1. ORR by RECIST Version 1.1
2. DOR by RECIST Version 1.1
3. ORR by RECIST Version 1.1 and/or CA-125 response
4. PRO as assessed by the EORTC QLQ-C30 Global Health Status score

### 9.2.2 Stand-alone Secondary Endpoints

Stand-alone secondary endpoints for the treatment part of the study outside of the step down are as follows:

- PFS by BICR
- Interim OS
- PRO as assessed by the EORTC QLQ-C30 and QLQ-OV28

## 9.3 Exploratory Efficacy Variables

- To evaluate PFS of study treatment followed by PFS2, defined as the time from randomization to the second event of disease progression or death, as assessed by the investigator
- To evaluate disease control rate (RECIST Version 1.1 defined as confirmed CR, PR, or prolonged SD > 12 weeks, by investigator assessment)
- To evaluate PRO utilizing the EQ-5D assessment
- To assess efficacy in BRCA-mutation subgroups (ie, germline/somatic and BRCA1/BRCA2)
- To explore the efficacy during the crossover part

# 10 EFFICACY ANALYSIS

All efficacy analyses will be performed both in the Efficacy and the ITT Populations. The primary endpoint and key secondary endpoints will be tested using a hierarchical step-down procedure as outlined in Section 11.3.

## 10.1 Primary Efficacy Analysis

The primary efficacy endpoint is invPFS for the treatment part. The time to invPFS will be calculated in months as the time from randomization to disease progression +1 day, as determined by RECIST 1.1 criteria or death due to any cause, whichever occurs first. Patients without a documented event of progression (or death) will be censored on the date of their last tumor assessment (ie, radiologic assessment) or date of randomization if no post-baseline tumor assessments have been performed. Patients who withdraw from treatment prior to progression will be followed for disease status and survival whenever possible. Only tumor scans and deaths up to and within 6 weeks of start of any subsequent anti-cancer treatment are included.

The primary endpoint of invPFS will be analyzed using the stratified Cox proportional hazard methodology. The stratified HR from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

### 10.1.1 Sensitivity Analyses for PFS

#### 10.1.1.1 Censoring Distribution

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

- All scans regardless if they are after start of subsequent anti-cancer treatment will be included as per European Medicines Agency (EMA) guidelines for PFS (Appendix 1 of the guidelines for the evaluation of anti-cancer medicinal products in man, EMA/ Committee for Medicinal Products for Human Use [CHMP]/27994/2008/Rev.1/20212).
- Patients who discontinued treatment in the randomized study part due to clinical progression or withdrew consent to treatment will be considered events of invPFS on the date of the last dose of study drug. Patients who are randomized but never took any study drug will use the date of randomization instead of last dose of study drug.

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 in the Step-down Procedure

### 10.2.1 Overall Response Rate by RECIST v1.1. as Assessed by Investigator

The ORR as assessed by the investigator will be analyzed in the subgroup of patients who are response evaluable at baseline (ie, measurable target lesions) for both the Efficacy Population and the ITT Population. The ORR is defined as proportion of patients with a confirmed CR or PR response by RECIST v1.1. The confirmed response is defined as a CR or PR on subsequent tumor assessment at least 28 days after first response documentation. The ORR will be summarized with frequencies and proportion together with 95% CI and compared between treatments by using a stratified Cochran-Mantel-Haenszel (CMH) test. In addition, the best confirmed response by RECIST v1.1. will be summarized with frequency and proportion by:

- Complete Response (CR)
- Partial Response (PR)
- Stable disease (SD), met the SD criteria at least once after study entry at a minimal of 49 days after randomization.
- Progressive disease (PD)
- Not evaluable (NE), discontinuations or deaths before first tumor assessment

Only tumor scans up to and within 6 weeks of start of any subsequent anti-cancer treatment are included.

### 10.2.2 Duration of Response by RECIST v1.1. as Assessed by Investigator

The DOR as assessed by investigator will be analyzed in the subgroup of patients who have a confirmed response by RECIST v1.1. DOR for any confirmed RECIST CR or PR will be measured from the date of the first response until the first date that PD 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. Only tumor scans up to and within 6 weeks of start of any subsequent anti-cancer treatment are included.

The DOR will be analyzed using the stratified Cox proportional hazard methodology and a stratified log-rank test. The stratified HR from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

### 10.2.3 ORR by RECIST v1.1. as Assessed by Investigator and/or CA-125 Response

The ORR and/or CA-125 response will be analyzed in the subgroup of patients who are response evaluable at baseline (ie, measurable target lesions) for both the Efficacy Population and ITT Population.

The ORR is defined as proportion of patients with a confirmed CR or PR by RECIST v1.1. The confirmed response is defined as a CR or PR on subsequent tumor assessment at least 28 days after first response documentation. Only tumor scans up to and within 6 weeks of start of any subsequent anti-cancer treatment are included.

Patients evaluable for CA-125 response must have a baseline CA-125 value at least twice the upper limit of normal (ULN; ie, 70 IU/mL) and at least 2 post baseline values. The endpoint of CA-125 response rate is defined as a 50% reduction from baseline. The response needs to be confirmed in a subsequent sample collected $\geq$ 21 days after the prior sample. The value of this confirmatory sample must be $\leq$ 110% of the prior sample. The date when the first sample with a 50% decrease from baseline is observed is the date of the CA-125 response. In patients who have measureable disease by RECIST Version 1.1, the date of response will be the date of the earlier of the two events. The number of patients evaluable for GCIG CA-125 response will also be summarized descriptively.

The proportion of patients with a confirmed RECIST v1.1. response and/or CA-125 response will be summarized with frequencies and proportion with 95% CI and compared between treatments by using a stratified CMH test.

### 10.2.4 Patient-reported Outcome Endpoint by EORTC QLQ-C30 Global Health Status

The PRO data will be scored and summarized in accordance with the scoring manual for the EORTC QLQ-C30 outlined in Appendix 1 (English version). The score of interest that will be used for the step-down testing is the EORTC QLQ-C30 Global Health Status score.

Changes from baseline for the EORTC QLQ-C30 global health status score using a repeated analysis of covariance (ANCOVA) over the first 6 treatment cycles in the treatment part will be analyzed and used as a covariate in the step down. Any patient with a baseline value and at least one post-baseline value for the EORTC QLQ-C30 Global Health Status score during the first 6 cycles will be included in the analysis. The repeated measures ANCOVA model will be used to estimate the average treatment effect over the first 6 cycles (months) using treatment, stratification variables, and baseline EORTC QLQ-C30 Global Health Status score as between-subject factors and change from baseline to each visit as a within-subject factor.

## 10.3 Secondary Efficacy Analyses Outside the Step-down Procedure

### 10.3.1 PFS by BICR

The PFS by BICR may, but is not required to, be performed at the time of the initial CSR. The same statistical test used for the primary endpoint (ie, stratified Cox proportional model) will be used to compare rucaparib to chemotherapy for this endpoint.

### 10.3.2 Interim Overall Survival

The time to OS will be calculated in months as the time from randomization to date of death due to any cause. Patients who are still alive will be censored on the date of their last available visit or last date known to be alive.

It is anticipated that the data for OS will be heavily censored at the time of the initial CSR analysis. In order to adjust for multiple analyses of OS at a later stage, a stopping rule will be applied. The Haybittle-Peto[4, 5] stopping rule will be applied where an OS result with a p-value $< 0.001$ can be used to claim superiority of rucaparib compared to chemotherapy. This means that a p-value $< 0.05$ can be utilized at the final analysis which is projected to be once 70% of the death events have been collected.

The same statistical test used for the primary endpoint (ie, stratified Cox proportional model) will be used to compare rucaparib to chemotherapy for this endpoint.

### 10.3.3 Patient-reported Outcome Endpoint by EORTC QLQ-C30 and QLQ-OV28

The PRO data will be scored and summarized in accordance with the scoring manual for the questionnaire. Appendix 1 and Appendix 2 includes the English version of the questionnaires used. Changes and/or percent changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for each subscale and total score. Patients that do not have both a baseline measurement and at least one post-baseline measurement will not be included.

At a given visit, the change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment and stratification variable as a categorical factor and baseline measurement for the parameter as a continuous covariate.

## 10.4 Exploratory Efficacy Analyses

The purpose of the exploratory endpoint is to further explore the efficacy and no multiple adjustment is performed for these analyses.

### 10.4.1 Progression-free Survival 2 (PFS2)

The second event of PFS, PFS2, is defined as the time from randomization to the second event of disease progression as assessed by the investigator, or death due to any cause. This second event of PFS may be a documented event per RECIST Version 1.1 guidelines or may be an event of symptomatic progression. Patients without a second event of progression (or death) will be censored on the last date the patient was known to be alive, study visit , or on the date of randomization if no post-baseline visits have been performed.

PFS2 will be analyzed using Cox proportional hazard method. The stratified HR from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

### 10.4.2 Disease Control Rate

Disease control rate during the treatment part is defined as RECIST Version 1.1 evaluation of CR, PR or SD ≥ 12 weeks and SD ≥ 24 weeks as assessed by the investigator. The number and percent of patients meeting the criteria for disease control rate will be summarized with frequencies and proportion with 95% CI and compared between treatments by using a stratified CMH test.

### 10.4.3 Patient Reported Outcome of EQ-5D

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 assessment and the EQ Visual Analogue Scale (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 using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

### 10.4.4 Assessing Efficacy in BRCA Mutation Subgroups

The primary endpoint and secondary efficacy endpoints will be further analyzed in the following subgroups based on BRCA mutation type:

- Mutation: BRCA1 vs BRCA2
- Mutation type: germline, somatic, or unknown
- BRCA reversion mutation-detected patients

In addition, the primary endpoint of PFS will be explored using a treatment-by-BRCA mutation type variable in the model.

### 10.4.5 Efficacy During the Crossover Part

The efficacy data for the patients crossing over from chemotherapy to rucaparib will be presented descriptively in patient listings. In addition, since the patients will be re-baselined for tumor assessment the invPFS, ORR rate, disease control rate and CA-125 response will be summarized for both the Safety Population and Efficacy Population for the crossover part.

# 11 STATISTICAL / ANALYTICAL ISSUES

## 11.1 Statistical Hypothesis

The primary statistical hypothesis for this study is to test for differences in PFS

using a stratified log-rank test.

$H_0$: HR (rucaparib/chemotherapy) $\geq 1$

$H_a$: HR (rucaparib /chemotherapy) $< 1$

The stratification factor used for randomization is the PFI after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive). All efficacy analyses will be based on the randomization strata given at randomization, however, a sensitivity analysis of invPFS may be performed using the actual strata if patients have been allocated incorrectly.

## 11.2 Handling of Dropouts or Missing Data

All data will be used to their maximum possible extent without any imputations for missing data, except for sensitivity analyses of PROs.

Imputation of missing baseline values for the PROs will be performed as supportive analyses. For patients without a baseline value, the baseline value will be imputed by using the PRO assessment performed closest to the date of randomization and may include assessments performed up to and including Cycle 2 Day 1.

## 11.3 Multiple Comparison / Multiplicity

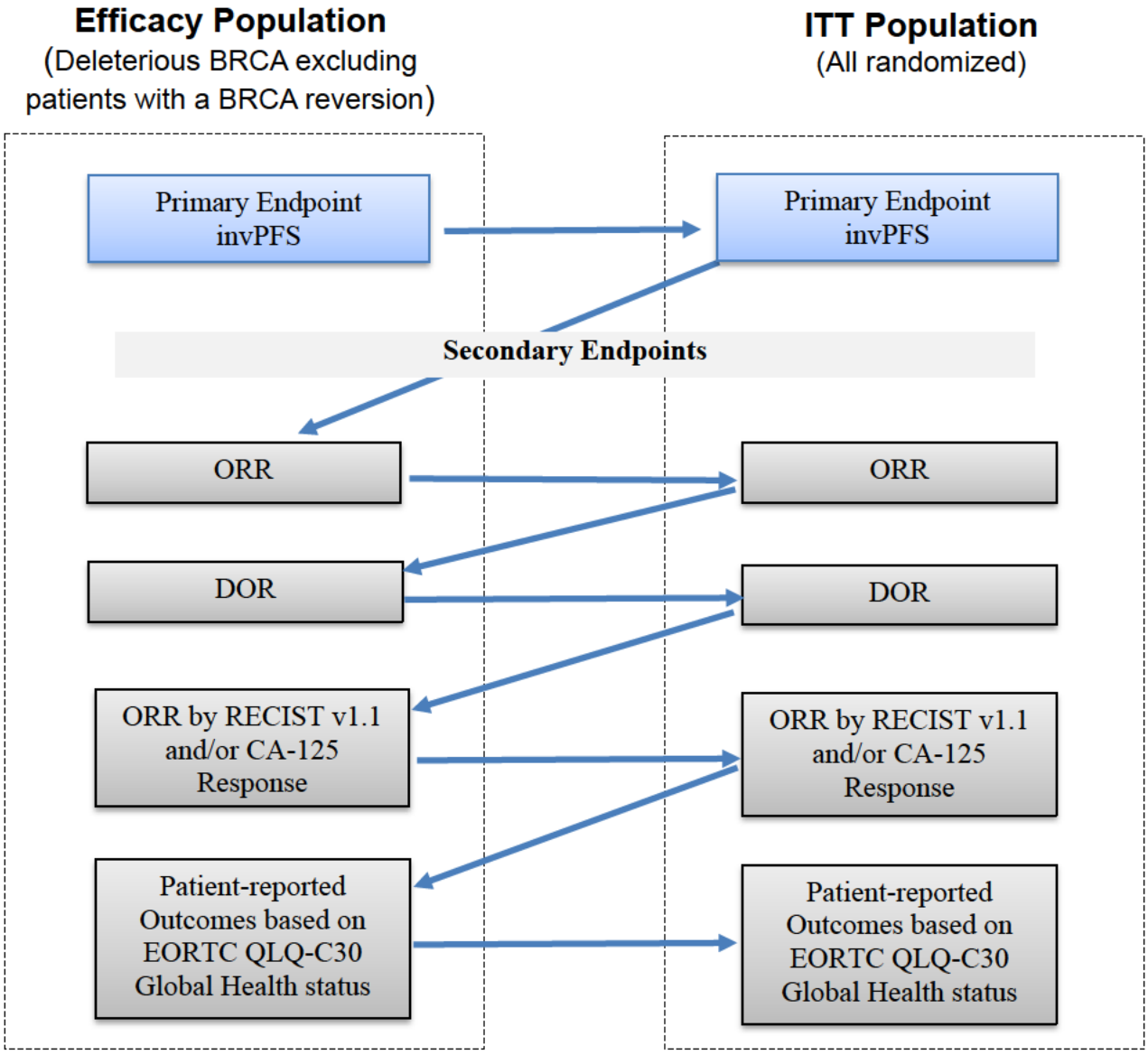
In order to preserve the overall Type 1 error rate, an ordered step-down (ie, fixed sequence) testing procedure for the primary endpoint and secondary endpoints have been pre-specified[2, 3]. The Efficacy Population will be tested first for each endpoint then it will step over to the full ITT Population. The primary and secondary endpoints for the Efficacy and ITT Populations will be tested using the ordered step-down procedure as illustrated in Figure 2, below.

If the primary efficacy endpoint reaches statistical significance at the 0.05 significance level (ie, two-sided) in the Efficacy Population, then the primary endpoint will be tested in the ITT Population. If both populations reaches statistical significance at the 0.05 significance level (ie, two-sided), then first secondary endpoint will be tested. The significance will only be declared for secondary endpoints if the primary endpoint and previous secondary endpoints are also statistically significant at the 0.05 significance level.

The secondary endpoints will be tested in the following order:

1. ORR by RECIST Version 1.1
2. DOR by RECIST Version 1.1
3. ORR by RECIST Version 1.1 and/or CA-125 response
4. PRO as assessed by the EORTC QLQ-C30 Global Health Status score

**Figure 2 Ordered Step-down Procedure**




Abbreviations: BRCA = breast cancer gene; CA-125 = cancer antigen-125; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; invPFS = progression-free survival, investigator assessed; ITT = intent-to-treat; ORR = overall response rate; RECIST = Response Evaluation Criteria in Solid Tumors.

## 11.4 Examination of Efficacy in Subgroups

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

- The stratification factor used for randomization is the PFI after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum sensitive).
- Age groups (< 65, 65-74, ≥ 75)
- Race (White, non-White)

In addition, subgroups based on BRCA mutation and type is also presented as part of exploratory endpoint specified in Section 10.4.4.

# 12 SAFETY ANALYSIS

The safety analyses will be presented for the Safety Population presenting the data by each treatment group separately for the treatment part. All safety data during the treatment part which is considered treatment-emergent will be summarized. Treatment-emergent during the treatment part is defined as safety data with an onset date on or after the date of first dose of randomized study medication until the date of the last study medication plus 28 days, or up to the date of first dose of rucaparib for those patients who cross over from chemotherapy, whichever is first.

Safety data will be presented for the crossover part separately, using the safety assessment before or on the date of first dose of rucaparib as the baseline value for the crossover part for the patients who cross over. The data that is deemed treatment emergent for the crossover part is defined as safety data with an onset date on or after the date of first dose of rucaparib in the crossover part until the date of the last study medication plus 28 days. These tables will not be split out by prior randomized treatment, but only presented overall for the crossover part.

Also, AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

## 12.1 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.

The number and percentage of patients who experienced treatment-emergent adverse events (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.

Separate tables will be presented as follows:

- All TEAEs
- TEAEs by CTCAE grade
- Grade 3 or greater TEAEs
- Treatment-related TEAEs
- Serious TEAEs
- TEAEs with an outcome of death
- TEAEs leading to discontinuation of study medication
- TEAEs resulting in reduction study medication
- TEAEs resulting in interruption of study medication
- TEAEs resulting in reduction or interruption of study medication
- Time to the first TEAE that results in a reduction or interruption 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 the first TEAE and first treatment-related TEAE that results in a dose reduction, delay, 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 AE. The cumulative incidence is 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.

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

MedDRA PTs were combined for the following similar terms

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

In addition, the analysis of combined terms for anemia is explored as a time to first event analysis as described above. Transfusions (blood or plasma) are provided in patient listings. The number of transfusions per patient will also be summarized.

## 12.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will be presented in standard international (SI) units. The on-treatment period for the treatment part will be defined as data with an onset date on or after the date of first dose of study medication until the date of the last study medication plus 28 days, or up to the date of first dose of rucaparib for those patients who cross over from chemotherapy, whichever is first. Laboratory values collected during the on-treatment period will be included in the summary tables.

The on-treatment period for the laboratory values for crossover part will be defined as all laboratory values on or after first dose of rucaparib in the crossover part until the date of the last study medication plus 28 days. The laboratory assessment before or on the date of first dose of rucaparib as the baseline value for the crossover part for the patients who cross over. These tables will not be split out by prior randomized treatment, but only presented overall for the crossover part.

The summary of laboratory data will include descriptive statistics (N, mean, StdD, 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.

Shift summary tables from baseline to the maximum on-treatment toxicity grade (CTCAE Version 4.03 or later) for each lab parameter will be summarized.

In addition, laboratory data including will be provided using by-patient listings.

## 12.3 Vital Signs

The on-treatment period for the treatment part 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 chemotherapy, whichever is first. Vital sign measurements collected during the on-treatment period will be included in the summary tables.

The on-treatment period for the vital sign measurements for crossover part will be defined as all vital sign values on or after first dose of rucaparib in the crossover until the date of the last study medication plus 28 days. The vital sign assessment before or on the date of first dose of rucaparib as the baseline value for the crossover part for the patients who cross over. These tables will not be split out by prior randomized treatment, but only presented overall for the crossover part. 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, StdD, minimum, median, and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, StdD, minimum, median, and maximum) 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 randomized treatment group.

## 12.4 Electrocardiograms

Local reads of heart rate, pulse rate, QRS, QT, QTc, and rhythm were collected in this study. ECGs were to be completed on Day 1 of each cycle for patients receiving rucaparib and chemotherapy. ECGs on intracycle visits (Day 8 and Day 15) may be performed if clinically indicated per investigator judgement. The on-treatment period for the treatment part 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 chemotherapy, whichever is first. The on-treatment period for ECG for crossover part will be defined as all values on or after first dose of rucaparib in the crossover until the date of the last study medication plus 28 days. The ECG data will be presented with descriptive statistics (N, mean, StdD, minimum, median, and maximum) of the maximum, minimum and last value during the on-treatment period. The data will be presented separately for each randomized treatment group.

The QT interval was corrected by using both Fridericia's (QTcF) and Bazett's (QTcB) formula. The QTcF and QTcB intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QTc intervals from baseline to end of treatment visits will be classified into the following categories: ≥ 450, ≥ 481, and ≥ 501 msec. For each patient's maximum change from the pretreatment ECG visit for QT and QTc, intervals will be classified into < 30 msec, ≥ 30 to < 60 msec, and ≥ 60 msec. The number and percentage of patients in each classified category will be presented.

## 12.5 Examination of Safety in Subgroups

Safety will be further explored in the following subgroups:

- BRCA mutation (BRCA1, BRCA2)
- BRCA mutation type (germline, somatic, unknown)
- Age groups (< 65, 65-74, ≥ 75)
- Race (White, Other, Unknown)

# 13 PROTOCOL SPECIFIED ANALYSES NOT PERFOMED AS PART OF THIS SAP

The following secondary endpoints will likely not be analyzed at the time of this blind break and initial CSR (primary efficacy snapshot) and thus will be summarized in the final CSR.

Final OS will likely not have reached 70% maturity of death events by the time of the primary endpoint analysis.

In addition, the following exploratory endpoints may be summarized in the final CSR:

- To assess molecular changes in tumor samples over time in matched pairs
- To assess circulating ctDNA as a molecular marker of efficacy
- To evaluate the impact of gene expression molecular subgroups on PFS and OS
- To explore the relationship between rucaparib exposure and responses (safety and efficacy)

# 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. Maurer W, Hothorn L, Lehmacher W. Multiple comparisons in drug clinical trials and preclinical assays: a priori ordered hypotheses. In: Vollmar J, editor. Biometrics in the Pharmaceutical Industry (Biometrie in der chemisch-pharmazeutischen Industrie). 6. Stuttgart: Fischer; 1995. p. 3-21.
3. Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Stat Plan Inference. 2001;99:25-40.
4. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol. 1971;44(526):793-7.
5. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer. 1976;34(6):585-612.

# 15 APPENDICES

## Appendix 1 EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

---

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

## For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

## Appendix 2 EORTC QLQ-OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 1. Did you have abdominal pain? | 1 | 2 | 3 | 4 |
| 2. Did you have a bloated feeling in your abdomen / stomach? | 1 | 2 | 3 | 4 |
| 3. Did you have problems with your clothes feeling too tight? | 1 | 2 | 3 | 4 |
| 4. Did you experience any change in bowel habit as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 5. Were you troubled by passing wind / gas / flatulence? | 1 | 2 | 3 | 4 |
| 6. Have you felt full too quickly after beginning to eat? | 1 | 2 | 3 | 4 |
| 7. Have you had indigestion or heartburn? | 1 | 2 | 3 | 4 |
| 8. Have you lost any hair? | 1 | 2 | 3 | 4 |
| 9. Answer this question only if you had any hair loss: Were you upset by the loss of your hair? | 1 | 2 | 3 | 4 |
| 10. Did food and drink taste different from usual? | 1 | 2 | 3 | 4 |
| 11. Have you had tingling hands or feet? | 1 | 2 | 3 | 4 |
| 12. Have you had numbness in your fingers or toes? | 1 | 2 | 3 | 4 |
| 13. Have you felt weak in your arms or legs? | 1 | 2 | 3 | 4 |
| 14. Did you have aches or pains in your muscles or joints? | 1 | 2 | 3 | 4 |
| 15. Did you have problems with hearing? | 1 | 2 | 3 | 4 |
| 16. Did you urinate frequently? | 1 | 2 | 3 | 4 |
| 17. Have you had skin problems (e.g. itchy, dry)? | 1 | 2 | 3 | 4 |
| 18. Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 19. Did you have night sweats? | 1 | 2 | 3 | 4 |

Please go on to next page

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 20. Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 21. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 22. How much has your disease been a burden to you? | 1 | 2 | 3 | 4 |
| 23. How much has your treatment been a burden to you? | 1 | 2 | 3 | 4 |
| 24. Were you worried about your future health? | 1 | 2 | 3 | 4 |

| **During the past 4 weeks:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 25. To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 26. To what extent were you sexually active? | 1 | 2 | 3 | 4 |

**Answer the following two questions only if you were sexually active:**

| | | | | |
|---|---|---|---|---|
| 27. To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |
| 28. Did you have a dry vagina during sexual activity? | 1 | 2 | 3 | 4 |