

Rucaparib

Clovis Oncology

CO-338 010 Statistical Analysis Plan Final CSR

## STATISTICAL ANALYSIS PLAN

### A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with *gBRCA* Ovarian Cancer or Other Solid Tumor

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Rucaparib

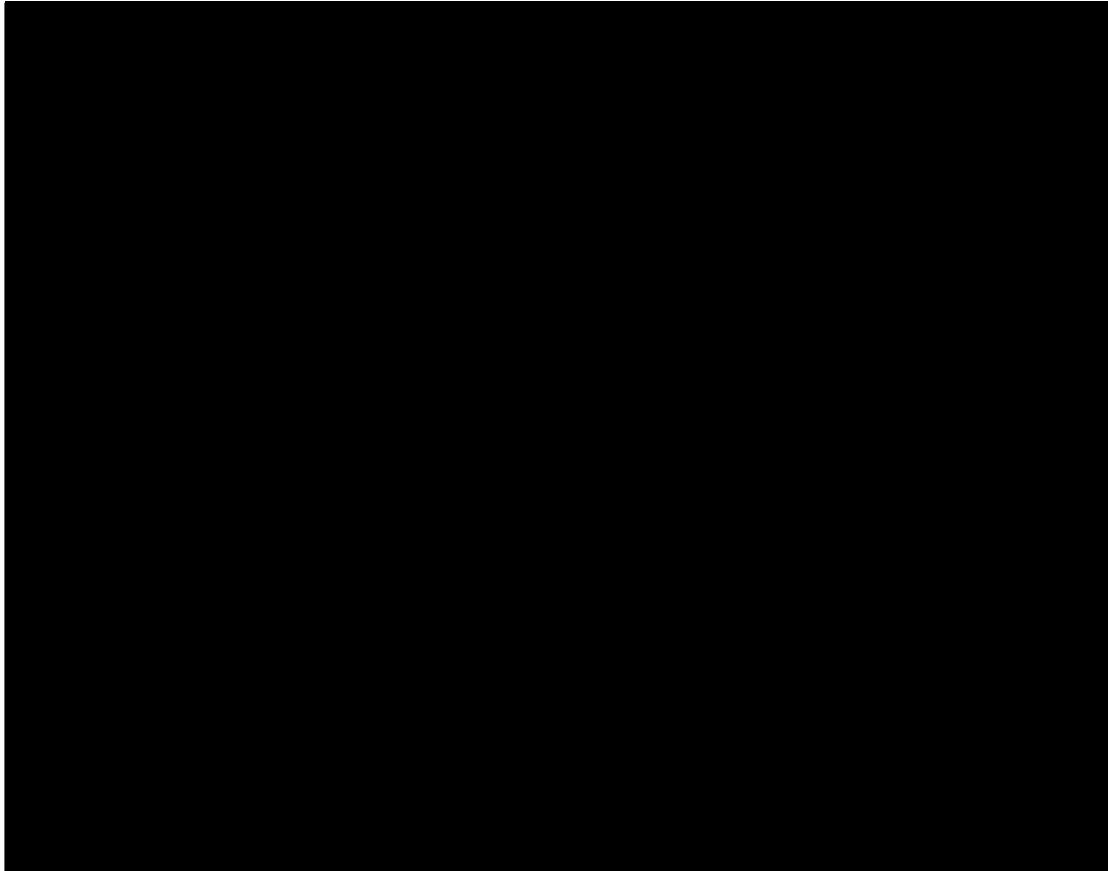
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**Approval Page**

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



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**1 LIST OF ABBREVIATIONS**

AE	Adverse event
BRCA	breast cancer susceptibility genes
CA-125	Cancer antigen 125
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCIG	Gynecologic Cancer Intergroup
MedDRA	Medical Dictionary for Drug Regulatory Activities
ORR	Objective response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose
SAP	Statistical analysis plan
SD	Standard deviation
SLD	Sum of Largest Diameter
TEAEs	Treatment-emergent adverse events
WHO	World Health Organization

## **2 INTRODUCTION**

This document describes the statistical analyses and data presentations to be performed for Clovis Oncology protocol CO-338-010. This statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of oral rucaparib (CO-338) in patients with ovarian cancer or other solid tumors.

The statistical analyses for this study were outlined in the original protocol dated 27 Sep 2011, and subsequent amendments (e.g., Amendment 1 dated 12 Jan 2012, Amendment 2 dated 23 April 2012, Amendment 3 dated 2 Oct 2012, and Amendment 4 dated 27 Nov 2013, and Amendment 5 dated 2 February 2015, Amendment 6 dated 27 April 2015, and Amendment 7 dated 29 June 2016).

All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.4 or higher.

### 3 OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

#### 3.1 Study Objectives and Endpoints

**Table 1: Primary and Secondary Objectives and Endpoints**

Primary Objectives	Primary Endpoints
1. To evaluate the safety profile of escalating doses of continuous daily oral rucaparib in patients with advanced solid tumors, and to determine the MTD and RP2D ( <i>Part 1 only</i> )	1. The incidence of Grade 3 or 4 AEs and clinical laboratory abnormalities defined as DLTs
2. To characterize the PK profile of oral rucaparib when administered as a continuous daily dose ( <i>Part 1 and Part 3 only</i> )	2. PK parameters: area under the curve from time zero to the time with the last measurable concentration ( $AUC_{0-t}$ ), AUC from time zero to infinity ( $AUC_{0-\infty}$ ), $C_{max}$ , time to maximum concentration ( $T_{max}$ ), elimination half-life ( $t_{1/2}$ ), elimination rate constant ( $k_{el}$ ), apparent volume of distribution at steady state after non-iv administration ( $V_{ss}/F$ ), and apparent total plasma clearance ( $Cl/F$ )
3. To evaluate ORR in patients with relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a <i>BRCA</i> mutation ( <i>Part 2 only</i> ) [henceforth abbreviated to ovarian cancer (OC) population]	3. ORR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1; secondary analysis including GCIG CA-125 criteria

<b>Secondary Objectives</b>	<b>Secondary Endpoints</b>
1. To characterize the single-dose PK profile of oral rucaparib after a high-fat breakfast compared to that in the fasted state <i>(Part 1 and Part 3 only)</i>	1. PK parameters $C_{max}$ and AUC (fasted and fed)
2. To evaluate the effects of oral rucaparib on the QT/QTc interval measured by ECG <i>(Part 1 only)</i>	2. Change from baseline in QT/QTc interval
3. To evaluate the safety and tolerability of oral rucaparib <i>(Parts 1, 2, and 3)</i>	3. The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
4. To evaluate duration of response in the OC population <i>(Part 2 only)</i>	4. Duration of response per RECIST v1.1.
5. To evaluate antitumor activity of oral rucaparib in various solid tumors <i>(Part 1 and Part 3 only)</i>	5. Response per RECIST v1.1; additional analyses including applicable tumor markers
6. To assess progression-free survival (PFS) in the OC population <i>(Part 2 only)</i>	6. PFS defined as the time to first occurrence of disease progression per RECIST v1.1 or death
7. To evaluate survival <i>(Part 2B only)</i>	7. Overall survival (OS)
<b>Exploratory Objectives</b>	<b>Exploratory Endpoints</b>
1. To explore the relationship between the PK of oral rucaparib and the potential changes in QT/QTc interval (Part 1 only)	1. QT/QTc interval correlated with plasma concentrations of oral rucaparib
2. To profile circulating metabolites of oral rucaparib at steady state at the RP2D (Part 1 only)	2. Metabolic profile in the Day 15 plasma samples
3. To explore the association between genomic alterations identified in tumor tissue and clinical outcome (Part 1, 2, and 3)	3. Mutational status of BRCA1/2 and other homologous recombination genes. Genomic scarring/ loss of heterozygosity (LOH) assessment in tumor tissue and response by RECIST v1.1 and/or tumor markers (ie, CA-125)



## 3.2 Trial Design

This is a 3-part, open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered once, twice, or three times a day for continuous 21-day cycles. Part 1 is a Phase I portion in patients with any solid tumor, including lymphoma, who have progressed on standard treatment. Part 2 is a Phase II portion in patients with relapsed high-grade serous or endometrioid ovarian cancer associated with a BRCA mutation. Part 2A enrolled patients with a gBRCA mutation with platinum-sensitive disease who have progressed after at least two, but no more than four, prior regimens. Part 2B enrolled patients with a gBRCA or sBRCA mutation who received three to four prior chemotherapy regimens. Part 3 is a Phase II PK portion to evaluate higher dose strength tablets in patients with any advanced solid tumor, inclusive of lymphoma, with evidence of a BRCA mutation (germline or somatic). Patients will enroll into either Part 1, Part 2, or Part 3 of the study, not in to multiple parts.

The study will encompass 3 parts:

- Part 1 (Phase I portion) = Six to twelve estimated dose-escalation cohorts in patients with solid tumors and RP2D Expansion in patients with a solid tumor and evidence of a deleterious gBRCA mutation
- Part 2 (Phase II portion) = Evaluation of the RP2D (i.e., 600 mg BID) in patients with relapsed high-grade serious or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a known deleterious BRCA mutation. Patients enrolled into Part 2 will be assessed for tolerability and efficacy. Part 2 is divided into 2 cohorts and includes Part 2A and Part 2B.
- Part 3 (Phase II PK portion) = Further evaluation of PK of higher dose strength tablets at the RP2D in patents with any advanced solid tumor, inclusive of lymphoma, with evidence of a BRCA mutation (germline or somatic)

Patients in all parts of this study received rucaparib until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study.

For all study parts, tumor assessments will be performed at screening, within 7 days prior to the start of Cycles 3, 5, and 7, within 7 days prior to the start of every three cycles thereafter, beginning with Cycle 10, and at the end-of-treatment visit. In addition, the efficacy is also assessed via tumor marker (CA-125) measurements collected at screening, on Day 1 of all cycles and at the end-of-treatment visit. The efficacy endpoints in each of the parts of the study will be evaluated using RECIST Version 1.1.

### 3.2.1 Sample Size

The total enrollment planned for this study is approximately 140 patients:

- Part 1: approximately 50 – 60 patients with locally advanced or metastatic solid tumors, inclusive of lymphoma, who have progressed on standard treatment will be enrolled at up to six study sites.

- Part 2: This part has two cohorts (Part 2A and Part 2B) whereof each cohort is planned to enroll up to approximately 40 patients each.
- Part 3: Approximately 20 patients with an advanced solid tumor, inclusive of lymphoma, with evidence of a BRCA mutation will be enrolled into Part 3.

Patients can only be enrolled in either Part 1, Part 2, or Part 3 of the study, and not in more than one part.

### 3.2.1.1 Sample size justification in Part 1

In Part 1, there will be an estimated six to twelve dose-escalation cohorts, with a minimum of three patients enrolled in each cohort, and an expanded evaluation of the RP2D in up to 15 patients.

All dose escalations will be based on assessment of DLTs, overall safety and tolerability, and PK that occur within each cohort, and will be agreed upon between the investigators and sponsor.

### 3.2.1.2 Sample size justification in Part 2A

Clinical trials of olaparib in relapsed ovarian cancer patients associated with a *gBRCA* mutation demonstrated overall response rates of 13-41%.<sup>1,2,3</sup> For this study of rucaparib in platinum-sensitive, relapsed, high-grade serous and endometrioid epithelial ovarian, fallopian tube, and primary peritoneal cancer associated with a *gBRCA* mutation, an ORR of 20% will be set as the target.

The study will use a Simon 2-stage design to evaluate the efficacy of rucaparib in Part 2 (Phase II portion). Initially, 21 patients will be treated in Stage 1 of the study; if two or more patients in Stage 1 have an objective response (CR or PR), then the remaining 20 patients will be treated in Stage 2. If fewer than two patients in Stage 1 have an objective response, then no further patients will be enrolled.

Characteristics of the Simon 2-stage design include:

- 5% probability of accepting a poor drug
- 90% probability of accepting a good drug
- ORR of 5% for a poor drug
- ORR of 20% for a good drug

A promising drug will have five or more patients with an objective response (CR or PR) out of 41 patients at the end of Stage 2. The criteria for Stage 1 success were met in April 2014.

### 3.2.1.3 Sample size justification in Part 2B

The efficacy of rucaparib in ovarian cancer patients with a deleterious *BRCA* mutation (germline or somatic) who received  $\geq 3$  prior chemotherapy regimens and were treated with 600 mg BID rucaparib in Studies CO-338-017 (ARIEL2) and Part 2A of CO-338-010 has been evaluated. In

this group, which included both patients with platinum-sensitive and platinum-resistant disease, ORRs of 47% (RECIST) and 73% (RECIST & GCIG CA-125) have been observed, suggesting that rucaparib may be a suitable treatment alternative in this patient population with advanced disease and limited treatment options.

The rationale for evaluating an additional *BRCA*-mutant OC cohort in this study is to better characterize the efficacy and safety in a heavily pre-treated patient population with a deleterious *BRCA* mutation (germline or somatic). An ORR  $\geq 20\%$  in this population would be worthy of further exploration. The table below provides 95% confidence intervals (CIs) for ORRs of 30% to 50% assuming a sample size of 40 patients.

#### Confidence Intervals for Observed Response Rates

ORR(%)	[95% CI]
30	17,47
40	25, 57
50	34,66

CI=Confidence intervals of ORR using Clopper-Pearson methodology.<sup>5</sup>

Therefore based on a sample size of 40 patients, an observed ORR of 30% would show similar response as current treatment; however, an observed ORR of 40% or greater has a 95% CI which exceeds the 20%.

#### 3.2.1.4 Sample size justification in Part 3

For Part 3, the study will be an initial randomized, two treatment, two period, crossover design, to explore food effect, with subsequent continuous BID dosing; it is estimated that enrolling approximately 20 evaluable patients will provide sufficient data for PK analysis.

## 4 GENERAL ANALYSIS CONVENTIONS

The summary tables and figures will be presented separately by each study part and cohort (i.e., Part 1, Part 2A, Part 2B and Part 3). There will not be any pooling of data and patients across study parts due to the difference in objectives for each study part. In addition for Part 1, tables and graphs will also be presented by dose groups.

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

The Kaplan-Meier methodology will be used to summarize any time to event endpoint. If estimable, the 50th (median) together with a 95% Confidence Interval (CI) together with range will be presented. The number of patients with events and the number of censored patients will also be presented.

Baseline is defined as the last measurement on or prior to the first day of study drug administration.

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

## 5 ANALYSIS POPULATIONS

**PK-Evaluable Population (Part 1 and Part 3 only)**—all patients who have received at least one dose of rucaparib and have had adequate PK samples available for determination of the PK profile. Adequacy will be determined on a case-by-case basis and will be assessed prior to analysis of the blood samples.

**Food-Effect PK Population (Part 1 and Part 3 only)**—all patients enrolled as part of the food-effect in Part 1 or Part 3 of the study and who received rucaparib on both Day -7 and Day 1 (Cycle 1), complied with the fed and fasted requirements, and have sufficient PK data for a comparison to be made between the fasted and fed state.

**ECG-Evaluable Population (Part 1 only)**—all patients who have received at least one dose of rucaparib and had adequate PK and ECG assessments performed for determination of the ECG effects in relationship to the PK of rucaparib.

**Safety Population**—all patients who have received at least one dose of rucaparib.

**DLT-Evaluable Population (Part 1 only)**—all patients enrolled into Part 1 of the study who received at least 17 complete days of rucaparib and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1.

**Efficacy Population**—all patients who met eligibility criteria, received at least one dose of rucaparib, have measurable tumor lesions at baseline, and have at least one post-baseline disease assessment.

Separate PK and ECG reports will be included as appendices to the clinical study report, hence only the Safety population, DLT-Evaluable Population and Efficacy population will be summarized for the statistical output in the body of the report.

## 6 PATIENT DISPOSITION

Patient disposition (analysis population allocation, discontinued, along with primary reason for discontinuation) will be summarized using frequency counts, and the corresponding percentages.

## 7 PROTOCOL VIOLATIONS

The number of patients with major protocol deviations (e.g., inclusion or exclusion criteria or deviations during the study) will be determined prior to data base snapshot and will be provided in a patient listing.

## 8 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

### 8.1 Demographics

The demographic variables will be summarized with frequency tabulations focused on identifying the extreme values of the distributions. Descriptive statistics may also be used to summarize the quantitative variables. The demographic variables will include age, height, weight, gender, race, region and ECOG Performance Status using the following categorizations:

- Age (years):  $\leq 50$ , 51-60, 61-70, 71-80, 81-90,  $> 90$ ;
- Height (cm):  $\leq 75$ ,  $> 75$ -100,  $> 100$ -125,  $> 125$ -150,  $> 150$ -175,  $> 175$ ;
- Weight (kg):  $\leq 50$ ,  $> 50$ -75,  $> 75$ -100,  $> 100$ -125,  $> 125$ -150,  $> 150$ ;
- Gender: Male, Female
- Race: American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other
- ECOG Performance Status: 0, 1,  $\geq 2$
- Region: North America, Europe, and Other

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

## 8.2 Baseline Clinical Characteristics

The following variables will be summarized with frequency tabulations

- Time since diagnosis (months):  $\leq 3$ , >3-6, >6-12, >12-24, >24;
- Baseline laboratory parameters: graded based on CTCAE;
- BRCA mutation (BRCA1, BRCA2);
- Number of prior anti-cancer regimens (1, 2, 3, 4, >4);
- Number of prior platinum-containing regimens (1, 2, 3, 4, >4);
- Number of prior chemotherapy regimens (1, 2, 3, 4, >4); and
- Progression-free interval following last platinum-regimen administered (<6 months, 6-12 months, and >12 months)
- Platinum status (i.e. platinum-sensitive, -resistant, or -refractory)

Descriptive statistics may also be used to summarize these variables.

## 8.3 Medical History

Medical history data will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system with version 19.1 summarized using frequency tabulations by system organ class and preferred term.

## 9 STUDY DRUG EXPOSURE AND COMPLIANCE

The following variables will be summarized:

- Number of cycles initiated (each cycle defined as 21 days)
- Duration of treatment
- Dose intensity (i.e., actual dose received divided by the assigned dose amount)
- Number of patients with dose reductions by dose level

The duration of treatment will be investigated by summarizing the number of days from the date of the first dose to the last date of treatment administration +1.

## 10 PRIOR AND CONCOMITANT MEDICATIONS

All concomitant treatments documented during the study period will be summarized in frequency tabulations. Prior/concomitant medication coding will utilize World Health Organization (WHO) Drug version 2016DEC01DDE (Enhanced).

Concomitant medications will be defined as those medications that were ongoing as of the day of the first dose of study drug administration, or that were initiated after first dose of study drug. For all cases where the start date and/or the stop date of the medication is missing such that it is unclear whether the medication was stopped prior to first dose of study drug administration, that medication will be included in the summary of the concomitant medications.

## 11 EFFICACY ENDPOINTS

### 11.1 Primary Efficacy Endpoints

The primary endpoint for Part 1 is to evaluate the safety profile of escalating doses of continuous daily oral dosing of rucaparib and determine the MTD and RP2D. The recommended starting dose from Part 1 was established as 600 mg BID. The primary endpoint for Part 1 was based on safety review and analyses described in section 14.

The primary efficacy variable for Part 2A and Part 2B is the objective response rate (ORR) as assessed by RECIST v1.1. In addition, the primary endpoint will include an analysis including GCIG CA-125 response criteria.

The primary PK endpoints for Part 1 and Part 3 include a list of rucaparib PK parameters following continuous oral administration of rucaparib. PK analysis for oral rucaparib will be summarized in a separate PK report. This PK report includes details around the statistical analysis performed for these endpoints, hence no further detail around this endpoint will be included in this SAP.

### 11.2 Secondary Efficacy Endpoints

Secondary efficacy variables include:

- Characterize PK after a high-fat meal compared to the PK in a fasted state (Food effect) (Part 1 and Part 3 only). The PK analysis, including the analysis plan, will be included in the separate PK report as mentioned above, thus no further information around food effect will be included here.
- Evaluate the effects of oral rucaparib on  $Q_t/Q_{Tc}$  intervals by ECG (Part 1 only). A separate analysis plan and report based on this objective has been completed. Thus, no further info around this endpoint will be included here.
- Safety and tolerability as further detailed in section 14
- Duration of response in Ovarian Cancer patients (Part 2A and 2B only)
- Evaluate antitumor activity in various solid tumors (Objective Response in Part 1 and Part 3)
- Progression-Free Survival (PFS) in the Ovarian Cancer population (Part 2 only)
- Overall Survival (Part 2B only)

- ORR per RECIST v 1.1 and Gynecologic Cancer Intergroup (GCIG) CA-125 criteria in the Ovarian Cancer Population (Part 2 Only)

### 11.3 Exploratory Efficacy Variables

- To explore the relationship between the PK of oral rucaparib and the potential changes in QT/QTc interval (*Part 1 only*). A separate analysis plan and report is based on this objective and thus no further info around this endpoint will be included here.
- To profile circulating metabolites of oral rucaparib at steady state at the RP2D (*Part 1 only*). A separate analysis plan and report is based on this objective and thus no further info around this endpoint will be included here.
- To explore the association between genomic alterations identified in tumor tissue and clinical outcome (Parts 1, 2, and 3).
- Time to first response per RECIST v 1.1 in Part 2A and Part 2B
- Change from Baseline in Sum of the Longest Diameters (SLD) of Target Lesions for patients in Part 2A and Part 2B.



## 12 EFFICACY ANALYSIS

### 12.1 Primary Efficacy Analysis for Part 2A and Part 2B

The primary efficacy endpoint is defined as best confirmed response according to RECIST v1.1 as assessed by investigator as outlined below.

#### Confirmatory Response Rate by RECIST v1.1.

The confirmed response rate by RECIST v1.1 is defined as the proportion of patients with a confirmed CR or PR on subsequent tumor assessment at least 28 days after first occurrence of response. The ORR will be summarized with frequencies and proportion together with 95% Confidence Interval (CI) of the proportion using Clopper-Pearson methodology. In addition, the frequency and proportion of patients will be summarized for each of the confirmed response assessment in the following categories:

- Complete Response
- Partial Response
- Stable disease, including the following classifications
  - Patients with confirmed SD
  - CR/PR/SD followed by PD if the CR/PR/SD is at least 49 days from treatment start date.
  - Patients ongoing with a single response
  - Ongoing without a response
- Progressive Disease
- Not evaluable (e.g., discontinuations or deaths before first tumor assessment)

The primary efficacy endpoint was evaluated in the efficacy population in Part 2A and Part 2B of the study. In addition, the endpoint will also be summarized for the safety population (i.e., all treated patients).

#### Confirmatory Response Rate by RECIST v1.1 or GCIG CA-125 Criteria

The endpoint of ORR assessed by RECIST or GCIG CA-125 criteria<sup>4</sup> is defined as a best confirmed response of CR or PR using RECIST v1.1 or a confirmed response per GCIG CA-125 criteria. The endpoint of CA-125 response rate is defined as a 50% reduction from baseline in CA-125 measurement as assessed by GCIG criteria and it is further described in Appendix A.

Only patients with elevated levels of CA-125 baseline value at least twice the upper limit of normal (>70 iU/mL) will qualify to have a response per GCIG CA-125 criteria.

The combined ORR will be assessed as indicated in Table 2.

<b>Table 2: Overall Response by RECIST v1.1 and GCIG CA-125 Criteria</b> <b>Error! Reference source not found.</b>		
<b>RECIST Response</b>	<b>GCIG CA-125 Response</b>	<b>RECIST + GCIG CA-125 Combined</b>
CR (requires normalization of CA-125)	CA-125 within normal range	Response
PR	Response	Response
PR	No Response	Response
SD	Response	Response
SD	No Response	No Response
PD	Response	No Response
PD	No Response	No Response

CR= Complete Response, PD = Progressive Disease, PR= Partial Response, SD = Stable Disease.

The response rate will be summarized with frequencies and percentages in addition to 95% Confidence Interval (CI) of the proportion using Clopper-Pearson methodology.

### **12.1.1 Primary Efficacy Subgroups**

The primary endpoint will be explored in the following subgroups:

- BRCA mutation type (germline, somatic)
- Progression-free interval to the last platinum-based regimen prior to rucaparib (<6 months, 6 to 12 months, and >12 months).
- Platinum-response status (sensitive, resistant, refractory) relative to most recent platinum containing regimen., where status is defined as
  - Refractory: Best response of PD and PD occurs during or up to 2 months after regimen
  - Resistant: PD 0-<6 months after last platinum with best response other than PD
  - Sensitive: PD  $\geq$ 6 months after last platinum

This may only be presented descriptively if there are few patients in a proposed subgroup.

## 12.2 Secondary Efficacy Analyses

The secondary endpoints are to further explore clinical benefit in terms of response in cancer antigen and duration of response.

### 12.2.1 Progression-free Survival (Part 2)

PFS will be calculated as 1+ the number of days from the date of first dose of study drug to disease progression or death, due to any cause, whichever occurs first. Patients without a documented event of progression will be censored on the date of their last adequate tumor assessment (i.e., radiologic assessment) or date of first dose of study drug if no tumor assessments have been performed. PFS will be summarized using Kaplan-Meier methodology.

### 12.2.2 Duration of Response (Part 2A and Part 2B)

Duration of response (DOR) for any confirmed RECIST CR or PR will be measured from the date of the first occurrence of a response until the first occurrence of PD per RECIST. DOR will be summarized as a time to event variable. For patients who continue treatment post-progression, the first date of progression will be used for the analysis. Any patients with an ongoing response will be censored at the date of the last post-baseline scan. The Kaplan-Meier methodology will be used to summarize DOR. If able to be estimated, the 50th (median) together with a 95% Confidence Interval (CI), will be presented. The number of patients with PD events and the number of censored patients will also be presented.

### 12.2.3 Overall Survival (Part 2B)

Overall survival is defined as 1+ the number of days from the date of first dose of study drug to death, due to any cause. Patients without a documented event of death will be censored on the date of their last visit. Overall survival will be summarized using Kaplan-Meier methodology time from randomization until death from any cause and is measured in the intent-to-treat population.

### 12.2.4 Antitumor Activity (Part 1 and 3)

No formal statistical analysis of efficacy was performed for Part 1 and Part 3. For patients with measurable disease, response to treatment per RECIST v1.1. was reported via descriptive statistics by dose level in patient listings.

## 12.3 Exploratory Efficacy Analyses

### 12.3.1 To explore the association between genomic alterations identified in tumor tissue and clinical outcome (Part 1, 2, and 3)

No formal statistical analysis of efficacy was performed for Part 1 and Part 3, thus genomic data and tumor response data will be presented in patient listings.

For Part 2A and Part 2B, the proportion of patients with the best confirmed response by RECIST Version 1.1 of CR or PR and the proportion of patients with best confirmed response by RECIST Version 1.1 or response according to the GCIG CA-125 criteria were summarized by BRCA

mutation type (BRCA1 or BRCA2). The ORR will be summarized with frequencies and proportion together with 95% Confidence Interval (CI) of the proportion using Clopper-Pearson methodology for each subgroup.

### ***12.3.2 Time to first Response per RECIST version 1.1 (Part 2A and Part 2B).***

The frequency and percentages of patients with a response (CR or PR) will be summarized by the first occurrence using the following time points;  $\leq 8$  weeks (Cycle 2),  $\leq 14$  weeks (Cycle 4),  $\leq 20$  weeks (Cycle 6),  $\leq 30$  weeks (Cycle 8), and  $> 30$  weeks.

### ***12.3.3 Change from Baseline in Sum of the Longest Diameters (SD) of Target Lesion (Part 2A and Part 2B)***

The largest percent decrease from baseline in the sum of the diameters (SD) of target lesions as identified by RECIST v1.1 will be displayed graphically using a waterfall plot. This will be based on the investigator assessed tumor responses and only presented for patients with measurable disease at baseline and one valid post-baseline evaluation of the target lesions.

## **13 STATISTICAL/ANALYTICAL ISSUES**

### **13.1 Handling of Dropouts or Missing Data**

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

### **13.2 Pooling of Centers in Multi-Center Studies**

Data from all centers will be pooled.

### **13.3 Multiple Comparison/Multiplicity**

No adjustments for multiple comparisons will be made.

## 14 SAFETY ANALYSIS

The safety analyses will be performed using the safety population for each part of the study separately.

### 14.1 Adverse Events

Adverse events will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system with version 19.1 or higher. The severity of the toxicities will be graded according to the NCI CTCAE v.4.03 or higher. Treatment-emergent adverse events (TEAEs) are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days. Adverse events will be considered treatment-emergent if all or part of the date of onset of the adverse event is missing and it cannot be determined if the adverse event meets the definition for treatment-emergent.

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

Separate tables will be presented as follows:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs;
- Serious TEAEs;
- Serious treatment-related TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of rucaparib;
- TEAEs resulting in interruption of rucaparib; and
- TEAEs resulting in reduction of rucaparib
- TEAEs resulting in reduction/interruption of rucaparib.
- Time to the first TEAE that results in a reduction, delay, interruption or discontinuation of rucaparib; and
- Time to the first treatment-related TEAE that results in a reduction, delay, interruption or discontinuation of rucaparib.

The incidence of TEAEs will be summarized by relationship to study drug according to the following categories: “treatment-related,” or “not treatment-related”. The category of treatment-related is defined as a relationship of “Possible/Probable”, “Definitely”, or missing. If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once as a relationship category of treatment related.

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

The time to the first TEAE and first treatment-related TEAE event 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 adverse event. The cumulative incidence is presented in a 1-KM graph and the median time to onset will be calculated together with the 95% Confidence interval.

Dose-limiting toxicities will be presented in a patient listing.

Non-TEAEs will be presented in a patient data listing for the safety population.

MedDRA PTs were combined for the following similar terms:

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

In addition, the analysis of combined terms for anemia may be explored as a time to first event analysis as described above.

## 14.2 Clinical Laboratory Evaluations

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

The summary of laboratory data will include descriptive statistics (N, mean, SD, minimum, median, and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given.

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

Laboratory data including normal ranges and abnormal laboratory flags will be provided using by-patient listings.

### 14.3 Vital Signs

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

The summary of vital sign data will include descriptive statistics (N, mean, SD, minimum, median, third quartile and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, SD, 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 and overall.

### 14.4 Electrocardiograms (ECG)

Electrocardiogram (ECG) was analyzed intensively for Part 1 and reported separately in an ECG report. For the other study parts (Part 2A, 2B and Part 3) local reads of ECG was collected at each visit. 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 the pretreatment visit and treatment period visits will be classified as  $\leq 450$  msec,  $>450$  to  $\leq 480$  msec,  $>480$  to  $\leq 500$  msec, and  $>500$  msec. For each patient's maximum change from the pretreatment ECG visit for QT and QTc, intervals will be classified into  $<30$  msec,  $\geq 30$  to  $<60$  msec, and  $\geq 60$  msec. Patients will also be classified according to the CTCAE grade 3 criteria of at least 2 on treatment QTc values  $>500$  ms. The number and percentage of patients in each classified category will be presented.

Descriptive statistics will be used to summarize other ECG parameters of PR, QRS, QT, and RR interval, and the corresponding changes from pretreatment ECG visit at each time point.

## 15 REFERENCES

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