STATISTICAL ANALYSIS PLAN

A Phase 2, Open-Label Study of Rucaparib in Patients with Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

PROTOCOL NUMBER: CO-338-017

[redacted]**:** [redacted]

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SPONSOR: Clovis Oncology
[redacted]

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Approval Page

The document is hereby signed and approved by:

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ABBREVIATIONS AND SPECIALIST TERMS

AE	Adverse event
ATC	Anatomical Therapeutical Chemical (coding)
BRCA	breast cancer susceptibility genes
CA-125	Cancer antigen 125
ctDNA	circulating cell-free tumor DNA
CI	Confidence interval
C_{min}	minimum concentration
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCIG	Gynecologic Cancer Intergroup
HGSOC	High Grade Serous Ovarian Cancer
HRD	homologous recombination deficiency
HRR	Homologous recombination repair
IRR	Independent Radiology Review
LOH	loss of heterozygosity
MedDRA	Medical Dictionary for Drug Regulatory Activities
nbHRD	Non-*BRCA* HRD
NGS	Next generation sequencing
NJEJ	non-homologous end-joining
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	statistical analysis software
SD	Stable Disease

tBRCA	Tumor tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA
TCGA	The Cancer Genome Atlas
TEAEs	Treatment-emergent adverse events
ULN	Upper limit of normal
Wt	Wild type

1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for Clovis Oncology's protocol CO-338-017. This statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of rucaparib (CO-338) in patients with relapsed high-grade serious ovarian cancer (HGSOC), fallopian tube cancer or primary peritoneal cancer

The Statistical Analysis Plan (SAP) provides further detail of the statistical analyses, which were originally outlined in the original protocol [redacted] and subsequent amendments [redacted]

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

2 OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

2.1 Study Objectives and Endpoints

Table 1 Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	Primary Endpoints
1. To determine PFS in patients with relapsed platinum-sensitive ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature (Part 1)	1. Disease progression (RECIST v1.1) as assessed by investigator, or death from any cause, in molecularly-defined subgroups identified by a prospectively defined HRD signature
2. To estimate ORR in heavily pre-treated patients with relapsed ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature (Part 2)	2. ORR by RECIST v1.1 in molecularly-defined subgroups identified by a prospectively defined HRD signature

Secondary Objectives	**Secondary Endpoints**
1. To estimate ORR (Part 1)	1. ORR by RECIST v1.1
2. To estimate ORR including CA-125 response criteria	2. ORR by RECIST v1.1 and GCIG CA-125 criteria
3. To evaluate duration of response (DOR)	3. DOR by RECIST v1.1
4. To determine PFS (Part 2)	4. Disease progression (RECIST v1.1) as assessed by investigator, or death from any cause
5. To evaluate survival (Part 2)	5. Overall survival
6. To evaluate the safety and tolerability of rucaparib	6. The incidence of adverse events (AEs), clinical laboratory abnormalities, and dose modifications
7. To evaluate steady state trough level PK	7. Trough (C_{min}) level rucaparib concentrations
Exploratory Objectives	**Exploratory Endpoints**
1. To assess efficacy in molecularly-defined HRD subgroups as defined by HRR gene alterations	1. PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria. HRD subgroups as defined by HRR gene alterations
2. To optimize the tumor LOH algorithm by testing additional signatures of interest based on higher or lower genomic LOH	2. PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria. Additional signatures of interest based on higher or lower genomic LOH.
3. To assess changes in HRD status over time	3. Changes in HRD status (LOH and gene alterations) between fresh biopsy versus archival tumor tissue samples
4. To assess whether the BROCA panel can identify mutations in additional HRR genes that may be associated with efficacy	4. ORR by RECIST v1.1 and GCIG CA-125 criteria in relation to HRR gene mutations identified in BROCA
5. To assess if a gene expression signature for HRD correlates with efficacy	5. PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria in relation to gene signature defined by a gene expression profiling assay
6. To assess NHEJ pathway integrity and correlate it with efficacy	6. NHEJ protein expression by immunohistochemistry (IHC) and PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria
7. To assess ctDNA as a molecular marker of efficacy	7. Levels of ctDNA in relation to PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria

2.2 Trial Design

This is a two-part open-label study that enrolled patients with relapsed, high-grade, epithelial ovarian, fallopian tube, or primary peritoneal cancer who had disease that could be biopsied and was measurable. Part 1 enrolled patients who had received ≥1 prior platinum-based regimen and had platinum-sensitive disease. Part 2 enrolled patients who had received at least 3, but no more than 4, prior chemotherapy regimens.

The purpose of Part 1 of this study was to define a molecular signature of HRD in ovarian cancer that correlates with response to rucaparib and enables selection of appropriate ovarian cancer patients for treatment with rucaparib. The HRD signature was based on an association between genomic scarring, as defined by a *BRCA* mutation or high level of loss of genomic heterozygosity (LOH), observed in a patient's tumor and observed clinical benefit from rucaparib treatment (see Section 3.1).

The objective of Part 2 of this study was to further explore the safety and efficacy in more heavily pre-treated ovarian cancer patients.

All patients, with the exception of Part 2 patients known to harbor a deleterious *gBRCA* mutation, were required to undergo a screening biopsy for collection of tumor tissue. Archival tumor tissue was also collected. *tBRCA* mutation and/or tumor genomic LOH analysis was performed using Foundation Medicine's next generation sequencing (NGS) test. Analysis of tumor genomic LOH was expected to identify tumors with HRD regardless of the underlying mechanism(s). *tBRCA* mutation and/or the extent of tumor genomic LOH was correlated with the clinical outcome experienced with rucaparib treatment.

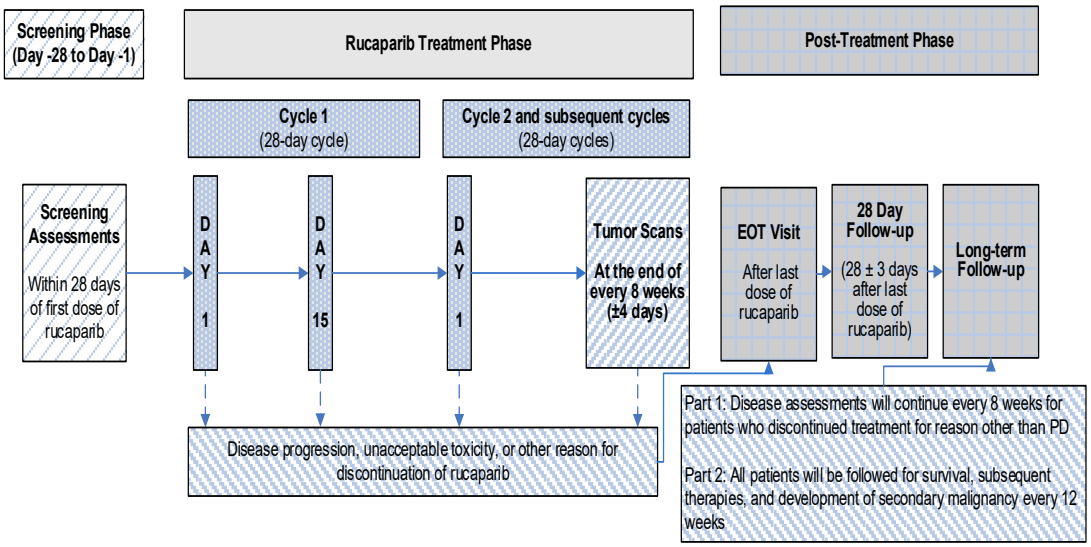
Patients took 600 mg rucaparib orally twice daily for continuous 28-day cycles until disease progression as assessed by the investigator, or other reason for discontinuation. If the patient met criteria for radiologic progression by RECIST Version 1.1[2], but the patient was still receiving benefit from rucaparib (e.g., patient had mixed radiologic response or was continuing to have symptomatic benefit) according to the investigator, then continuation of treatment was considered. In such cases, the decision to continue was made jointly between the investigator and the sponsor and had to be documented prior to continuing treatment with rucaparib.

Tumor scans were performed at the end of every 8 weeks (± 4 days) while on study. A confirmatory scan should have been performed ≥4 weeks after an initial response of PR or CR was observed. Patients who had been on study at least 18 months were permitted to decrease the frequency of disease assessments to every 16 (±2) weeks. Disease assessment was to be ongoing/completed for all patients who discontinued treatment for reason other than disease progression or death.

Patients in Part 2 were followed for survival, subsequent therapy, and secondary malignancy every 12 weeks until death, loss to follow-up, withdrawal of consent from study or study closure, whichever happened first. Tumor response was interpreted using RECIST Version 1.1. Figure 1 shows a schema for this study.

Copies of CT/MRI scans were collected from all patients in Part 2 of the study and for selected patients in Part 1 of the study and sent to an independent radiology review (IRR) vendor. The protocol specified that the IRR would be conducted on all or a subset of CT scans. Clovis elected to only have IRR reads for scans that were collected from the subset of patients who had a BRCA mutation as this population was the molecular subgroup that had the highest degree of benefit and the IRR-assessed ORR was supportive of the Investigator-assessed ORR that supported regulatory filings in the US and Europe. As only a subset of scans had a central read by IRR, no IRR analyses will be performed or summarized in this final CSR. Please refer to Section 14 of this SAP for changes to protocol-specified analyses for this final CSR.

Figure 1 The Study Schema



2.3 Sample Size Justification

The total enrollment planned for this study was approximately 480 patients, N=180 in Part 1 and up to N=300 in Part 2.

Part 1: It was anticipated that approximately 180 patients were required in order to ensure each subgroup of patients (tBRCA, nbHRD, and biomarker negative) contained an adequate number of patients. Other than the cap on patients with a known deleterious *gBRCA* mutation (n=15), there were no specific requirement to enroll defined numbers of patients into each planned subgroup. The likely size of each subgroup was estimated based on: a) frequencies of HRD-associated genetic abnormalities at initial diagnosis as reported in the literature and b) the hypothesis that the inclusion criterion of sensitivity to platinum following the most recent line of platinum therapy will enrich the population for patients with tumors harboring mutations of HRD pathway genes (i.e., that the frequency will be greater than that described in the newly-diagnosed population). Table 2 provides estimated HRD subgroup sizes in Part 1 of this trial.

Table 2 Estimated HRD Subgroup Sizes[a]

HRD Subgroup	Expected Frequency at Diagnosis	Estimated Frequency with Enrichment for Platinum Sensitivity	Estimated Number of Patients
tBRCA	21%	30%	15 with known deleterious *gBRCA* mutation (fixed) ***plus*** 20 – 25 with somatic *BRCA* mutation ***plus*** 5 – 25 additional with newly diagnosed *gBRCA* mutation
nbHRD	22 – 32%	30 – 50%	50 – 90
Biomarker Negative	60 – 70%	20 – 40%	36 – 72

[a] Expected frequency estimates are from TCGA[1]

Enrollment of patients known a priori to harbor a *gBRCA* mutation classified as deleterious (pathogenic), suspected deleterious, or favor deleterious (or the equivalent interpretation of any of these) on the most recent assessment by a testing laboratory was limited to 15 in Part 1. Fifteen patients with a known *gBRCA* mutation was considered sufficient to establish that the frequency of *gBRCA* mutation reversions is low. In particular, if none of the 15 patients with a known *gBRCA* mutation was shown to have a reversion between archival tissue and tumor tissue collected at screening, then the frequency of *gBRCA* reversions was likely less than 20% as the upper bound on the 90% confidence interval (CI) is 18%. Additional patients, previously untested or tested and found to be $gBRCA^{wt}$, may be identified as having a *BRCA* mutation in tumor tissue, therefore the BRCA subgroup will likely contain at least 40 patients.

The benefit of rucaparib is expected to be the greatest in patients in the t*BRCA* subgroup, followed by patients in non-tBRCA LOH+ subgroup, and lowest in patients in the biomarker negative subgroup (i.e., non-tBRCA LOH-). This study will provide evidence as to whether the benefit of rucaparib is clinically meaningful in each of these subgroups.

With a total of 180 patients enrolled in Part 1 of the study, the comparison of any 2 subgroups will likely contain about 100 patients. Therefore with 100 patients, there is 80% power at a 2-sided 10% significance level to detect a difference in PFS distributions assuming the hazard ratio between 2 subgroups is 0.50.

Part 2: The objective of Part 2 is to estimate the ORR in each of the HRD subgroups in a more heavily pre-treated patient population (at least 3, but no more than 4, prior chemotherapy regimens). Up to 300 patients were to be enrolled in Part 2 of the study in order to enroll at least 80 patients in each HRD subgroup. A total of 300 patients should be

sufficient assuming an approximate 33.3% allocation to each HRD subgroup in the enrollment population.

Table 3 below provides 95% CIs for observed response rates ranging from 10 to 60% assuming a total of 80 patients within each HRD subgroup.

Table 3 Confidence Intervals for Objective Response Rates (ORR)

ORR(%)	[95% CI]
10	4.4, 18.8
20	11.8, 30.4
30	20.3,41.3
40	29.2,51.6
50	38.6, 61.4
60	48.4, 70.8

CI=Confidence intervals of ORR using Clopper-Pearson methodology.

An ORR ≥20% in any subgroup would be worthy of further exploration in these subgroups.

2.4 Data Cutoff used for Final CSR

A visit cutoff of 01 Feb 2019 was applied in order to clean the data and do a snapshot for the final CSR. Part 1 was fully enrolled in Dec 2014 and Part 2 was fully enrolled by August 2016. At the time of the visit cutoff (01 Feb 2019), there were still 14 patients receiving rucaparib treatment in this study. However, all data are mature enough to fully evaluate the primary study objectives; therefore, the sponsor has deemed the study completed.

3 GENERAL ANALYSIS CONVENTIONS

Data will be summarized for each study part separately. The summary tables will be presented for all treated patients and by the subgroups defined by HRD status (tBRCA [somatic and germline], non-tBRCA LOH+, non-tBRCA LOH-, and unknown).

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

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

Unless otherwise specified, baseline is defined as the last measurement on or prior to the first day of study drug administration.

3.1 Definition of HRD Subgroups

Clovis is collaborating with Foundation Medicine, Inc. (FMI) to develop a tumor tissue-based NGS test. The HRD status group definition is based on *BRCA* mutations and the percentage of the genome with Loss of Heterozygosity (LOH). All analyses will be performed separately for the subgroups defined by HRD status (tBRCA, non-tBRCA LOH+, non-tBRCA LOH-, and non-tBRCA unknown) defined as follows:

- **tBRCA**: Patients with deleterious BRCA mutation detected in their tumor
- **Non-tBRCA LOH+**: Patients who are found to not have the a BRCA mutation in their tumor, but where the percent of LOH is ≥14% (in Part 1) or ≥18% (in Part 2). For further rationale around this definition see Appendix A.
- **Non-tBRCA LOH-**: Patients who are found to not have a BRCA mutation in their tumor, but where the percent of LOH is <14% (in Part 1) or <18% (in Part 2). For further rationale around this definition see Appendix A.
- **Non-tBRCA Unknown**: Patients who are found to not have a BRCA mutation in their tumor, but where the percent of LOH is unknown due to missing results and/or failed test result(s)

The proposed FMI test identifies sequence variants in the BRCA1 and BRCA2 genes for all tBRCA patients.

4 ANALYSIS POPULATIONS

Safety Population: The safety population will consist of all patients who received at least one dose of rucaparib.

Efficacy Population: The efficacy population consist of all patients who received at least one dose of rucaparib, have tumor measurable disease at baseline, and have at least one post-baseline tumor scan assessment by RECIST v1.1. Efficacy population is not used for the PFS analysis, but only for assessing tumor response.

GCIG CA-125 evaluable Population: The efficacy population of patient evaluable for GCIG CA-125 response will consist of all patients who received at least one dose of rucaparib, with an elevated tumor marker of CA-125 at baseline (i.e., values at least twice the upper limit of normal), and who had at least two post-baseline CA-125 measurements.

5 PATIENT DISPOSITION

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

6 PROTOCOL VIOLATIONS

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

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

7.1 Demographics

The demographic variables will be summarized with frequency tabulations that will focus on identifying 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, BMI, gender, race, region, and ECOG Performance Status using the following categorizations:

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

7.2 Baseline Clinical Characteristics

The following variables were to be summarized with frequency tabulations:

- Time since diagnosis of HGSOC (months): > 6-12, > 12-24, > 24;
- Baseline laboratory parameters: graded based on CTCAE;
- HRD status; tBRCA, non-tBRCA LOH+, non-tBRCA LOH- or non-tBRCA unknown;
- Number of prior anti-cancer regimens: 0,1,2,3,4,5, >5;
- Number of prior chemotherapy regimens 0,1,2,3,4,5, >5;
- Number of prior platinum therapies 0,1,2,3, >3;
- Progression-free interval following the last platinum regimen received (months): <6, ≥6-12, >12-24, > 24;
- (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 ≥6 months after last platinum

Descriptive statistics could also be used to summarize these variables.

7.3 Medical History

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

8 STUDY DRUG EXPOSURE AND COMPLIANCE

The following variables will be summarized:

- Number of cycles initiated
- Duration of treatment
- Number of dose reductions per patient and by dose level
- Dose intensity (i.e., actual dose received divided by the assigned dose amount)

The duration of treatment initiated will be investigated by summarizing the number of days from treatment start date to treatment end date +1 or if the subject is ongoing then we use the date of the visit cutoff.

9 PRIOR, CONCOMITANT MEDICATIONS AND SUBSEQUENT TREATMENT

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).

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

In Part 2 of the study the subsequent anti-cancer treatment information for all patients that were in follow up was collected. This data will be presented in a patient listing.

10 EFFICACY VARIABLES

10.1 Primary Efficacy Variable

The primary efficacy variables for each of the study parts are as follows:

Part 1: The primary efficacy endpoint is progression-free survival (PFS) according to RECIST v1.1, as assessed by the investigator or death from any cause in molecularly-defined HRD subgroups.

Part 2: ORR by RECIST v1.1 in molecularly-defined subgroups identified by a prospectively defined HRD signature.

10.2 Secondary Efficacy Variables

Secondary variables include:

- ORR assessed by RECIST v1.1 in Part 1
- ORR assessed by GCIG CA-125 response criteria
- DOR by RECIST v1.1
- Progression-Free Survival (PFS) in Part 2
- Overall Survival in Part 2
- AEs, clinical lab abnormalities, and dose modifications
- Steady State Trough (C_{min}) level rucaparib concentrations

10.3 Exploratory Efficacy Variables

The following are the exploratory variables described in this SAP and planned for the final CSR:

- Efficacy as defined by homologous recombination repair (HRR) gene alterations
- Efficacy based on lower / higher genomic LOH cutoff (optimization)
- Time to first response by RECIST v1.1.
- Change from baseline in sum of diameter of target lesions

There are some exploratory endpoints that have been explored and summarized within publications. Due to the exploratory nature of those endpoints, they will not be re-analyzed within the context of this SAP nor described within the final CSR. The exploratory endpoints that were protocol specified, but not performed as part of this SAP, are listed in Section 14.

11 EFFICACY ANALYSIS

11.1 Primary Efficacy Analysis

Part 1: Progression-free Survival in HRD group

The primary efficacy endpoint of PFS will be calculated as 1+ the number of days from the first dose of study drug to disease progression by RECIST, as determined by the investigator 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.

The Kaplan-Meier methodology will be used to summarize PFS by HRD group. 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. In addition, cox proportional hazard methodology will be used to compare the PFS by HRD group. The hazard ratio with 95% CI and p-value will be presented for the comparison of the tBRCA group compared to non-tBRCA LOH-, and for the non-tBRCA LOH+ compared to non-tBRCA LOH- subgroup. The primary endpoint of PFS will be analyzed for the safety population.

Part 2: ORR by RECIST v1.1 in HRD group

The primary efficacy endpoint of ORR is defined as best confirmed response according to RECIST v1.1 as assessed by investigator. The primary efficacy endpoint will be analyzed for the efficacy population, but also summarized for the safety population as supportive analysis.

The tumor assessment is summarized by confirmed response by RECIST v1.1 criteria as outlined below in each HRD group. No statistical test will be performed between the HRD groups.

Confirmatory Response Rate

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 response documentation. The ORR will be summarized with frequencies and proportion together with 95% 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 (for example discontinuations or deaths before first tumor assessment)

11.2 Secondary Efficacy Analyses

11.2.1 ORR for Study Part 1

The ORR is a secondary endpoint for Part 1 of the study. The ORR is defined as best confirmed response according to RECIST v1.1 as assessed by investigator as outlined in Section 11.1. The ORR for Part 1 will be analyzed for the efficacy population, but also summarized for the safety population as supportive analysis within each of the HRD subgroups. No statistical test will be performed between the HRD groups.

11.2.2 Duration of Response

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 each HRD subgroup. 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% CI, will be presented. The number of patients with PD events and the number of censored patients will also be presented.

11.2.3 ORR by RECIST and GCIG CA-125 Criteria

The endpoint of ORR defined as a best response of CR or PR using RECIST v 1.1 or a response per GCIG CA-125 criteria[1]. The ORR will be summarized with frequencies and percentages in the efficacy population.

The endpoint of CA-125 response rate defined as a 50% reduction in CA-125 as assessed by GCIG criteria will be summarized with frequencies and percentages in the safety population. As a supportive analysis, the CA-125 response rate will also be evaluated in the patients evaluable for a CA-125 response as defined in Appendix B.

ORR will be reported separately and together for RECIST and GCIG. The combined ORR will be assessed as indicated in Table 4.

Table 4 Overall Response by RECIST v1.1 and GCIG CA-125 Criteria[2]

RECIST Response	GCIG CA-125 Response	RECIST + GCIG CA-125 Combined
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

The ORR will be summarized with frequencies and proportion together with 95% Confidence Interval (CI) of the proportion using Clopper-Pearson methodology.

11.2.4 Progression-free Survival in Part 2

PFS will be calculated as 1+ the number of days from the first dose of study drug to disease progression by RECIST, as determined by the investigator 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.

The Kaplan-Meier methodology will be used to summarize PFS by HRD group. 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. In addition, cox proportional hazard methodology will be used to compare the PFS by HRD group. The hazard ratio with 95% CI and p-value will be presented for the comparison of the tBRCA group compared to non-tBRCA LOH-, and for the non-tBRCA LOH+ compared to non-tBRCA LOH- subgroup.

11.2.5 Overall Survival in Part 2

Overall survival (OS) is defined as the number of days from the date of first dose of study drug to the date of death (due to any cause). Patients without a known date of death will be censored on the date the patient was last known to be alive.

The Kaplan-Meier methodology will be used to summarize OS by HRD group. If able to be estimated, the 50th (median) together with a 95% Confidence Interval (CI), will be presented. The number of patients with a death events and the number of censored patients will also be presented. In addition, cox proportional hazard methodology will be used to compare the OS by HRD group. The hazard ratio with 95% CI and p-value will be presented for the comparison of the tBRCA group compared to non-tBRCA LOH-, and for the non-tBRCA LOH+ compared to non-tBRCA LOH- subgroup.

11.2.6 Pharmacokinetic Analyses

As a secondary endpoint of the study, trough (C_{min}) concentrations of rucaparib will be summarized with descriptive statistics overall and by cycle in all patients with at least one PK sample collected.

11.3 Exploratory Efficacy Analyses

11.3.1 Efficacy by HRR Gene Subgroups

Results of HRR genes testing by FMI NGS in this study will be summarized in a patient listing. FMI sequences 28 genes that are associated with homologous recombination repair (HRR): BRCA1, BRCA2, ATM, ATR, ATRX, BARD1, BLM, BLIP1, CHECK1, CHECK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, and RPA1.

Five (BRCA1, BRCA2, RAD51C, RAD51D, and PALB2) of the above 28 HRR genes have been identified as genes more strongly linked to possible rucaparib sensitivity as compared to the other genes. PFS and ORR will therefore be summarized in the following HRR subgroups:

- BRCA1
- BRCA2
- RAD51C or RAD51D or PALB2
- Any of the 5 HRR genes (BRCA1, BRCA2, RAD51C, RAD51D, or PALB2)

The analyses for these mutation subgroups will be performed in the same manner as that described for each of the primary efficacy endpoints (Section 11.1).

11.3.2 Efficacy Based on Lower/Higher Genomic LOH Cutoff in Part 1

The objective of Part 1 was to give guidance for an optimal LOH cutoff ARIEL3 CO-338-014 study "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Rucaparib as Switch Maintenance Therapy Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, Relapsed High-Grade Serous Ovarian Cancer". The primary endpoint of PFS in Part 1 will be explored in all non-tBRCA patients with known LOH at different cutoff of LOH. A Cox proportional hazard model of primary endpoint of PFS will be done testing the patients with a LOH+ vs LOH- at different cutoffs (e.g., 10% to 35%) and LOH as a continuous variable in the model.

11.3.3 Time to First Response RECIST Version 1.1

The frequency and percentages of patients with a response (CR or PR) will be summarized by the first occurrence using the following time points; ≤ 9 weeks (Cycle 2), ≤ 17 weeks (Cycle 4), ≤ 25 weeks (Cycle 6), ≤ 33 weeks (Cycle 8), and > 33 weeks.

11.3.4 Change from Baseline in Sum of Diameters of Target Lesions

The largest percent decrease from baseline in the sum of diameters 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.

12 STATISTICAL / ANALYTICAL ISSUES

12.1 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-events are censored, and the rules for deriving the censoring value is described in more detail under each one of the time to event endpoints.

12.2 Pooling of Centers in Multi-Center Studies

The centers will be pooled.

12.3 Multiple Comparison / Multiplicity

No adjustments for multiple comparisons will be made.

13 SAFETY ANALYSIS

The safety analyses will be performed using the safety population.

13.1 Adverse Events

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

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

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 interruption of study medication; and
- TEAEs resulting in reduction of study medication
- TEAEs resulting in reduction, interruption of study medication.
- Time to the first TEAE that results in a reduction, delay, interruption or discontinuation of study drug.
- Time to the first Treatment-related TEAE that results in a reduction, delay, interruption or discontinuation of study drug.

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

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

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
- Anemia and/or Low/Decreased Haemoglobin
- Thromobocytopenia and/or Low/Decreased Platelets
- Neutropenia and/or Low/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) and concomitant medications / growth factor

support are provided in patient listings. The number of transfusions and the time to first transfusion is also summarized. Patient listing of any secondary malignancies may also be presented.

13.2 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 randomization 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.

Laboratory parameters of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and reticulocytes were only captured for Part 2 patients, hence, summary statistics and proportion of patient above the normal range is summarized for Part 2 only.

13.3 Vital Signs

The on-treatment period will be defined as the time from enrolment 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.

13.4 Electrocardiograms (ECG)

Local reads of ECG were collected at screening and end of study.

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: ≤450 msec, >450 to ≤480 msec, >480 to ≤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, ≥30 to <60 msec, and ≥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.

14 CHANGES IN THE PLANNED ANALYSES

The following analyses were planned in the protocol, but will not be performed as part of this SAP:

Exploratory Objectives

- Changes in HRD (LOH and gene alterations) in fresh biopsy versus archival tumor tissue samples.
- ORR by RECIST v1.1 and GCIG CA-125 criteria in relation to HRR gene mutations identified by BROCA analysis
- PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria in relation to gene signature defined by a gene expression profiling assay
- NHEJ protein expression by immunohistochemistry (IHC) and PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria
- Levels of ctDNA in relation to PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria

15 REFERENCES

1. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma, Nature, 2011; 474(7353):609-15
2. Rustin GJS, Vergote I, Eisenhauer E, et al. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 2011;21:419-23

16 APPENDIX A

Internal memo

[redacted]

CLOVIS ONCOLOGY

[redacted]

Prepared By:

Approved By:

[redacted]

1 Van Loo, P. *et al.* Allele-specific copy number analysis of tumors. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 16910-16915, doi:10.1073/pnas.1009843107 (2010).
2 Frampton, G. M. *et al.* Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nature biotechnology* **31**, 1023-1031, doi:10.1038/nbt.2696 (2013).
3 Thiagalingam, S. *et al.* Mechanisms underlying losses of heterozygosity in human colorectal cancers. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 2698-2702, doi:10.1073/pnas.051625398 (2001).

* Foundation Medicine's next generation sequencing-based T5 assay sequences the protein coding regions of 287 cancer-related genes as well as 3544 SNPs distributed across the genome.

CLOVIS ONCOLOGY

Internal memo

[redacted]

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[redacted]

Prepared By:

Approved By:

[redacted]

1 Van Loo, P. *et al.* Allele-specific copy number analysis of tumors. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 16910-16915, doi:10.1073/pnas.1009843107 (2010).
2 Frampton, G. M. *et al.* Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nature biotechnology* **31**, 1023-1031, doi:10.1038/nbt.2696 (2013).
3 Thiagalingam, S. *et al.* Mechanisms underlying losses of heterozygosity in human colorectal cancers. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 2698-2702, doi:10.1073/pnas.051625398 (2001).
4 Network, C. G. A. R. Integrated genomic analyses of ovarian carcinoma. *Nature* **474**, 609-615, doi:10.1038/nature10166 (2011).

* Foundation Medicine's next generation sequencing-based T5 assay sequences the protein coding regions of 287 cancer-related genes as well as 3544 SNPs distributed across the genome.

17 APPENDIX B

Modified Gynecological Cancer Intergroup (GCIG) Guidelines for Response Using CA-125

Adapted from Rustin et al., Int J Gynecol Cancer. 2011
GCIG CA 125 definitions are available at http://gcig.igcs.org/CA-125.html.

To be evaluable for response by CA-125 requires an elevated baseline value of at least twice the upper limit of normal (i.e., > 70 iU/L) and at least two additional samples after the start of treatment.

A response to CA-125 has occurred if there is at least a 50% decrease from baseline:

- in a sample collected after initiation of study treatment AND
- is confirmed in a subsequent sample collected ≥21 days after the prior sample. The absolute value of this confirmatory sample must be ≤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.