NCT #:NCT03522246

# STATISTICAL ANALYSIS PLAN

## ATHENA (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy)

# ATHENA-COMBO

**PROTOCOL:** CO-338-087

**VERSION:** v1.0

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**SPONSOR:** pharmaand GmbH (pharma&)

[redacted]

[redacted]

Phone Number: [redacted]

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# ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | Analysis of Covariance |
| AST | aspartate aminotransferase |
| BRCA | breast cancer gene |
| BICR | blinded independent central review |
| bicrPFS | progression-free survival, blinded independent central review |
| BID | "Bis In Die" twice (two times) a day |
| BSO | bilateral salpingo-oopherectomy |
| CA-125 | cancer antigen-125 |
| CFI | chemotherapy-free interval |
| CI | confidence interval |
| $CL_{cr}$ | creatinine clearance |
| cm | centimeter |
| CMH | Cochran-Mantel-Haenszel |
| $C_{min}$ | trough concentration |
| CR | complete response |
| CRF | Case Report Form |
| CRO | contract research organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor DNA |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic database capture |
| EMA | European Medicines Agency |
| ENGOT | European Network for Gynecological Oncological Trial groups |
| EQ-5D | Euro-Quality of Life 5D |
| EQ-5D-5L | Euro-Quality of Life 5D-5L |
| EQ VAS | Euro-Quality of Life Visual Analog Scale |
| FACT-O | Functional Assessment of Cancer Therapy - Ovarian |
| FMI | Foundation Medicine, Inc. |
| gBRCA | germline BRCA1/2 mutation |
| GCIG | Gynecologic Cancer InterGroup |
| GOG | Gynecologic Oncology Group |
| HR | hazard ratio |
| HRD | homologous recombination deficient |
| HRQoL | health-related quality of life |

| | |
|---|---|
| IDMC | Independent Data Monitoring Committee |
| invPFS | progression-free survival, investigator-assessed |
| ITT | intent-to-treat |
| IV | intravenous(ly) |
| LOH | loss of heterozygosity |
| LFT | liver function test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Events |
| NGS | next-generation sequencing |
| ORR | objective response rate |
| OS | overall survival |
| PARPi | poly (adenosine diphosphate-ribose) polymerase inhibitor |
| PD | progressive disease |
| PFS | progression-free survival |
| PFS2 | progression-free survival on subsequent line of treatment |
| PK | pharmacokinetic(s) |
| PR | partial response |
| PRO | patient-reported outcome |
| PT | preferred term |
| QoL | quality of life |
| QT | time from beginning of the Q wave to the end of the T wave |
| QTc | QT interval corrected for heart rate |
| QTcB | QT interval corrected using Bazett's formula |
| QTcF | QT interval corrected using Fridericia's formula |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SFU1 | Safety Follow-up Visit 1 |
| SFU2 | Safety Follow-up Visit 2 |
| SOC | System Organ Class |
| tBRCA | deleterious BRCA1/2 mutation in tumor tissue |
| TEAE | treatment-emergent adverse event |
| TFST | time to first subsequent anticancer treatment |
| TMB | tumor mutational burden |
| TOI | trial outcome index |
| TSST | time to second subsequent anticancer treatment |
| ULN | upper limit of normal |
| VAS | Visual Analog Scale |
| WHO | World Health Organization |

## Analysis Population Definitions

| | |
|---|---|
| **ITT Population** | All randomized patients |
| **Safety Population** | All patients who received at least 1 dose of protocol-specified treatment |

## Subgroup Definitions

| | |
|---|---|
| **PD-L1+** | Patients with positive immune cell (IC) score ≥ 5%. A secondary definition is patients with IC score ≥ 1%. |
| **HRD** | Patients with HRD+ tumors (an NGS HRD assay result), composed of tBRCA and non-tBRCA LOHhigh |
| **tBRCA** | Patient with deleterious *BRCA1/2* mutation in tumor tissue |
| **non-tBRCA LOH$^{high}$** | Patients without a tBRCA mutation and with percent of tumor genome LOH ≥ 16% |
| **non-tBRCA LOH$^{low}$** | Patients without a tBRCA mutation and with percent of tumor genome LOH < 16% |
| **non-tBRCA LOH$^{unknown}$** | Patients without a tBRCA mutation and with percent of tumor genome LOH unknown |

# 1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for evaluation of the ATHENA combination (ATHENA-COMBO) treatment as part of the Clinical Study Protocol: CO-338-087/GOG-3020 / ENGOT-ov45/NCRI/ATHENA (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy).

This SAP provides additional details concerning the statistical analyses for ATHENA-COMBO comparisons that are already outlined in the original protocol (dated 02 March 2018), Protocol Amendment 1 (dated 05 July 2018), Protocol Amendment 2 (dated 26 October 2020), protocol Amendment 3 (September 2021), Protocol Amendment 4 (29 November 2021), and Protocol Amendment 5 (16 June 2023).

Since this study will still be ongoing as of the maturity of the primary analysis for ATHENA-COMBO, a visit cut-off will be applied to all data sets and fully documented in the statistical package data set documentation.

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 Outlined in Protocol

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

| |
|---|
| ***Primary Objectives*** |
| • To evaluate PFS by RECIST, as assessed by the investigator (invPFS) |
| ***Secondary Objectives*** |
| 1. To evaluate PFS by RECIST, as assessed by the BICR |
| 2. To evaluate survival benefit |
| 3. To evaluate ORR and DOR, as assessed by the investigator, in patients with measurable disease at baseline |
| 4. To evaluate safety |
| ***Exploratory Objectives*** |
| 1. To evaluate PFS2 |
| 2. To evaluate the contribution of nivolumab monotherapy vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety) |
| 3. To evaluate the contribution of combination rucaparib + nivolumab vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety) |
| 4. To evaluate Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) |
| 5. To evaluate patient-reported outcome (PRO) utilizing the Euro-Quality of Life 5D-5L (EQ-5D-5L) |
| 6. To assess mutations in non-tBRCA HRR genes as a molecular marker of efficacy |
| 7. To assess PD-L1 expression and TMB as molecular markers of efficacy |
| 8. To study variants in circulating tumor DNA (ctDNA) as markers of response and |
| 9. To characterize PK of rucaparib as monotherapy and in combination with nivolumab |
| 10. To characterize PK of nivolumab as a monotherapy and in combination with rucaparib |
| 11. To evaluate immunogenicity of nivolumab when administered as a monotherapy and in combination with rucaparib |
| 12. To explore exposure-response relationship between selected exposure measures of rucaparib and nivolumab, and safety and efficacy endpoints |

## 2.2 Study Design

ATHENA is a Phase 3, randomized, double-blind, dual placebo-controlled study of rucaparib in combination with nivolumab in patients with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer who have responded to their first-line platinum-based regimen.

The study will enroll patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who completed first-line platinum-based chemotherapy and surgery with a response of either a CR or a PR, defined as RECIST v1.1 PR or a CA-125 PR by GCIG criteria[1] to their first platinum-based regimen. Patients must have received 4 to 8 cycles of first-line platinum doublet treatment per standard clinical practice, including a minimum of 4 cycles of a platinum/taxane combination; no other prior treatment for ovarian cancer, including maintenance treatment, is permitted. Patients need to have had completed cytoreductive surgery, including at least a BSO and partial omentectomy, either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking).

Patients will be required to provide archival tumor tissue or a screening biopsy for central laboratory analysis prior to enrollment. Genes of interest will be sequenced using Foundation Medicine's (FMI) NGS test, which examines a panel of cancer-related genes, including BRCA1/2 and the degree of tumor LOH.

The results from the NGS test will be utilized to classify patients into the following randomization stratification groups:

- tBRCA (deleterious BRCA1 or BRCA2 mutation)
- non-tBRCA LOH$^{high}$ (LOH ≥ 16%)
- non-tBRCA LOH$^{low}$ (LOH < 16%)
- non-tBRCA LOH$^{unknown}$

The sponsor will remain blinded to all NGS test results (including all tBRCA results), as well as existing local BRCA testing results, until the primary efficacy analysis is conducted.

Approximately 1000 patients will be randomized in the Double-blind Treatment Phase using a 4:4:1:1 ratio into the following four treatment groups:

- Arm A: oral rucaparib + IV nivolumab (n = 400);
- Arm B: oral rucaparib + IV placebo (n = 400);
- Arm C: oral placebo + IV nivolumab (n = 100); or
- Arm D: oral placebo + IV placebo (n = 100).

The randomization is stratified by the following factors:

- HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$);
- Disease status (no residual disease vs residual disease); and
- Timing of surgery (primary surgery vs interval debulking).

Randomization to study treatment must occur within 8 weeks following a patient's first day of the last cycle of chemotherapy.

During the Double-blind Treatment Phase (continuous 28-day treatment cycles), the double blinded oral study treatment will be administered on Day 1 of Cycle 1 and continue BID throughout the cycle as monotherapy. IV study drug administration will begin on Day 1 of Cycle 2 during the Double-blind Treatment Phase. Patients will have clinic visits on Day 1 and Day 15 of Cycles 1 and 2, and on Day 1 of every cycle thereafter. Study treatments will continue until 24 months after planned initiation of oral/ IV combination study treatment (C2D1), disease progression, unacceptable toxicity, or withdrawal of participant consent, whichever happens first.

During the Treatment Phase patients will be monitored for safety and efficacy. Assessments will include AEs, physical examination, vital signs and weight measurement, central laboratory hematology, serum chemistry, and CA-125 measurement, concomitant medications, therapies, and procedures, ECOG performance status, disease status assessment, ctDNA analysis, study drug administration and accountability, and PRO. ECGs and urinalysis will be performed as clinically indicated. Blood samples will also be collected to determine whether any mutation identified is of germline or somatic origin.

Patients will be assessed for disease status per RECIST v1.1 every 12 calendar weeks (flexibility with scheduling within 1 week prior to planned imaging date is permitted) following initiation of oral/ IV combination study treatment on Day 1 of Cycle 2 (the first scan will be 16 weeks after initiation of oral study treatment) for the first 3 years after initiation of oral/ IV study treatment and every 24 weeks thereafter until objective radiological disease progression; disease status will also be assessed at discontinuation of treatment and as clinically indicated. Disease progression will only be determined by RECIST v1.1. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, will be discontinued from treatment and enter the Follow-up Phase of the study. If the patient has met criteria for radiologic progression by RECIST, but the patient is still receiving benefit from the study drug(s) according to the investigator, then continuation of treatment will be considered for a maximum duration of 24 months after planned initiation of oral/ IV combination study treatment.

All CT/MRI scans will be sent to an external vendor for BICR. However, all treatment decisions will be based on investigator assessment of scans.

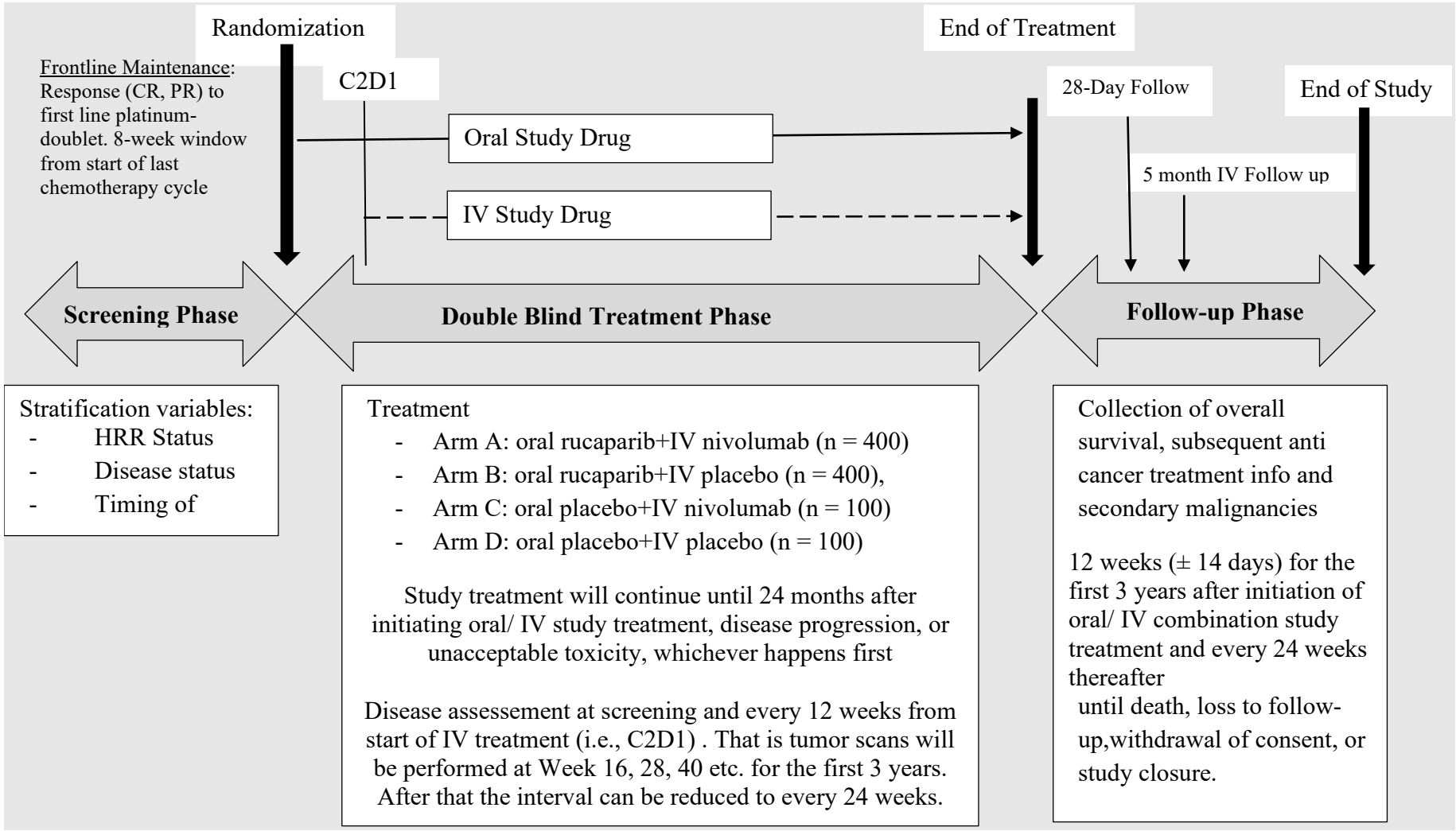
After the treatment is discontinued, all patients will be followed for at least 5 months after the last dose of IV study drug treatment. There will be 2 follow-up visits: Safety Follow-up Visit 1 (SFU1) should occur 28 days (± 7 days) after last dose of the oral and/or IV study drug (whichever occurs later), and Safety Follow-up Visit 2 (SFU2) should occur approximately 5 months (± 7 days) after the last dose of IV study drug treatment. If a patient remains on oral study drug after discontinuation of IV study drug, SFU2 visit can be performed at a cycle visit, provided it has been at least 5 months since the last IV study drug dose. Patients who discontinued treatment for a reason other than disease progression or death should continue to have tumor scans performed at 12--week intervals from C2D1 for the first 3 years after initiation of oral/IV combination study drug treatment and then every 24 weeks thereafter until objective radiological disease progression by RECIST v1.1, as assessed by the investigator, is documented.

Patients will also be followed long-term for survival, subsequent treatments, disease progression (if treatment discontinuation was for reason other than disease progression or death), and monitoring for secondary malignancy every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent, or study closure.

An open-label safety cohort in Japan, with patients receiving open-label oral rucaparib + IV nivolumab combination treatment, is part of the overall ATHENA study. The analyses for this open-label cohort are detailed and summarized in Section 11.6.

Figure 1 shows the schedule of the study design with the screening phase followed by the randomized treatment phase and lastly the post-treatment phase.

**Figure 1 Schema of Study Design**



## Protocol Amendments

This statistical analysis plan (SAP) incorporates the amendments in Table 2.

**Table 2 Protocol Amendments**

| Amendment | Date of Issue | Summary of Major Changes |
|---|---|---|
| Amendment 1 | 05 July 2018 | • Inclusion of patients who have achieved a partial response (PR) to their first platinum-based regimen has been justified.<br>• Language was added as requested by the MHRA to align safety assessments to the SmPC for nivolumab. |
| Amendment 2 | 26 October 2020 | • The original comparison of rucaparib + nivolumab vs placebo was moved from the primary endpoint analysis to an exploratory endpoint analysis<br>• Clarification that alpha will be split between the remaining 2 independent comparisons of ATHENA-COMBO (rucaparib + nivolumab vs rucaparib) and ATHENA-MONO (rucaparib vs placebo) treatment and that they will mature at different timepoints and be read out separately;<br>• Update to the step-down analysis for the monotherapy comparison (rucaparib vs placebo), from tBRCA → HRD → ITT to HRD → ITT, due to a low proportion of tBRCA patients enrolled to the study. |
| Amendment 3 | 08 September 2021 | • The step-down for ATHENA-COMBO was changed from an HRD → ITT analysis to an ITT analysis only. No changes to sample size and power assumptions were made.<br>• Added an exploratory analysis for tBRCA, HRD, and PD-L1 subgroups of the combination comparison. |
| Amendment 4 | 29 November 2021 | The following changes were made per US FDA request:<br>• Removed bicrPFS from the hierarchical step-down and added bicrPFS as a stand-alone secondary endpoint.<br>• Added language clarifying the key secondary endpoints in the step-down analysis are OS and ORR and that secondary endpoints of bicrPFS and DOR were outside of the step-down procedure.<br>• Included further details on PFS censoring methodology |

| | | |
|---|---|---|
| Amendment 5 | 16 June 2023 | • Clovis Oncology has transferred Sponsor responsibilities to pharma&; added language to update pharma& contacts.<br>• Updated the current rucaparib approvals in the US, EU, and UK.<br>• Discontinued the requirement for ctDNA collection in the long-term follow-up portion of the study.<br>• Updated the use of log-rank test for official test for step-down procedure (per FDA request).<br>• Added information on ARIEL4 study.<br>• Updated the safety overview. |

## 2.3 ATHENA Sample Size Considerations

Up to approximately 1000 patients will be randomized in a 4:4:1:1 ratio to receive treatment with 1 of the following 4 arms:

- Arm A: Oral rucaparib + IV nivolumab (n = 400);
- Arm B: Oral rucaparib + IV placebo (n = 400);
- Arm C: Oral placebo + IV nivolumab (n = 100); or
- Arm D: Oral placebo + IV placebo (n = 100).

Two separate comparisons of the treatment arms will be evaluated independently, and at different time points based on the maturity of the parts of the study, in order to evaluate both rucaparib monotherapy and rucaparib in combination with nivolumab.

- ATHENA-MONO: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV]); *Primary Endpoint of invPFS evaluated using a data-cutoff of 23 March 2022*
- ATHENA-COMBO: Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo).

The level of statistical significance will be split into two so that each of the above comparisons will be made independently at a one-sided 0.0125 (two-sided 0.025) significance level. The 2 treatment comparisons are set up as independent and can thus be unblinded to treatment allocations and read out at different time points for this study. The treatment comparison of Arm A (oral rucaparib + IV nivolumab) vs Arm D (placebo [oral and IV]) will be performed as an exploratory analysis to support contribution of each component in the rucaparib-nivolumab combination.

## 2.4 ATHENA-COMBO Sample Size

The median PFS for patients in Arm A (rucaparib+nivolumab) from all randomized patients (ie, the ITT Population inclusive of both tBRCA and non-tBRCA subgroups) is expected to

be approximately 28 months while the median PFS for patients in Arm B (rucaparib monotherapy [rucaparib + IV placebo]) is expected to be about 20 months.

The following table provides the sample size and power for the ATHENA-COMBO comparison of Arm A (rucaparib+nivolumab) to Arm B (rucaparib monotherapy) in the ITT Population.

| Group | Hazard Ratio | Cumulative N (4:1) | Number of Events | Median PFS (months) | Power | One-sided Alpha |
|---|---|---|---|---|---|---|
| ITT | 0.725 | 800 (400:400) | 600 | 20 vs 28 | 90% | 0.0125 |

Abbreviations: ITT =intent-to-treat, PFS = progression-free survival
Assumed accrual duration is 24 months.

## 2.5 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will monitor the safety and efficacy for this trial. The IDMC will be comprised of two oncologists with experience in treating women with ovarian cancer and a statistician, all of whom are not otherwise involved in the study as investigators.

The IDMC will:
- Review safety and efficacy of rucaparib and nivolumab compared with placebo, as well as the rucaparib + nivolumab combination compared to monotherapy to ensure the study is beneficial to patients.
- Ensure the study is conducted in a high-quality manner.
- Monitor the size of the tBRCA subgroup.

Following data review, the IDMC will recommend continuation, revision, or termination of the study and/or continuing or halting enrollment into a particular subgroup.
No formal efficacy interim analyses for early stopping are planned for this study.

# 3 GENERAL ANALYSIS CONVENTIONS

Efficacy analyses will be analyzed in the ITT Population as described in Section 10 below.

All safety analyses will be based on the Safety Population, which consists of all patients who received at least 1 dose of protocol-specified treatment of oral study drug and/or IV study drug. Further, for safety analyses, patients randomized to either arm containing IV Nivolumab (ie, Arm A or Arm C) who never receive Nivolumab, will be analyzed in the analogous arm containing IV Placebo (ie, Arm B or Arm D, respectively).

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

The Kaplan-Meier methodology will be used to summarize time-to-event variables. The 50th (median) percentile with the 95% CI will be summarized for each randomized treatment group. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The number of patients with events and the number of censored patients will also be presented.

The primary endpoint of invPFS, secondary endpoint of OS, bicrPFS (if applicable), ORR and exploratory analyses for the ITT population will be analyzed using the stratification factors of HRD classification, disease status, and timing of surgery. If the model does not converge or if there are only patients from a single treatment arm per stratum or if one or more of the strata contain few patients (eg, <5 patients) then the stratification factor of disease status will be omitted first, then timing of surgery, if necessary. Additionally, the Firth correction in the PHREG procedure will be used.

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

Baseline is defined as the last measurement on or prior to the first day of oral study drug administration or randomization date if the patient was never treated.

Results of all statistical analysis will be presented using 95% CIs and two-sided p-values. The significance level for ATHENA-COMBO is set at a one-sided p=0.0125 (two-sided p=0.025).

All statistical analyses will be conducted with the statistical analysis software (SAS®) System, Version 9.4 or higher.

## 3.1 Populations Definitions

**Intent-to-Treat Population:** The intent-to-treat (ITT) population will consist of all randomized patients.

**Safety Population:** The Safety Population will consist of all patients who received at least 1 dose of protocol-specified treatment of oral study drug and/or IV study drug.

In addition to the population definitions above, exploratory efficacy will be performed in subgroups including the mutually exclusive (non-nested) molecular subgroups within the ITT Population as outlined in Section 10.3 below.

## 3.2 Definition of HRD Subgroups

The results from the NGS test will be utilized to classify patients into the following randomization stratification groups in this study:

- **tBRCA:** Patient with deleterious BRCA1/2 mutation in tumor tissue;
- **Non-tBRCA LOH$^{high}$:** Patients without a tBRCA mutation and with percent of tumor genome LOH ≥ 16%;
- **Non-tBRCA LOH$^{low}$:** Patients without a tBRCA mutation and with percent of tumor genome LOH < 16% ; and
- **Non-tBRCA LOH$^{unknown}$:** Patients without a tBRCA mutation and with percent of tumor genome LOH unknown.

The exploratory efficacy analyses of these subgroups are outlined in Section 10.3.

## 3.3 Statistical Hypothesis and treatment comparisons

The primary statistical hypothesis /objective of the ATHENA-COMBO comparison is to test for improvement in PFS for the combination of rucaparib and nivolumab over rucaparib monotherapy as follows:

- $H_0$: HR (Arm A/Arm B) ≥ 1
- $H_a$: HR (Arm A /Arm B) < 1

In order to test the main hypothesis for ATHENA-COMBO, Arm A (oral rucaparib+IV nivolumab) will be compared against Arm B (oral rucaparib+IV placebo). All efficacy analyses will be tested at a one-sided 0.0125 level (two sided 0.025).

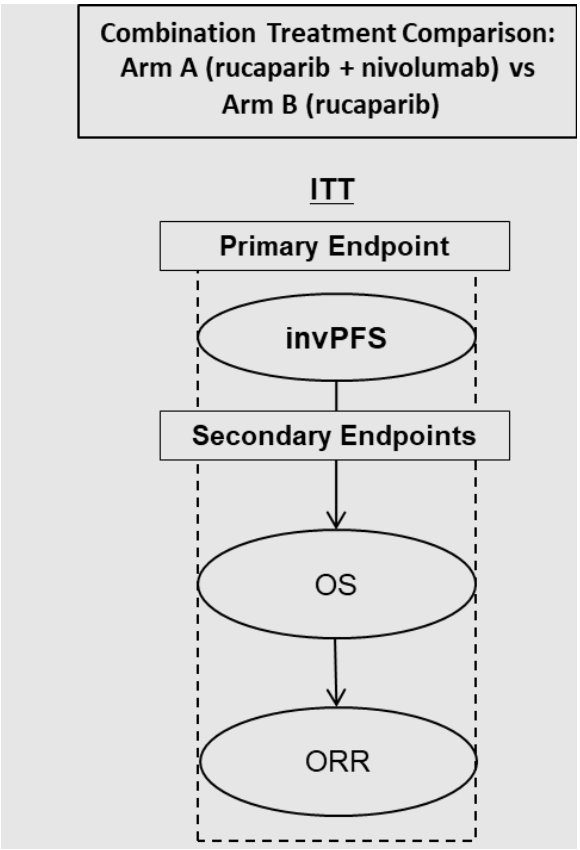
## 3.4 Step-down Procedure of Primary and Secondary Endpoints

In order to preserve the overall Type 1 error rate, while testing the primary and secondary endpoints across the ATHENA-COMBO treatment comparison, a hierarchical step-down procedure has been specified. Statistical significance will only be declared for any of the endpoints if the previous endpoints are also statistically significant at the one-sided significance level of 0.0125 (two-sided alpha=0.025). The step-down procedure is outlined in Figure 2.

The ATHENA-COMBO treatment arm comparison (A vs B) will be tested using a one-sided alpha of 0.0125 (two-sided alpha=0.025) in sequential order for the primary endpoint of invPFS and key secondary endpoints of OS and ORR, respectively (see Figure 2).

Therefore, the invPFS in the ITT Population will be tested first at a one-sided 0.0125 significance level (two-sided alpha=0.025). If invPFS is statistically significant, then the first secondary endpoint of OS will be tested at the one-sided 0.0125 significance level (two-sided alpha=0.025) in the ITT Population. If OS in the ITT Population is statistically significant, then testing will continue to the last key secondary endpoint of ORR. Once statistical significance is not achieved, statistical significance will not be declared for subsequent analyses in the ordered step-down procedure for the ATHENA-COMBO comparison in the ITT Population.

**Figure 2. Ordered Step-down Procedure for the ATHENA-COMBO Comparison**




Note: As described in Section 10.2.2, OS will be analyzed at the time of the primary analysis (interim OS analysis) and again for a final OS analysis. If the interim OS results are not statistically significant, p-values for all secondary endpoints will be considered descriptive until the final OS analysis has been performed as part of the step-down procedure.

## 3.5 Stopping Rule, IDMC, and Unblinding

There are no pre-specified stopping rules for the study. As discussed in more detail in Section 2.5 above, there is an IDMC for the ATHENA study, which will provide recommendations about the continuation, revision, or termination of the study. Additional details regarding the IDMC will be documented in a separate IDMC charter.

The patient, investigator, and study staff will be blinded to the patients' tumor HRD status and identity of the assigned treatment from the time of randomization until blind break of the ATHENA-COMBO comparison. Prior to enrollment, the investigator will receive tissue BRCA mutation results for patients in order to make an informed decision prior to enrolling patients into this study considering the approval of PARPi in current patient populations in certain countries. If an individual's role on the trial requires information about HRD status or treatment assignment (eg, an individual is involved in emergency unblinding or entry of HRD status for stratification), procedures will be used to ensure all other personnel remain

blinded. Study treatment assignment will be available to the investigator upon request for post-study treatment planning.

The sponsor study team was unblinded to study arm B (rucaparib + IV placebo) and arm D (oral placebo and IV placebo) on 23 March 2022 when the ATHENA-MONO primary analysis was performed but remained blinded to study arms A (rucaparib + nivolumab) and C (oral placebo + nivolumab). A separate blinding plan has been implemented for ATHENA outlining the details of the blinding process and is used for training with all study personnel and sponsors.

# 4 PATIENT DISPOSITION

The following patient disposition will be summarized by treatment arm:

- Number of patients in each analysis population;
- Number of patients that have discontinued oral study drug and the primary reason for discontinuation, for all patients and broken out by those that continued treatment post-radiological progression and those who did not continue treatment post-radiological progression;
- Number of patients that have discontinued IV study drug and the primary reason for discontinuation;
- Number of patients by end-of-treatment status of both Oral and IV study drug; Study drug never initiated, Study drug never initiated due to COVID-19, Study drug discontinued, and Study drug completed; and.
- Number of patients by the end of study status; discontinued treatment for oral and IV study drug, withdrew consent, lost to follow-up, death, and still in active long-term follow-up (ie, discontinued both oral and IV treatment, but are still being actively followed for post-progression endpoints and overall survival).

## 4.1 Disposition and Summary of COVID-19 Impact

The number of patients who were ongoing and impacted by COVID-19 will be summarized. This is defined as all patients ongoing, or in Long-term Follow-up starting with visits dated on and after 01 February 2020. The number of tumor scans missed, visits missed, and the number of telehealth visits will also be summarized for both the ITT Population and the Safety Population.

# 5 PROTOCOL DEVIATIONS

Major protocol deviations will be identified prior to releasing the treatment codes for the primary efficacy analysis in accordance with pharma& SOP8223 (Protocol Deviations Management). 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 will be summarized by treatment group and overall for the ITT and Safety Populations. Additional analyses for the PD-L1 (IC ≥5% and IC ≥1%) and HRD stratification (ie, tBRCA, non-tBRCA LOH$^{high}$ , non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$) subgroups may also be performed.

## 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, ECOG performance status, and geographic region using the following categorizations:

- Age (years): ≤ 50, 51-60, 61-70, 71-80, 81-90, > 90; and < 65, 64-74, ≥ 75;
- Height (cm): ≤ 75, > 75-100, > 100-125, > 125-150, > 150-175, > 175;
- Weight (kg): ≤ 50, > 50-75, > 75-100, > 100-125, > 125-150, > 150;
- Gender: Female;
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other, or Not Reported;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, or Not Reported;
- ECOG performance status: 0, 1;
- Smoking status: Current smoker, Former smoker, never smoked;
- Country; and
- Geographic region (United States/Canada, Western Europe, Eastern Europe, Latin America, Asia/Africa/Oceania).

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

## 6.2 Cancer History and Prior Anticancer Treatment, and Disease Burden at Randomization

### 6.2.1 Cancer History and Prior Anticancer Treatment and Surgery

A summary table on the baseline clinical characteristics across patients by treatment and overall will be summarized according to the following:

- Time since diagnosis (months): 0 to 3, > 3 to 6, > 6 to 9, >9 to 12, >12;
- Type of ovarian cancer (ie, Epithelial, Primary Peritoneal, Fallopian Tube);
- Cancer histology and stage at enrollment;
- Number of prior chemotherapy regimens, and platinum-based regimen;
- Number of cycles of prior chemotherapy regimen, and platinum-based agent;
- Number of patients by administrative setting of front-line regimen (IV only with HIPEC, IV only without HIPEC, IP only with HIPEC, IP only without HIPEC, IV and IP with HIPEC, IV and IP without HIPEC);
- Number of patients with prior bevacizumab use;
- Duration between randomization and the date of first day on the last dose of chemotherapy (in weeks);
- Randomization stratification of disease status (no residual disease vs residual disease);
- Disease status (no residual disease vs residual disease) based on EDC data;

- Randomization stratification of timing of surgery (primary surgery vs interval debulking);
- Timing of surgery (primary surgery vs interval debulking) based on EDC data;
- Best radiological response to front-line treatment (CR, PR, No Disease post-surgery, Inevaluable, or Other);
- Best GCIG CA-125 Response to front-line treatment (Response, No Response, Inevaluable, Other);
- Disease Free with normal CA-125 defined as Best radiological response (CR, No Disease Post-surgery) and CA-125 ≤ ULN (Yes, No)
- Number of prior surgeries (0, 1, 2, > 2);
- Type of surgery (BSO, hysterectomy, partial omentectomy, and full omentectomy and Other); and
- Cytoreductive Surgery Outcome (Complete Resection=R0, microscopic residual < 1 cm, Macroscopic residual ≥1 cm, Not applicable).

Descriptive statistics may also be used to summarize these variables.

### 6.2.2 Disease Burden at Randomization

A summary table on the disease burden characteristics across patients by treatment and overall will be summarized according to the following:

- Patients with measurable disease by investigator (ie, target lesions identified by RECIST v1.1);
- Patients with non-measurable disease by investigator (ie, non-target lesions only identified by RECIST v1.1);
- Patients without any disease by investigator (ie, no target lesions and no non-target lesions identified by RECIST v1.1); and
- Number of patients with CA-125 values within normal limits at baseline based on central laboratory results.

## 6.3 PD-L1 Expression, HRD Classification and BRCA Results

A summary table of the PD-L1 expression, HRD classification and BRCA test results by treatment and overall will be presented. The PD-L1 expression is based on the archival tumor tissue or a screening biopsy tested by CellCarta. The HRD classification is based on the archival tumor tissue or a screening biopsy tested by FMI. In addition, blood samples will also be collected and tested by an external central laboratory for any germline BRCA mutation. The patients may also have had local BRCA testing with the result entered in the eCRF during Screening. The following test results will be summarized:

- PD-L1 expression utilizing a 5% IC cut-off and a 1% IC cut-off
- The randomization stratification variables from FMI:

  - HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, or non–tBRCA LOH$^{unknown}$) by central laboratory analysis;
- BRCA by local testing (BRCA1, BRCA2, or not detected);
- BRCA by central blood testing (BRCA1, BRCA2, or not detected);
- Overall BRCA status from local and central (BRCA1, BRCA2, or not detected); and
- Overall Germline/Somatic status (see Table 3 below for categories).

The tumor tissue-based assay used in this study identifies sequence variants in the BRCA1 and BRCA2 genes; however, it does not distinguish between the mutation type of germline or somatic. In order to further explore the mutation type, data from local BRCA test and/or a central blood test of germline BRCA will be used to derive the mutation type according to Table 3 below.

**Table 3 Algorithm for Determination of Germline/Somatic Status**

| CTA 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 |

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

## 6.4 Medical History

The medical history will be summarized for the Safety Population. Medical history events will be classified using the MedDRA classification system version 25.0 or higher. Medical history data will be summarized using frequency tabulations by SOC and PT.

# 7 STUDY DRUG EXPOSURE AND COMPLIANCE

## 7.1 Extent of Exposure

Analyses in this section will be performed in all treated subjects by treatment group as treated. Listings will include all available exposure data.

Table 4 summarizes the key parameters used to calculate exposure.

## Table 4 Key Parameters used to Calculate Exposure

| | Administration of study therapy: definition of parameters | |
|---|---|---|
| | **Rucaparib** | **Nivolumab** |
| Dosing schedule per protocol | 600 mg BID | 480 mg every 4 weeks |
| Dose | *Dose (mg)* is defined as Total Dose administered. Dose administered in mg at each dosing date are collected on the eCRF. | *Dose (mg)* is defined as Total Dose administered. Dose administered in mg at each dosing date are collected on the eCRF. |
| Relative dose intensity (%) | Time normalized actual dose received /600 mg BID | [Cumulative dose (mg) / ( (Last dose date – first dose date + 28) × 480/28)] × 100 |
| Duration of treatment | Last dose date - Start dose date +1 | Last dose date - Start dose date +1 |

Oral and IV study drug exposure will be summarized for all patients in the Safety Population. At the time of the visit cut-off, all patients will have discontinued treatment for protocol-specified reasons or because they reached the treatment cap of 24 months for treatment with the oral/IV combination. 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 oral study drug, the number of patients with at least 1 dose reduction due to a TEAE based on the dosing log will be summarized with frequencies and percentages. Any dose reduction regardless of duration will be summarized. In addition, protocol-specified dose reductions will be broken up by dose level and by reason (ie, AE, non-compliance, or other). That is, the number of patients on each protocol-specified oral dose level will be summarized (ie, 600 mg BID, 500 mg BID, 400 mg BID, 300 mg BID, etc.) in order to assess patients with multiple levels of oral dose reductions. Dose reduction is defined as 3 or more consecutive days at that protocol-specified dose level. The number of patients with at least 1 dose re-escalation will be summarized for each protocol-specified oral dose level from which they escalated.

The number of IV cycles given per treatment arm will also be summarized.

The following parameters will also be summarized for IV study drug:

- Cumulative dose (sum of the doses administered per patient) and infusion duration (stop time – start time for each infusion).
- Dose delays: number of patients with at least 1 delay, number of delays per patient, reasons for delays, and length of delays.

- Infusion interruptions: number of patients with at least 1 interruption, number of interruptions per patient, and reasons for interruptions.

# 8 CONCOMITANT MEDICATIONS

Concomitant medications to oral or IV study drug will be summarized for all patients in the Safety Population. All treatments taken concomitantly with oral or IV study drug will be summarized in frequency tabulations for each randomized treatment group and overall. All treatments will be coded utilizing the WHO Drug Dictionary version 202103 (WHODrug-Global-B3) or later.

Concomitant to oral or IV study drug is defined as all treatments that are either ongoing at the date of the first oral or IV dose or are started prior to the end of the treatment-emergent window (ie, within 28 days of date of last dose of oral study drug or within 5 months of the last dose of IV study drug). A listing of all concomitant treatments will be provided. In addition, a listing of all treatments that are deemed either prior to or post oral or IV treatment will be included in a separate listing. 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 oral or IV study drug, then that medication will be classified as concomitant to oral or IV study drug.

# 9 EFFICACY VARIABLES

## 9.1 Primary Efficacy Variable

The primary efficacy variable is investigator determined PFS (invPFS).

## 9.2 Secondary Efficacy Variables Included in the Step Down Analysis

- OS
- ORR by RECIST v1.1 in patients with measurable disease at baseline

## 9.3 Secondary Efficacy Variables Not Included in the Step Down Analysis

- BicrPFS
- DOR by RECIST v1.1 in patients with measurable disease at baseline

## 9.4 Exploratory Efficacy Variables

- PFS of study treatment followed by the subsequent line of treatment (PFS2), defined as the time from randomization to the second event of disease progression or death, as assessed by the investigator
- To evaluate the contribution of nivolumab monotherapy vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety)

- To evaluate the contribution of combination rucaparib + nivolumab vs nivolumab (invPFS, bicrPFS, OS, ORR, DOR, and safety)
- To evaluate the contribution of combination rucaparib + nivolumab vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety)
- To evaluate efficacy in HRD subgroups (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, non-tBRCA LOH$^{unknown}$, and HRD (tBRCA + non-tBRCA LOH$^{high}$) for the comparison of rucaparib + nivolumab vs rucaparib
- Health-related Quality of Life (HRQoL) as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy - Ovarian (FACT-O)
- Patient-reported outcome (PRO) utilizing the Euro-Quality of Life 5D (EQ-5D)
- Mutations in non-tBRCA HRR genes as a molecular marker of efficacy
- PD-L1 expression and TMB as molecular markers of efficacy
- Variants in circulating tumor DNA (ctDNA) as markers of response and resistance
- PK of rucaparib as monotherapy and in combination with nivolumab
- PK of nivolumab as a monotherapy and in combination with rucaparib
- Immunogenicity of nivolumab when administered as a monotherapy and in combination with rucaparib
- Exposure-response relationship between selected exposure measures of rucaparib and nivolumab, and safety and efficacy endpoints

# 10 EFFICACY ANALYSIS

## 10.1 Primary Efficacy Analysis

The primary efficacy endpoint is PFS as assessed by the investigator (invPFS). The time to invPFS will be calculated in months as the time from randomization to disease progression +1 day, as determined by RECIST v1.1 criteria or death due to any cause, whichever occurs first. Only scans or deaths prior to and on the start of any subsequent anticancer treatment will be used in PFS analysis. Any deaths or progression events occurring within 2 missing expected scan assessments will be included in the analysis. Two missed scans or visits is defined as a duration of 26 weeks (12 x 2+2) for the first 3 years and 50 weeks (24 x 2+2) thereafter. Events occurring immediately after 2 consecutive missed scans will be censored as below.

Censoring rule: Any patients who do not experience an event of either disease progression or death will be censored on the last on-study tumor assessment prior to start of any subsequent anticancer treatment. Any patient with an event of either disease progression or death following 2 or more missed expected consecutive scans will be censored on the date of the last on-study tumor assessment prior to the gap in scan collection. If a patient has an evaluable non-PD scan immediately following the gap, the gap-clock will reset and subsequent scans and events (progression or death) may be used in the primary PFS assessment (barring intervening SACT, as above). If a patient does not have any on-study tumor assessments, then the patient will be censored on the date of randomization (ie, Day 1).

The overall tumor assessment date for visits where multiple scans were utilized to make the assessment will be based on the following rule: the scan date showing the disease progression will be used for events where there is disease progression. For censored patients, the later date of the tumor scans within the assessment will be used.

The randomization stratification factors included in the primary analysis of invPFS are:

- HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, or non-tBRCA LOH$^{unknown}$) by central laboratory analysis;
- Disease status post-chemotherapy (residual disease vs no residual disease); and
- Timing of surgery (primary surgery vs interval debulking).

The primary endpoint will be tested using a stratified log-rank test of invPFS between the randomized treatment groups and will be considered the official test used for the hierarchical testing outlined in Section 3.4.

A graphical presentation of unstratified invPFS distributions, median invPFS with 95% CI, and event rates will be presented as supportive statistics. Furthermore, the probability of being progression free at 6, 12, 18 and 24 months will be summarized by treatment group using the Kaplan-Meier estimates, both unstratified and stratified, at each time point with 95% CIs using a log-log distribution.

Additionally, the primary endpoint will be analyzed using the stratified Cox proportional hazard methodology, presenting the hazard ratio with 95% confidence interval between the randomized treatment groups.

### 10.1.1 Sensitivity Analyses for PFS

#### 10.1.1.1 Stratification factors

A sensitivity analysis of invPFS may be performed using the actual supportive data from FMI CTA and EDC to derive the randomization strata groups:

- HRD status based on FMI CTA
- Disease status (no residual disease vs residual disease) based on EDC data; and
- Timing of surgery (primary surgery vs. interval debulking) based on EDC data.

A summary table, broken out by treatment group and overall, with the number of patients that have data that is different between the randomization stratification factors compared to the collected data will also be provided together with a patient listing with details.

#### 10.1.1.2 Censoring Distribution

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

The following sensitivity analyses will be performed:

- **All scans and data:** According to the study protocol, tumor scans were to continue to be performed during follow up for patients who discontinued without a documented disease progression event by RECIST v1.1. As such, a sensitivity analysis will be performed in which all tumor scans or death events will be included for assessment of PFS even if the patient discontinued study treatment or initiated a subsequent anticancer therapy. This is in accordance with the EMA guidelines.[2]
- **Clinical progression or withdrawal:** To evaluate further impact on early treatment discontinuations, a sensitivity analysis will be performed in which patients who discontinued oral study drug due to clinical progression or who withdrew consent from treatment will also be considered events of invPFS on the date of the 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

### 10.2.1 PFS by Blinded Independent Radiology Review (bicrPFS)

Note: Blinded independent radiology review (BICR) of scan data is on hold and analysis of this data will only be performed if the primary endpoint of investigator PFS is statistically significant.

The secondary endpoint of bicrPFS by RECIST v1.1 is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by BICR, or death due to any cause, whichever occurs first. The time to bicrPFS will be calculated in months as the time from randomization to disease progression +1 day. Only scans or deaths prior to and on the start of any subsequent anticancer treatment will be used in PFS analysis. Any death or progression occurring within two missing expected scan assessments will be included in the analysis. Two missed scans or visits is defined as a duration of 26 weeks (12 x 2 + 2) for the first 3 years and 50 weeks (24 x 2 + 2) thereafter. Events occurring immediately after 2 consecutive missed scans will be censored as below.

Censoring rule: Any patients who do not experience an event of either disease progression or death will be censored on the last on-study tumor assessment prior to start of any subsequent anticancer treatment. Any patients with an event of either disease progression or death following two or more missed expected consecutive scans will be censored on the date of the last on-study tumor assessment prior to gap in scan collection. If a patient does not have any on-study tumor assessments, then the patient will be censored on the date of randomization (ie, Day 1).

The overall tumor assessment date is defined as the latest scan for each visit where multiple scans were utilized to make the overall assessment.

The bicrPFS will be analyzed using the stratified Cox proportional hazard methodology, presenting the estimated hazard ratio with 95% confidence interval between the randomized treatment groups. In addition, a stratified log-rank test of bicrPFS between the randomized treatment groups together with a graphical presentation of unstratified bicrPFS distributions, median bicrPFS with 95% CI, and event rates will be presented as supportive statistics.

BicrPFS is a stand-alone secondary endpoint and will be summarized for the ITT population. In addition, bicrPFS may be summarized by the subgroups of patients by PD-L1 status and HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$ and HRD [tBRCA + non-tBRCA LOH$^{high}$]) as needed.

### 10.2.2 Overall Survival

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

The overall survival will be analyzed using the stratified Cox proportional hazard methodology and a stratified log-rank test (considered the official test for the hierarchical testing). The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

It is anticipated that the data for overall survival may be somewhat immature at the time of the primary endpoint analysis. In order to adjust for multiple analyses of overall survival at a later stage, a stopping rule will be applied. The Haybittle-Peto[3,4] stopping rule will be applied where any interim (early) overall survival with a p-value<0.001 can be used to claim superiority. This means that a p-value very close to 0.0125 one-sided (two-sided alpha=0.025) can still be utilized at the final analysis which is projected to be once 70% (n~560) of the death events has been collected.

### 10.2.3 Objective 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 have measurable target lesions at baseline as assessed by investigator. The confirmed response rate by RECIST v1.1 will be summarized. The confirmed response rate is defined as the proportion of patients with a confirmed CR or PR (confirmed = subsequent tumor assessment at least 28 days after first response documentation with PR or CR). The ORR will be summarized with frequencies and proportions together with 95% CI and compared between treatments by using a stratified Cochran-Mantel-Haenszel (CMH) test which will be the official test used for the hierarchical testing outlined in Section 3.4. In addition, the frequency and proportion of patients will be summarized based on the below best confirmed response categories:

- CR;
- PR;
- SD;
- PD; and
- Not evaluable

### 10.2.4 Duration of Response by RECIST v1.1. as assessed by investigator

The Duration of Response (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 progressive disease is documented. DOR will be calculated in months as the time from the first date of the scan showing a response to the first scan with disease progression +1 day. Any patients with an ongoing response will be censored at the date of the last post-baseline scan.

The DOR will be analyzed using Cox proportional hazard methodology and a log-rank test. In addition, a graphical presentation of DOR distributions, median DOR with 95% CI, and event rates will be presented.

## 10.3 Exploratory Efficacy Analyses

The purpose of the exploratory endpoints is to further explore the efficacy; no multiple comparison adjustments are performed for these analyses.

### 10.3.1 PD-L1 Expression as Molecular Marker of Efficacy

The primary and secondary efficacy endpoints will be summarized by PD-L1 expression subgroups.

#### 10.3.1.1 PD-L1 Definitions

Definition of PD-L1 expression is described as follows.

- PD-L1 expression missing: Subjects without an available tumor biopsy specimen for PD-L1 evaluation will be considered as PD-L1 expression missing.

For subjects with an available tumor biopsy specimen(s), the following will be considered:

- PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per Dako PD-L1 IHC assay unless otherwise specified. This is referred to as *quantifiable PD-L1 expression*. If the PD-L1 staining could not be quantified, it is further classified as:
- Indeterminate: Tumor cell membrane staining hampered for reasons attributed to the biology of the tumor biopsy specimen and not because of improper sample preparation or handling
- Not evaluable: Tumor biopsy specimen was not optimally collected or prepared (eg, PD-L1 expression is neither quantifiable nor indeterminate)

**Baseline PD-L1 expression**: If more than one tumor biopsy specimen is available, baseline PD- L1 expression will be determined from the most recently collected specimen (prior to randomization) with a quantifiable result. If more than one baseline PD-L1 expression measurement is available at the same day for a subject, the highest baseline PD-L1 expression measurement will be used. If all specimens for a given subject are either indeterminate or not evaluable, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered not evaluable.

PD-L1 status is a dichotomized variable using an X% cut-off for quantifiable PD-L1 expression. The PD-L1 positive immune cell score is determined by the % of tumor area that is covered by PD-L1 positive immune cells.

#### 10.3.1.2 Efficacy Analysis by PD-L1 expression

The primary and secondary efficacy endpoints will be analyzed using a pre-identified cut-off of PD-L1 positive immune cell score defined as ≥ 5% for the ATHENA study. Hence, an ATHENA patient will be classified as being PD-L1 high if the PD-L1 immune cell score in their tumor tissue sample is ≥ 5%. A secondary cut-off of PD-L1 positive immune cell

score of ≥1% will also be used for the ATHENA study. These cut-offs were selected based on results from the IMagyn050 [5] study of an immune checkpoint inhibitor containing combination in front-line ovarian cancer that employed the PD-L1 SP142 assay and demonstrated improved clinical benefit in patients with a PD-L1 positive immune cell score of ≥ 5%. Additional cutoffs may be explored.

In addition, efficacy based on PD-L1 expression defined by the combined positive score (CPS) may be evaluated, including cut-offs of CPS ≥1 and CPS≥10. CPS is the ratio of the number of all PD-L1–expressing cells (tumor cells, lymphocytes, macrophages) to the number of all tumor cells.

### 10.3.2 TMB as Molecular Marker of Efficacy

TMB is measured in ATHENA using the FoundationOne Dx (F1CDx). The F1CDx is a next-generation sequencing (NGS) assay targeting the full coding regions of 324 genes. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering). The resulting number is communicated as mutations per megabase unit (mut/Mb). The cutoff used for analysis will be ≥ 10 mut/Mb.

### 10.3.3 Progression Free Survival 2 (PFS2)

The second event of progression, 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. The second event will be the disease progression event as reported during the subsequent anticancer follow up. Subsequent anticancer treatments will be collected for all patients every 12 or 24 weeks (± 14 days), until death, loss to follow-up, withdrawal of consent from study, or closure of the study. The subsequent anticancer data with start and stop date and any date of progression will be documented. The date of progression on subsequent anticancer treatments may be a documented event per RECIST guidelines or may be an event of symptomatic/clinical or CA-125 progression. Patients who have not died or had a second event of disease progression will be censored on the date the patient was last known to be alive or last visit. PFS2 will be analyzed using Cox proportional hazard methodology and a stratified log-rank test. The stratified hazard ratio (and 95% confidence interval) from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

### 10.3.4 Efficacy for Arm C (nivolumab) monotherapy vs placebo

The primary and secondary efficacy endpoints will be summarized for nivolumab (Arm C) compared to placebo (Arm D). The endpoints will be analyzed as described in sections 10.1 and 10.2.

### 10.3.5 Efficacy for Arm A (Combination) vs placebo

The Primary and secondary efficacy endpoints will be summarized for Arm A (rucaparib + nivolumab) compared to the placebo (Arm D). The endpoints will be analyzed as described in sections 10.1 and 10.2.

### 10.3.6 Health-related Quality of Life (QoL) as assessed by the trial outcome indication (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)

PRO utilizing the TOI FACT-O will be assessed at screening, on Day 1 (Cycle 1 through 3, and Cycle 5), then every 12 weeks (aligning with CT scans) until treatment discontinuation. In addition, PRO assessments will be performed at End of Treatment, and at the FU1 (28-day Safety Follow-up) and the FU2 (5-month Safety Follow-up) for all patients.

Patients will complete the instruments on an electronic device before any other scheduled study procedures are performed and dosing occurs (if applicable). The patient reported outcome data will be scored and summarized in accordance with the scoring manual for the questionnaire. Appendix A includes the English version of the questionnaires used with the subscale domains outlined.

Analyses of changes and/or percent changes from baseline will be analyzed for each scheduled postbaseline visit and for the final visit for each subscale, total score, and FACT-O TOI. Patients that do not have both a baseline measurement and at least one postbaseline measurement will not be included. The final visit is defined as the last assessment within 28 days after date of last dose of oral study drug or within 5 months of IV study drug, whichever is later.

For the protocol-specified post-baseline visits; the QoL assessment will be grouped in the following visit windows as described in Table 3 below.

**Table 3 Algorithm for Visit Window of QoL**

| Visits | Visit Window Start Date | Visit Window End Date |
|---|---|---|
| Cycle 2 Day 1 | EDC Cycle 2 Day 1 date - 3 days | EDC Cycle 3 Day 1 date - 4 days |
| Cycle 3 Day 1 | EDC Cycle 3 Day 1 date - 3 days | EDC Cycle 4 Day 1 date + 7 days |
| Cycle 5 Day 1 | EDC Cycle 5 Day 1 date -7 days | EDC Cycle 6 Day 1 date + 7 days |
| Cycle 8 Day 1 | EDC Cycle 8 Day 1 date -7 days | EDC Cycle 9 Day 1 date + 7 days |
| Cycle 11 Day 1 | EDC Cycle 11 Day 1 date -7 days | EDC Cycle 12 Day 1 date + 7 days |
| Cycle 14 Day 1 | EDC Cycle 14 Day 1 date -7 days | EDC Cycle 15 Day 1 date + 7 days |
| Etc…<br>Cycle X Day 1, (where X is every 3 cycles) | EDC Cycle X Day 1 date -7 days | EDC Cycle (X+1) date + 7 days |

If more than one assessment falls within a given visit window, the one that is closest to the actual scheduled EDC visit date will be used. In the case of ties, the assessment prior to the scheduled visit date will be used. The data sets should highlight the value for the patient that

was included in the summary table, wherever feasible. The summary tables and graphs will only display data if the number of observations is greater than 10 in each treatment arm.

At a given visit, the change from baseline will be analyzed for the treatment comparisons using an Analysis of Covariance (ANCOVA) with treatment and stratification variables as categorical factors and baseline measurement for the parameter as a continuous covariate. In addition, a graphical presentation of mean changes over time may be presented.

In addition, a repeated measures ANCOVA model may be used to estimate the average treatment effect over the first 12 months and 24 months.

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

Analyses of changes and/ or percent changes from baseline will be analyzed for each scheduled postbaseline visit and for the final visit for the EQ5D instrument and the EQ VAS. Patients who do not have both a baseline measurement and at least one postbaseline measurement will not be included.

The final visit is defined as the last assessment within 28 days after date of last dose of oral study drug or within 5 months of last IV study drug, whichever is later. For the protocol-specified post-baseline visits; the EQ-5D-5L assessment will be grouped in actual scheduled visit windows as described in Table 3. If more than one assessment date falls within a given visit window, the one that is closest to the actual scheduled EDC visit date will be used. In the case of ties, the assessment prior to the scheduled visit date will be used. The data sets should highlight the value for the patient that was included in the summary table, wherever feasible. The summary tables and graphs will only display data if the number of observations is greater than 10 in each treatment arm.

At a given visit, the change from baseline will be analyzed for the treatment comparisons using an Analysis of Covariance (ANCOVA) with treatment and stratification variables as categorical factors and baseline measurement for the parameter as a continuous covariate. In addition, a graphical presentation of mean changes over time may be presented.

### 10.3.8 Assess Mutations in non-tBRCA HRR Genes as a Molecular Marker of Efficacy

Patients will be required to provide archival tumor tissue or a screening biopsy for central laboratory analysis prior to enrollment. Genes of interest will be sequenced using Foundation Medicine's NGS test, which examines a panel of cancer-related genes, including BRCA1/2. The invPFS for the subset of patients with non-tBRCA HRR genes will be explored and compared for the treatment comparisons.

### 10.3.9 Evaluation of Post-Progression Efficacy Endpoints

Following treatment discontinuation, subsequent anti-cancer treatments will be collected for all patients every 12 or 24 weeks (± 14 days), until death, loss to follow-up, withdrawal of consent from study, or closure of the study. The subsequent anti-cancer data with start and stop date and any date of progression is documented. The date of progression may be a

documented event per RECIST guidelines or may be an event of symptomatic/clinical or CA-125 progression. The following endpoints will be derived based on this data.

- **Chemo-Free Interval (CFI),** will be calculated in months as the time since the last dose of the most recent chemotherapy regimen to the date of the first dose of a subsequent chemotherapy + 1 day. Patients without a documented start of a subsequent chemotherapy after study drug will be censored on the date of their last available assessment.
- **Time to First Subsequent anti-cancer Treatment (TFST),** will be calculated in months as the time from randomization to the date of the first dose of the first subsequent anti-cancer treatment regimen + 1 day. Patients without a documented start date of a subsequent anti-cancer treatment after study drug will be censored on the date of their last available assessment.
- **Time to Second Subsequent anti-cancer Treatment (TSST),** will be calculated in months as the time from randomization to the date of the first dose of the second subsequent anti-cancer treatment regimen + 1 day. Patients without a documented start of a second subsequent anti-cancer treatment after study drug will be censored on the date of their last available assessment.

The same statistical test used for the primary endpoint (ie, stratified log rank test and a stratified Cox proportional model) will be used to compare treatments for this endpoint.

#### 10.3.10 Other Exploratory Endpoints described in a separate report

The following exploratory endpoints that are mentioned in the protocol will be summarized in a separate statistical report:

- To study variants in circulating tumor DNA (ctDNA) as markers of response and resistance
- To characterize PK of rucaparib as monotherapy and in combination with nivolumab
- To characterize PK of nivolumab as a monotherapy and in combination with rucaparib
- To evaluate immunogenicity of nivolumab when administered as a monotherapy and in combination with rucaparib
- To explore exposure-response relationship between selected exposure measures of rucaparib and nivolumab, and safety and efficacy endpoints

## 10.4 Examination of Efficacy in Subgroups

The primary endpoint (invPFS) may be further explored within the ITT population for subgroups.

- The stratification factor used for randomization.
    - HRD classification (tBRCA, non-tBRCA LOHhigh, non-tBRCA LOHlow, and non-tBRCA LOHunknown)

  - Disease status (no residual disease vs residual disease)
  - Timing of surgery (primary surgery vs. interval debulking).
- PDL1 expression as described in section 10.3.1
- Age groups (< 65, 65-74, ≥75)
- Race (White, Other, Unknown)
- Prior use of Bevacizumab (Yes or No)
- Mutation: BRCA1 vs BRCA2
- Mutation type: Germline, Somatic, or unknown
- Country (for registration requirements), eg, Japan, South Korea

# 11 SAFETY ANALYSIS

Safety and tolerability is one of the secondary study objectives. Overall safety and tolerability will be measured by the incidence of adverse events, serious adverse events, adverse events leading to discontinuation, deaths, specific laboratory abnormalities (worst grade) and changes from baseline.

The safety analyses will be presented for the safety population presenting the data for each treatment group separately (Arm A [rucaparib and nivolumab], Arm B [rucaparib], Arm C [nivolumab], and Arm D [placebo]). The analyses will be presented by the actual treatment given. Patients randomized to either treatment group containing IV Nivolumab (ie, Arm A or Arm C) who never receive Nivolumab, will be analyzed in the analogous treatment group containing IV Placebo (ie, Arm B or Arm D, respectively).

Summary tables are based on data that are found to be “on-treatment”/ “treatment-emergent” for the oral or IV study drug as outlined in the below sections.

All safety data which is considered treatment-emergent will be summarized. Treatment-emergent is defined as safety data with an onset date on or after the date of first dose of study medication until the date of last dose of oral study drug plus 28 days or date of last IV dose plus 5 months (ie, 152 days), whichever is the latest date.

Descriptive statistics of safety will be presented using the NCI CTCAE v5.0. All AEs, drug-related adverse events, serious adverse events (SAEs) and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE v5.0 by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function, thyroid, adrenal and renal function will be summarized using worse grade by NCI CTCAE v5.0.

## 11.1 Adverse Events

AEs will be classified using the MedDRA version 22.0 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) v5.0 or later. Treatment-emergent adverse events (TEAEs) are defined as events with an onset date on or after the date of first dose of study medication until the date of the last oral study medication plus 28 days or date of last IV dose plus 5 months (ie, 152 days), whichever is the latest date. Also, AEs will be considered treatment-emergent if all or part of the date of onset of the adverse event is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

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

Separate tables will be presented as follows:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs, for oral treatment and IV treatment separately, and also both;
- Serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study medication for oral treatment and IV treatment separately, and also both;
- TEAEs resulting in reduction oral study medication;
- TEAEs resulting in interruption of oral treatment and IV treatment separately, and also both;
- TEAEs resulting in reduction or interruption of oral treatment ;
- Time to the first TEAE that results in a reduction of oral treatment;
- Time to the first TEAE that results in an interruption of oral treatment or IV treatment separately, and also both;
- Time to the first TEAE that results in discontinuation of oral treatment or IV treatment separately, and also both.

The incidence of TEAEs will be summarized by relationship to either oral or IV 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 for oral study drug and for IV 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% CI.

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

MedDRA PTs will be combined for the following similar terms:

- Anaemia or Haemoglobin decreased;
- Asthenia or Fatigue;

- ALT or AST increased;
- Neutropenia or Neutrophil count decreased;
- Thrombocytopenia or Platelet count decreased.

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 will also be summarized.

## 11.2 Immune-Mediated Adverse Events

Adverse events that meet the definition of Immune-Mediated AEs will be summarized similarly as described in Section 11.1.

## 11.3 Clinical Laboratory Evaluations

This study uses a central laboratory assessment of all safety lab data. Local laboratory values that are clinically relevant will be added to the case report forms. All aggregate analyses of data will be done using only the central laboratory data, but the local laboratory data will be presented in patient level data listings.

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will be presented in standard units. The on-treatment period with an onset date on or after the date of first dose of study medication until the date of the last oral study medication plus 28 days or date of last IV dose plus 5 months (ie, 152 days), whichever is the latest date. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected outside of the on-treatment period will only be presented in the data listings.

For visit-based summaries; the laboratory evaluations that are during the actual scheduled cycle visit (ie, EDC visit structure) will be used, otherwise, any unscheduled laboratory evaluations that are closest to and within the same actual scheduled cycle will be used. The data sets should highlight the value for the patient that was included in the summary table, wherever feasible. The summary tables and graphs will only display data if the number of observations is greater than 10 in each treatment arm.

The summary of laboratory data will include descriptive statistics 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.

Shifts from baseline to the maximum on-treatment toxicity grade (CTCAE Version 5.0 or later) for each lab parameter will be summarized.

Figures of the mean values over time with standard error bars will be presented for key safety laboratory parameters.

## 11.4 Vital Signs

The on-treatment period will be defined as the time from the first dose of study drug until the date of the last oral study medication plus 28 days or date of last IV dose plus 5 months (ie, 152 days), whichever is the latest date. 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.

For visit-based summaries, vital signs evaluated during the actual scheduled cycle visit will be used, otherwise, any unscheduled vital signs evaluations that are closest and within the same actual scheduled cycle will be used. The data sets should highlight the value for the patient that went into the summary table, wherever feasible. The summary tables and graphs will only display data if the number of observations is greater than 10 in each treatment arm.

The summary of vital sign data will include descriptive statistics 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.

## 11.5 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.

## 11.6 Examination of Safety in Subgroups

Safety will be further explored in the following subgroups:

- Age groups (< 65, 65-74, ≥75)
- Race (white, non-White)

For treatment comparison of Arm A (nivolumab + rucaparib) vs Arm B (rucaparib monotherapy) key safety analyses may also be summarized for specific molecular analysis populations (eg, by PD-L1 or HRD/tBRCA status).

Safety may be further explored by specific countries (eg, Japan, South Korea) for registration requirements, if needed.

## 11.7 Japanese Open-label

The safety data from the Japanese Open–label cohort evaluating the combination of rucaparib and nivolumab will be summarized with standard demographics and safety tables.

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# APPENDIX A: FACT-O (VERSION 4)

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

## Physical Well-being

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| 2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| 3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| 4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| 5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| 6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| 7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

## Social/Family Well-being

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| 2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| 3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| 4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| 5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| 6 | I feel close to my partner (or the person why is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.* | | | | | |
| 7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

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

## Emotional Well-being

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| 2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| 3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| 4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| 5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| 6 | I worry my condition will get worse | 0 | 1 | 2 | 3 | 4 |

## Functional Well-being

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I am able to work (include work from home) | 0 | 1 | 2 | 3 | 4 |
| 2 | My work (include work from home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| 3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| 4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| 5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| 6 | I enjoy the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| 7 | I am content with the quality of life right now | 0 | 1 | 2 | 3 | 4 |

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

## Additional Concerns

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I have swelling in my stomach area | 0 | 1 | 2 | 3 | 4 |
| 2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| 3 | I have control of my bowls | 0 | 1 | 2 | 3 | 4 |
| 4 | I have been vomiting | 0 | 1 | 2 | 3 | 4 |
| 5 | I am bothered by hair loss | 0 | 1 | 2 | 3 | 4 |
| 6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| 7 | I like the appearance of my body | 0 | 1 | 2 | 3 | 4 |
| 8 | I am able to get around by myself | 0 | 1 | 2 | 3 | 4 |
| 9 | I am able to feel like a woman | 0 | 1 | 2 | 3 | 4 |
| 10 | I have cramps in my stomach area | 0 | 1 | 2 | 3 | 4 |
| 11 | I am interested in sex | 0 | 1 | 2 | 3 | 4 |
| 12 | I am concerned about my ability to have children. | 0 | 1 | 2 | 3 | 4 |

# APPENDIX B: CLINICAL LABORATORY EVALUATION

**CTCAE Version**

The summary of laboratory data includes tables based on NCI Common Terminology Criteria for Adverse Events (CTCAE), which is a descriptive terminology utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term. In general, CTCAE version 5.0 is used however, in some cases version 4.03 is substituted as quantitative grading is not available in version 5.0.

The table below lists terms using version 4.03 or a slight modification to version 5.0.

| CTCAE Term | Notes |
|---|---|
| Hyperglycemia<br>Hypophosphatemia<br>Hyponatremia | Version 5.0 is based on clinical observations or interventions initiated that are not available in the clinical database. Version 4.03 is applied. |
| Hyperkalemia<br>Hypernatremia | Version 5.0 is based on a combination of lab results and interventions. The logic associated with lab results is used. |
| Hypokalemia | Both grades 1 and 2 use <LLN-3.0 mmol/L. Grade 2 additionally requires clinical observations or interventions that are not available in the clinical database. Grade 1 is not used. The range is applied to grade 2. |

**Grading of Central and Local Laboratory Data**

The central laboratory provides CTCAE grades according to their lab Tox Grade Report. However, in some instances the Report indicates grading is derived without the use of a baseline result where v5.0 requires use of upper limit of normal (ULN) for normal baseline and increments above baseline for abnormal baseline. Therefore, the CTCAE grading criteria will be applied in a consistent manner across all laboratory assessment using stacked data that includes both central and local results.

**Normal Reference Ranges**

A reference range is a set of values that includes upper and lower limits based on a group of otherwise healthy people. The values may depend on age, gender, and specimen type and can also be influenced by circumstantial situations such as fasting and exercise.

Normal reference ranges for central laboratory assessments are contained within the data provided by the central laboratory. Each of the local laboratories provided normal ranges specific to the lab in which the test was done. These local ranges were entered into EDC and applied to results via the lab admin tool.

**Liver Function Tests**

Baseline results for four LTFs (ALT, AST, ALP and bilirubin) will not receive a numeric grade (grade 1-5). They will be categorized in relation to the ULN (eg, <=ULN, >ULN-3xULN, >3xULN-5xULN). Shifts in grade from baseline to maximum on-treatment post-baseline for these events (alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, and blood bilirubin increased) will not be summarized.

**Creatinine Clearance**

Estimated GFR (eGFR) by Cockcroft-Gault is collected in both central and local laboratory data. These results will be provided in data listings and will not be summarized.

Renal impairment at baseline (creatinine clearance) will be re-calculated using serum creatinine, age and weight using the Cockcroft-Gault formula.

$$\text{Female } CL_{cr} = \left[\frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}\right] \times 0.85$$

This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL; the calculated units are mL/min.

**CTCAE Grading: Hematology**

| CTCAE Description | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Anemia, g/L | 100<= AVAL <LLN | 80<= AVAL <100 | AVAL <80 | |
| Lymphocyte count decreased, 10^9/L | 0.8<= AVAL <LLN | 0.5<= AVAL < 0.8 | 0.2<= AVAL < 0.5 | <0.2 |
| Lymphocyte count increased, 10^9/L | | 4< AVAL <=20 | AVAL >20 | |
| Neutrophil count decreased, 10^9/L | 1.5<= AVAL <LLN | 1<= AVAL <1.5 | 0.5<= AVAL <1 | AVAL <0.5 |
| Platelet count decreased, 10^9/L | 75<= AVAL <LLN | 50<= AVAL <75 | 25<= AVAL <50 | AVAL <25 |
| White blood cell decreased, 10^9/L | 3.0<= AVAL <LLN | 2.0<= AVAL <3.0 | 1.0<= AVAL<2.0 | AVAL <1.0 |

## CTCAE Grading: Chemistry

| CTCAE Description | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Hypoalbuminemia, g/L | 30<= AVAL <LLN | 20<= AVAL <30 | AVAL <20 | |
| Alkaline phosphatase increased, U/L | If baseline is normal: | | | |
| | ULN< AVAL <=2.5xULN | 2.5xULN< AVAL <=5xULN | 5xULN< AVAL <=20xULN | AVAL >20xULN |
| | If baseline is abnormal: | | | |
| | 2xBASE<= AVAL <=2.5xBASE | 2.5xBASE< AVAL <=5xBASE | 5xBASE< AVAL <= 20xBASE | >20xBASE |
| Alanine aminotransferase increased, U/L | If baseline is normal: | | | |
| | ULN< AVAL <=3xULN | 3xULN< AVAL <=5xULN | 5xULN< AVAL <=20xULN | AVAL >20xULN |
| | If baseline is abnormal: | | | |
| | 2xBASE<= AVAL <=2.5xBASE | 2.5xBASE< AVAL <=5xBASE | 5xBASE< AVAL <=20xBASE | >20xBASE |
| Aspartate aminotransferase increased, U/L | If baseline is normal: | | | |
| | ULN< AVAL <=3xULN | 3xULN< AVAL <=5xULN | 5xULN< AVAL <=20xULN | AVAL >20xULN |
| | If baseline is abnormal: | | | |
| | 1.5xBASE<= AVAL <=3xBASE | 3xBASE< AVAL <=5xBASE | 5xBASE< AVAL <=20xBASE | >20xBASE |
| Blood bilirubin increased, umol/L | If baseline is normal: | | | |
| | ULN< AVAL <=1.5xULN | 1.5xULN< AVAL <=3xULN | 3xULN< AVAL <=10xULN | AVAL >10xULN |
| | If baseline is abnormal: | | | |
| | BASE<= AVAL <=1.5xBASE | 1.5xBASE< AVAL <=3xBASE | 3xBASE< AVAL <=10xBASE | >10xBASE |
| Hypocalcemia, mmol/L | 2.0<= AVAL <LLN | 1.75<= AVAL <2.0 | 1.5<= AVAL <1.75 | AVAL <1.5 |
| Hypercalcemia, mmol/L | ULN< AVAL <=2.9 | 2.9< AVAL <=3.1 | 3.1< AVAL <=3.4 | AVAL >3.4 |
| Cholesterol high, mmol/L | ULN< AVAL <=7.75 | 7.75< AVAL <=0.34 | 10.34< AVAL <=12.92 | AVAL >12.92 |
| Creatinine increased, umol/L | ULN< AVAL <=1.5xULN | 1.5xBASE< AVAL <=3xBASE; 1.5xULN< AVAL <=3xULN | AVAL >3xBASE; 3xULN< AVAL <=6xULN | AVAL >6xULN |
| Hypoglycemia, mmol/L | 3.0<= AVAL <LLN | 2.2<= AVAL <3.0 | 1.7<= AVAL <2.2 | AVAL <1.7 |
| Hyperglycemia, mmol/L | ULN< AVAL <=8.9 | 8.9< AVAL <=13.9 | 13.9< AVAL <=27.8 | AVAL >27.8 |
| Hypokalemia, mmol/La | | 3.0<= AVAL <LLN | 2.5<= AVAL <3.0 | AVAL <2.5 |
| Hyperkalemia, mmol/L | ULN< AVAL <=5.5 | 5.5< AVAL <=6.0 | 6.0< AVAL <=7.0 | AVAL >7.0 |
| Hypomagnesemia, mmol/L | 0.5<= AVAL <LLN | 0.4<= AVAL <0.5 | 0.3<= AVAL <0.4 | AVAL <0.3 |

| CTCAE Description | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Hypermagnesemia, mmol/L | ULN< AVAL <=1.23 | | 1.23< AVAL <=3.30 | AVAL >3.30 |
| Hypophosphatemia, mmol/L | 0.8<= AVAL <LLN | 0.6<= AVAL <0.8 | 0.3<= AVAL <0.6 | AVAL <0.3 |
| Hyponatremia, mmol/L | 130<= AVAL <LLN | | 120<= AVAL <130 | AVAL <120 |
| Hypernatremia, mmol/L | ULN< AVAL <=150 | 150< AVAL <=155 | 155< AVAL <=160 | AVAL >160 |
| Hypertriglyceridemia, mmol/L | 1.71<= AVAL <=3.42 | 3.42< AVAL <=5.7 | 5.7< AVAL <=11.4 | AVAL >11.4 |

# STATISTICAL ANALYSIS PLAN

## ATHENA (A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-line Platinum-based Chemotherapy)

## ATHENA-MONO

| | |
|---|---|
| **PROTOCOL:** | CO-338-087 |
| **VERSION:** | Version 2.0 |
| **DATE FINAL:** | 10 February 2022 |
| **SPONSOR:** | Clovis Oncology, Inc.<br>5500 Flatiron Parkway, Ste 100<br>Boulder, CO 80301 US<br>[redacted] |

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# ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | Analysis of Covariance |
| AST | aspartate aminotransferase |
| BRCA | breast cancer gene |
| BICR | blinded independent central review |
| bicrPFS | progression-free survival, blinded independent central review |
| BID | "Bis In Die" twice (two times) a day |
| BSO | bilateral salpingo-oopherectomy |
| CA-125 | cancer antigen-125 |
| CFI | chemotherapy-free interval |
| CI | confidence interval |
| $CL_{cr}$ | creatinine clearance |
| cm | centimeter |
| $C_{min}$ | trough concentration |
| CR | complete response |
| CRF | Case Report Form |
| CSP | clinical service provider |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor DNA |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic database capture |
| EMA | European Medicines Agency |
| ENGOT | European Network for Gynecological Oncological Trial groups |
| EQ-5D-5L | Euro-Quality of Life 5D-5L |
| EQ VAS | Euro-Quality of Life Visual Analog Scale |
| FIGO | International Federation of Gynecology and Obstetrics |
| FACT-O | Functional Assessment of Cancer Therapy - Ovarian |
| FMI | Foundation Medicine, Inc. |
| gBRCA | germline BRCA1/2 mutation |
| GCIG | Gynecologic Cancer InterGroup |
| GOG | Gynecologic Oncology Group |
| HR | hazard ratio |
| HRD | homologous recombination deficient |
| HRQoL | health-related quality of life |

| | |
|---|---|
| IDMC | Independent Data Monitoring Committee |
| invPFS | progression-free survival, investigator-assessed |
| ITT | intent-to-treat |
| IV | intravenous(ly) |
| LOH | loss of heterozygosity |
| LFT | liver function test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Events |
| NGS | next-generation sequencing |
| ORR | objective response rate |
| OS | overall survival |
| PARPi | poly (adenosine diphosphate-ribose) polymerase inhibitor |
| PD | progressive disease |
| PFS | progression-free survival |
| PFS2 | progression-free survival on subsequent line of treatment |
| PK | pharmacokinetic(s) |
| PR | partial response |
| PRO | patient-reported outcome |
| PT | preferred term |
| QoL | quality of life |
| QT | time from beginning of the Q wave to the end of the T wave |
| QTc | QT interval corrected for heart rate |
| QTcB | QT interval corrected using Bazett's formula |
| QTcF | QT interval corrected using Fridericia's formula |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SFU1 | Safety Follow-up Visit 1 |
| SFU2 | Safety Follow-up Visit 2 |
| SOC | System Organ Class |
| tBRCA | deleterious BRCA1/2 mutation in tumor tissue |
| TDT | time to treatment discontinuation of oral dose |
| TEAE | treatment-emergent adverse event |
| TFST | time to first subsequent anticancer treatment |
| TOI | trial outcome index |
| TSST | time to second subsequent anticancer treatment |
| ULN | upper limit of normal |
| VAS | Visual Analog Scale |
| WHO | World Health Organization |

## Analysis Population Definitions

| | |
|---|---|
| ITT Population | All randomized patients |
| HRD Population | Patients with $HRD^{+}$ tumors (an NGS HRD assay result), composed of tBRCA and non-tBRCA $LOH^{high}$ |
| Safety Population | All patients who received at least 1 dose of protocol-specified treatment |

## HRD Subgroup Definitions

| | |
|---|---|
| tBRCA | Patient with deleterious *BRCA1/2* mutation in tumor tissue |
| non-tBRCA $LOH^{high}$ | Patients without a tBRCA mutation and with percent of tumor genome LOH ≥ 16% |
| non-tBRCA $LOH^{low}$ | Patients without a tBRCA mutation and with percent of tumor genome LOH < 16% |
| non-tBRCA $LOH^{unknown}$ | Patients without a tBRCA mutation and with percent of tumor genome LOH unknown |

# 1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for the ATHENA monotherapy (ATHENA-MONO) treatment comparison as part of the Clinical Study Protocol: CO-338-087/GOG-3020 / ENGOT-ov45/NCRI/ATHENA (A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-ine Platinum-based Chemotherapy). ATHENA-MONO consists of the relevant endpoints pertaining to the comparison of treatment Arm B (oral rucaparib + IV placebo) versus Arm D (oral placebo + IV placebo).

This SAP provides additional details concerning the statistical analyses for ATHENA-MONO comparisons, already outlined in the original protocol (dated 02 March 2018), Protocol Amendment 1 (dated 05 July 2018), Protocol Amendment 2 (dated 26 October 2020), protocol Amendment 3 (08 September 2021), and Protocol Amendment 4 (dated 29 November 2021).

Since this study is still ongoing as of the maturity of the primary analysis for ATHENA-MONO, a visit cut-off will be applied to all data sets and fully documented in the statistical package data set documentation.

# 2 OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

## 2.1 Study Objectives Outlined in Protocol

**Table 1 Primary, Secondary, and Exploratory Objectives for the Monotherapy Treatment Comparison**

| |
|---|
| ***Primary Objectives*** |
| To evaluate PFS by RECIST, as assessed by the investigator (invPFS) |
| ***Secondary Objectives*** |
| 1. To evaluate PFS by RECIST, as assessed by the BICR (bicrPFS) |
| 2. To evaluate survival benefit |
| 3. To evaluate ORR and DOR, as assessed by the investigator, in patients with measurable disease at baseline |
| 4. To evaluate safety |
| ***Exploratory Objectives*** |
| 1. To evaluate PFS2 |
| 2. To evaluate efficacy and safety in the tBRCA subgroup for the comparison of rucaparib vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety) |
| 3. To evaluate HRQoL as assessed by the TOI of the FACT-O |
| 4. To evaluate PRO utilizing the EQ-5D-5L |
| 5. To characterize PK of rucaparib as a monotherapy |

## 2.2 Study Design

ATHENA is a Phase 3, randomized, double-blind, dual placebo-controlled study of rucaparib in combination with nivolumab in patients with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer who have responded to their first-line platinum-based regimen.

The study will enroll patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who completed first-line platinum-based chemotherapy and surgery with a response of either a CR or a PR, defined as RECIST v1.1 PR or a CA-125 PR by GCIG criteria[1] to their first platinum-based regimen. Patients must have received 4 to 8 cycles of first-line platinum doublet treatment per standard clinical practice, including a minimum of 4 cycles of a platinum/ taxane combination; no other prior treatment for ovarian cancer, including maintenance treatment, is permitted. Patients need to have had completed cytoreductive surgery, including at least a BSO and partial omentectomy, either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking).

Patients will be required to provide archival tumor tissue or a screening biopsy for central laboratory analysis prior to enrollment. Genes of interest will be sequenced using Foundation Medicine's (FMI) NGS test, which examines a panel of cancer-related genes, including BRCA1/2 and the degree of tumor LOH.

The results from the NGS test will be utilized to classify patients into the following randomization stratification groups:

- tBRCA (deleterious BRCA1 or BRCA2 mutation)
- non-tBRCA LOH$^{high}$ (LOH ≥ 16%)
- non-tBRCA LOH$^{low}$ (LOH < 16%)
- non-tBRCA LOH$^{unknown}$

The sponsor will remain blinded to all NGS test results (including all tBRCA results), as well as existing local BRCA testing results, until the primary efficacy analysis is conducted.

Approximately 1000 patients will be randomized in the Double-blind Treatment Phase using a 4:4:1:1 ratio into the following four treatment groups:

- Arm A: oral rucaparib + IV nivolumab (n = 400);
- Arm B: oral rucaparib + IV placebo (n = 400);
- Arm C: oral placebo + IV nivolumab (n = 100); or
- Arm D: oral placebo + IV placebo (n = 100).

The randomization is stratified by the following factors:

- HRD status (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$);
- Disease status (no residual disease vs residual disease); and
- Timing of surgery (primary surgery vs interval debulking).

Randomization to study treatment must occur within 8 weeks following a patient's first day of the last cycle of chemotherapy.

During the Double-blind Treatment Phase (continuous 28-day treatment cycles), the double blinded oral study treatment will be administered on Day 1 of Cycle 1 and continue BID throughout the cycle as monotherapy. IV study drug administration will begin on Day 1 of Cycle 2 during the Double-blind Treatment Phase. Patients will have clinic visits on Day 1 and Day 15 of Cycles 1 and 2, and on Day 1 of every cycle thereafter. Study treatments will continue until 24 months after planned initiation of oral/ IV combination study treatment

(C2D1), disease progression, unacceptable toxicity, or withdrawal of participant consent, whichever happens first.

During the Treatment Phase patients will be monitored for safety and efficacy. Assessments will include AEs, physical examination, vital signs and weight measurement, central laboratory hematology, serum chemistry, and CA-125 measurement, concomitant medications, therapies, and procedures, ECOG performance status, disease status assessment, ctDNA analysis, study drug administration and accountability, and PRO. ECGs and urinalysis will be performed as clinically indicated. Blood samples will also be collected to determine whether any mutation identified is of germline or somatic origin.

Patients will be assessed for disease status per RECIST v1.1 every 12 calendar weeks (flexibility with scheduling within 1 week prior to planned imaging date is permitted) following initiation of oral/IV combination study treatment on Day 1 of Cycle 2 (the first scan will be 16 weeks after initiation of oral study treatment) for the first 3 years after initiation of oral/IV study treatment and every 24 weeks thereafter until objective radiological disease progression; disease status will also be assessed at discontinuation of treatment and as clinically indicated. Disease progression will only be determined by RECIST v1.1. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, will be discontinued from treatment and enter the Follow-up Phase of the study. If the patient has met criteria for radiologic progression by RECIST, but the patient is still receiving benefit from the study drug(s) according to the investigator, then continuation of treatment will be considered for a maximum duration of 24 months after planned initiation of oral/IV combination study treatment.

All CT/MRI scans will be sent to an external vendor for BICR. However, all treatment decisions will be based on investigator assessment of scans.

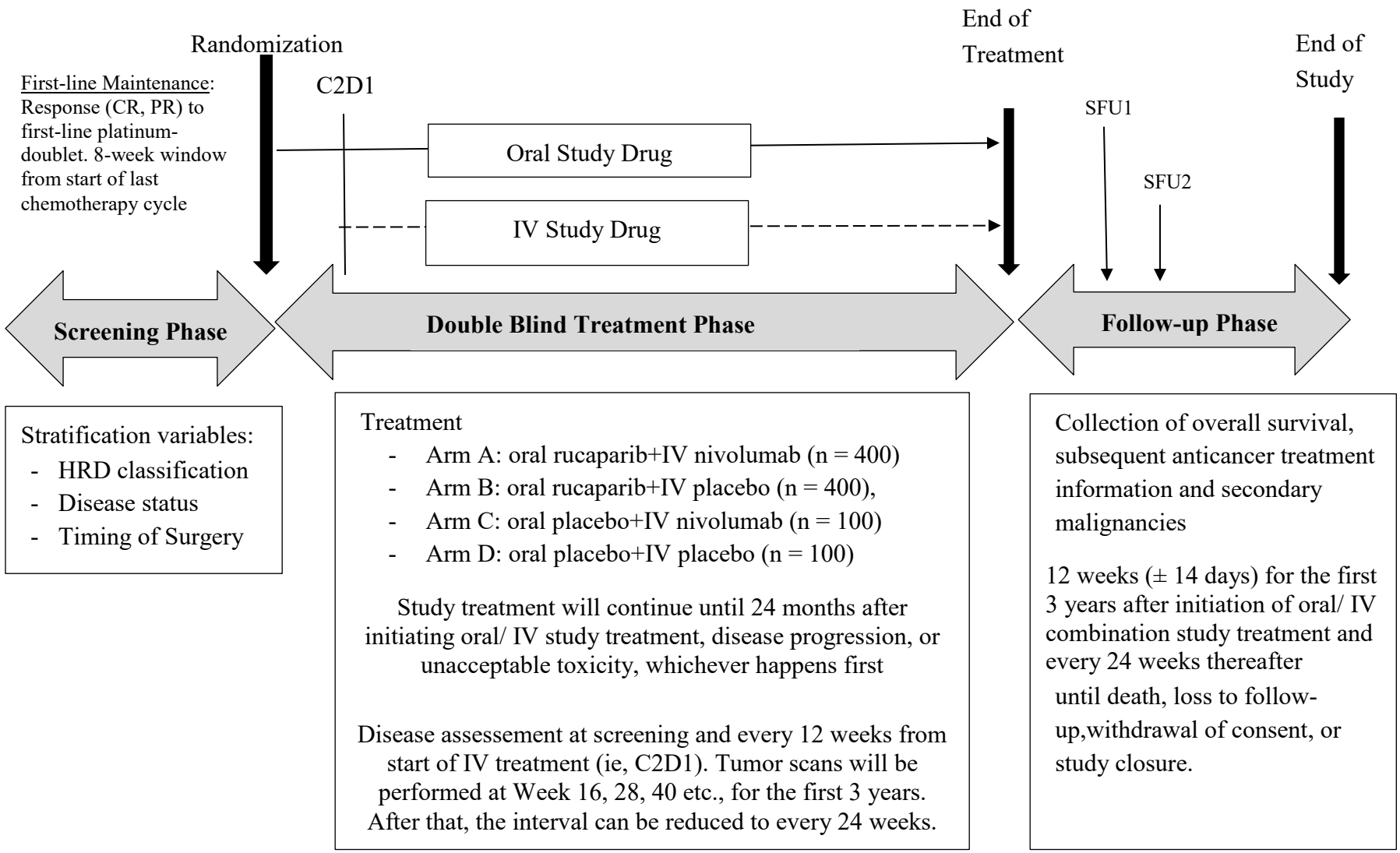
After the treatment is discontinued, all patients will be followed for at least 5 months after the last dose of IV study drug treatment. There will be 2 follow-up visits: Safety Follow-up Visit 1 (SFU1) should occur 28 days (± 7 days) after last dose of the oral and/or IV study drug (whichever occurs later), and Safety Follow-up Visit 2 (SFU2) should occur approximately 5 months (± 7 days) after the last dose of IV study drug treatment. If a patient remains on oral study drug after discontinuation of IV study drug, SFU2 visit can be performed at a cycle visit, provided it has been at least 5 months since the last IV study drug dose. Patients who discontinued treatment for a reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals from C2D1 for the first 3 years after initiation of oral/IV combination study drug treatment and then every 24 weeks thereafter until objective radiological disease progression by RECIST v1.1, as assessed by the investigator, is documented.

Patients will also be followed long-term for survival, subsequent treatments, disease progression (if treatment discontinuation was for reason other than disease progression or death), and monitoring for secondary malignancy every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent, or study closure.

An open-label safety cohort in Japan, with patients receiving open-label oral rucaparib + IV nivolumab combination treatment, is part of the overall ATHENA study. The analyses for the open-label cohort will not be summarized in ATHENA-MONO, but it will be further detailed and summarized in the ATHENA combination treatment comparison (ATHENA-COMBO) SAP.

Figure 1 includes a study design outlining key assessments within the Screening Phase, Double-blind Randomized Treatment Phase, and lastly, the Follow-up Phase.

## Figure 1 Schema of Study Design



## 2.3 Sample Size Determination

Up to approximately 1000 patients will be randomized in a 4:4:1:1 ratio to receive treatment with 1 of the following 4 arms:

- Arm A: Oral rucaparib + IV nivolumab (n = 400);
- Arm B: Oral rucaparib + IV placebo (n = 400);
- Arm C: Oral placebo + IV nivolumab (n = 100); or
- Arm D: Oral placebo + IV placebo (n = 100).

The randomization is stratified by the following factors; HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unkown}$), disease status (no residual disease vs residual disease), and timing of surgery (primary surgery vs interval debulking).

### 2.3.1 Sample Size Determination From Original Protocol

Three separate comparisons of the treatment arms will be evaluated independently:

1. Arm A (oral rucaparib + IV nivolumab) versus Arm B (oral rucaparib + IV placebo);
2. Arm A (oral rucaparib + IV nivolumab) versus Arm D (placebo [oral and IV]); and
3. Arm B (oral rucaparib + IV placebo) versus Arm D (placebo [oral and IV]).

The level of statistical significance will be split into 3 so that each of the above comparisons will be made independently at a one-sided 0.0083 significance level.

The median PFS for patients in Arm A (rucaparib + nivolumab) from all randomized patients (ie, the ITT Population inclusive of both tBRCA and non-tBRCA subgroups) is expected to be approximately 24 months while the median PFS for patients in Arm B (rucaparib monotherapy [rucaparib + IV placebo]) is expected to be about 17 months.

The following table provides the sample size and power for comparison 1 of Arm A (rucaparib+nivolumab) to Arm B (rucaparib monotherapy) within the HRD and ITT Populations. The tBRCA and non-tBRCA LOH$^{high}$ patients are likely to respond similarly to the rucaparib + nivolumab therapy so the ordered step-down procedure will only include the HRD and ITT Populations.

| Group | Hazard Ratio | Cumulative N (4:1) | Number of Events | Median PFS (months) | Power | One-sided Alpha |
|---|---|---|---|---|---|---|
| HRD | 0.67 | 540 (270:270) | 400 | 25 vs 37 | 90% | 0.008 |
| ITT | 0.725 | 800 (400:400) | 600 | 17 vs 24 | 90% | 0.008 |

Abbreviations: HRD = homologous recombination deficient (tBRCA + non-tBRCA LOH$^{high}$), ITT =intent-to-treat, PFS = progression-free survival

The following table provides the sample size and power for comparison 3 of Arm B (rucaparib monotherapy) to Arm D (placebo) for the tBRCA, HRD, and ITT Populations. The power associated with the comparison 2 of Arm A (rucaparib + nivolumab) to Arm D (placebo) is assumed to be higher than for the comparison 3 of Arm B (rucaparib monotherapy) to Arm D (placebo).

| Group | Hazard Ratio | Cumulative N (4:1) | Number of Events | Median PFS (months) | Power | One-sided Alpha |
|---|---|---|---|---|---|---|
| tBRCA | 0.50 | 170 (135:34) | 120 | 18 vs 36 | 90% | 0.008 |
| HRD | 0.60 | 340 (270:68) | 230 | 15 vs 25 | 90% | 0.008 |
| ITT | 0.65 | 500 (400:100) | 340 | 12 vs 17 | 90% | 0.008 |

Abbreviations: HRD = homologous recombination deficient (tBRCA + non-tBRCA LOH$^{high}$), ITT =intent-to-treat, PFS = progression free survival, tBRCA = tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA

The results of the comparisons of Arm C (nivolumab monotherapy [oral placebo + nivolumab]) to Arm D (placebo) will be considered exploratory since these comparisons are not included in the multiple testing procedure described above.

### 2.3.2 Changes to Sample Size Assumptions in Protocol Amendment 2

The first patient was randomized in August 2018. At the time of development of Protocol Amendment 2, randomization was expected to close the third quarter of 2020. Based on the recently established standard of care of PARPi monotherapy in the first-line maintenance setting,[2,3] the treatment comparison of Arm A (oral rucaparib + IV nivolumab) vs Arm D (placebo [oral and IV]) from the original protocol will no longer be necessary. Therefore, 2 separate comparisons of the treatment arms will be evaluated independently, and at different time points based on the maturity of the parts of the study, in order to evaluate both rucaparib monotherapy and rucaparib in combination with nivolumab:

- ATHENA-MONO: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV]); and
- ATHENA-COMBO: Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo).

As such, in this amended protocol, the level of statistical significance will be split into two so that each of the above comparisons will be made independently at a one-sided 0.0125 (two-sided 0.025) significance level. The treatment comparison of Arm A (oral rucaparib + IV nivolumab) vs Arm D (placebo [oral and IV]) will be performed as an exploratory analysis to support contribution of each component in the rucaparib-nivolumab combination.

The 2 treatment comparisons are set up as independent and can thus be unblinded to treatment allocations and read out at different time points for this study. The monotherapy treatment comparison of Arm B (oral rucaparib + IV placebo) versus Arm D (placebo [oral and IV]) is expected to mature earlier than the combination treatment comparison of Arm A (oral rucaparib + IV nivolumab) versus Arm B (oral rucaparib + IV placebo). The proposed timing of sufficient maturity for the monotherapy treatment comparison is assumed to be at as early as 15 months from the last patient randomized, and once approximately 60% of the events have occurred.

Due to the approval of olaparib for BRCA-mutated patients in the first-line maintenance setting (SOLO1 study),[2] the enrollment of tBRCA is lower than originally anticipated in the sample size assumptions in the original protocol. Thus, the monotherapy treatment comparison, comparing Arm B (oral rucaparib + IV placebo) versus Arm D (placebo [oral and IV]), will start with the HRD Population, then ITT Population for the step-down hierarchical testing and the tBRCA subgroup will be explored as an exploratory endpoint.

The Phase 3 PRIMA study of niraparib also provided information regarding treatment effects in a similar population for those patients who are HRD and for the ITT Population[3]. Due to the above changes to the alpha level and step-down, the adjusted power assumption for the monotherapy treatment comparison, comparing Arm B (oral rucaparib + IV placebo) versus Arm D (placebo [oral and IV]), is summarized in the table below.

**Monotherapy Treatment Comparison: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV]), randomization allocation 4:1**

| Protocol Version | Group | Cumulative N (4:1) | Number of Events | HR Median PFS | Power | One-sided Alpha |
|---|---|---|---|---|---|---|
| **Original Protocol and Amendment 1** | tBRCA | 170 (135:34) | 120 | HR 0.50, 18 vs 36 months | 90% | 0.008 |
| | HRD | 340 (270:68) | 230 | HR 0.60, 15 vs 25 months | 90% | 0.008 |
| | ITT | 500 (400:100) | 340 | HR 0.65 12 vs 17 months | 90% | 0.008 |
| **Amendment 2** | HRD | 205 (164:41) | 123 | HR 0.45[3] 12 vs 26.7 months | 90% | 0.0125 |
| | ITT | 500 (400:100) | 300 | HR 0.60[3] 12 vs 20 months | 90% | 0.0125 |

Abbreviations: HR = hazard ratio; HRD = homologous recombination deficient (tBRCA + non-tBRCA LOH$^{high}$); ITT = intent-to-treat, IV = intravenous; PFS = progression-free survival.

The power assumption for the combination treatment comparison is still set at 90% power for both HRD Population and ITT Population as per the original protocol, as shown in the table below.

The following table provides the sample size and power for the clinically relevant comparison between Arm A (oral rucaparib + IV nivolumab) and Arm B (oral rucaparib + IV placebo) within the HRD Population and ITT Populations.

| **Combination Treatment Comparison: Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo), randomization allocation 4:4** | | | | | | |
|---|---|---|---|---|---|---|
| **Protocol Version** | **Group** | **Cumulative N (4:4)** | **Number of Events** | **HR Median PFS** | **Power** | **One-sided Alpha** |
| **Original Protocol and Amendment 1** | HRD | 540 (270:270) | 400 | HR 0.67<br>25 vs 37 months | 90% | 0.008 |
| | ITT | 800 (400:400) | 600 | HR 0.725<br>17 vs 24 months | 90% | 0.008 |
| **Amendment 2** | HRD | 380 (190:190) | 285 | HR 0.67<br>26.7 vs 39.9 months | 90% | 0. 0125 |
| | ITT | 800 (400:400) | 600 | HR 0.725<br>20 vs 28 months | 90% | 0. 0125 |

Abbreviations: HR = hazard ratio; HRD = homologous recombination deficiency (tBRCA + non-tBRCA LOH$^{high}$); ITT = intent-to-treat, IV = intravenous; PFS = progression-free survival.

### 2.3.3 Sample Size Assumptions as of Implementation of Protocol Amendment 3

The sample size and power assumptions are not changing in Amendment 3. The changes to remove the HRD Population from the primary and key secondary endpoints for the combination treatment comparison will not affect the current sample size design nor power of this study, due to the combination treatment comparison already being set at 90% power for the ITT Population and summarized in the table below.

| **Combination Treatment Comparison: Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo), randomization allocation 4:4** | | | | | | |
|---|---|---|---|---|---|---|
| **Protocol Version** | **Group** | **Cumulative N (4:4)** | **Number of Events** | **HR Median PFS** | **Power** | **One-sided Alpha** |
| **Amendment 2** | HRD | 380 (190:190) | 285 | HR 0.67<br>26.7 vs 39.9 months | 90% | 0. 0125 |
| | ITT | 800 (400:400) | 600 | HR 0.725<br>20 vs 28 months | 90% | 0. 0125 |
| **Amendment 3** | ITT | 800 (400:400) | 600 | HR 0.725<br>20 vs 28 months | 90% | 0. 0125 |

Abbreviations: HR = hazard ratio; HRD = homologous recombination deficiency (tBRCA + non-tBRCA LOH$^{high}$); ITT = intent-to-treat, IV = intravenous; PFS = progression-free survival.

### 2.3.4 Sample Size Assumptions as of Implementation of Protocol Amendment 4

The sample size or assumptions around power was not affected nor changed in this amendment.

# 3 GENERAL STATISTICAL DESIGN CONVENTIONS

Efficacy analyses will be analyzed in the HRD Population and the ITT Population as described in Section 3.1 below. All safety analyses will be based on the Safety Population, which consists of all patients who received at least 1 dose of protocol-specified oral treatment.

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

The Kaplan-Meier methodology will be used to summarize time-to-event variables. The 50th (median) percentile with the 95% CI will be summarized for each randomized treatment group. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The number of patients with events and the number of censored patients will also be presented.

The primary endpoint of invPFS, secondary endpoint of bicrPFS, and exploratory analyses for the HRD and ITT Population will be analyzed using the randomization factors of HRD classification, disease status, and timing of surgery. If the model does not converge or if there are only patients from a single treatment arm per stratum then the stratification factor of disease status will be omitted first, then timing of surgery, if necessary.

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

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

Results of all statistical analysis will be presented using 95% CIs and two-sided p-values. The significance level for ATHENA-MONO is set at a two-sided $p = 0.025$ due to the overall family-wise type 1 error rate is split equally between ATHENA-MONO and ATHENA-COMBO.

All statistical analyses will be conducted with the statistical analysis software (SAS®) System, Version 9.4 or higher.

## 3.1 Analysis Populations Definitions

**ITT Population:** The ITT Population will consist of all randomized patients. The ITT Population will consist of all mutually exclusive HRD classification groups; tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$.

**HRD Population:** The HRD Population will consist of all randomized patients that are either tBRCA or non-tBRCA LOH$^{high}$.

**Safety Population:** The Safety Population will consist of all patients who received at least 1 dose of protocol-specified treatment of oral study drug and/or IV study drug, The 2 safety populations will be summarized separately for oral vs IV study drug. Only patients who are treated in Arm B (rucaparib monotherapy) and Arm D (placebo) are included in the Safety Population and the Safety Population for oral study drug will be the key Safety Population summarized for ATHENA-MONO.

In addition to the population definitions above, exploratory efficacy will be performed in subgroups including the mutually exclusive (non-nested) molecular subgroups within the ITT Population as outlined in Section 3.2 below.

## 3.2 Definition of Non-nested Molecular Subgroups

The results from the NGS test will be utilized to classify patients into the following randomization stratification groups in this study:

- **tBRCA:** Patient with deleterious BRCA1/2 mutation in tumor tissue;
- **Non-tBRCA LOH$^{high}$:** Patients without a tBRCA mutation and with percent of tumor genome LOH ≥ 16%;
- **Non-tBRCA LOH$^{low}$:** Patients without a tBRCA mutation and with percent of tumor genome LOH < 16% ; and
- **Non-tBRCA LOH$^{unkown}$:** Patients without a tBRCA mutation and with percent of tumor genome LOH unknown.

The exploratory efficacy analyses of these subgroups are outlined in Section 10.4.

## 3.3 Statistical Hypothesis and Treatment Comparisons

The primary statistical hypothesis / objective is the improvement in PFS for rucaparib monotherapy (Arm B) compared to placebo (Arm D).

Hypothesis:

H0: HR (Arm B/Arm D) ≥ 1.

Ha: HR (Arm B /Arm D) < 1.

In order to preserve the overall family-wise type 1 error rate between the ATHENA-MONO and the ATHENA-COMBO, the overall one-sided alpha of 0.025 is equally split in two between these comparisons, which means that all efficacy analyses will be tested at a one-sided 0.0125 significance level (two-sided p = 0.025) for all endpoints in ATHENA-MONO.

## 3.4 Step-down Procedure of Primary and Secondary Endpoints

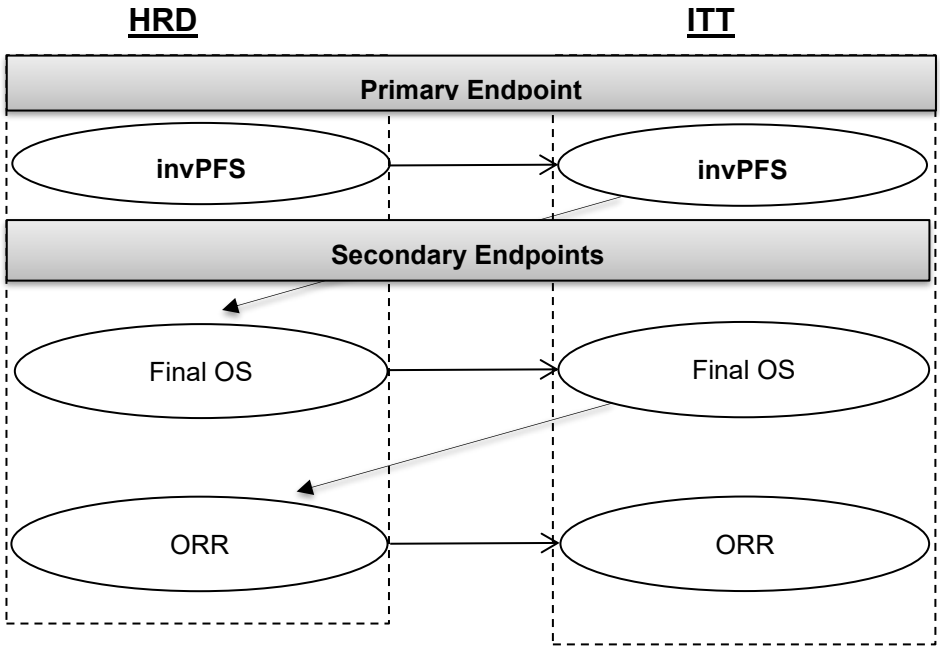
In order to preserve the overall Type 1 error rate, while testing the primary and secondary endpoints for ATHENA-MONO, a hierarchical step-down procedure has been specified. Statistical significance will only be declared for any of the endpoints if the previous endpoints are also statistically significant at the significance level of two-sided 0.025. The step-down procedure is outlined in Figure 2**.**

The primary endpoint of invPFS and key secondary endpoints of OS and ORR will be tested among the HRD Population first and then the ITT Population using a one-sided alpha of 0.0125 (two-sided alpha = 0.025).

That is, the invPFS in the HRD Population will be tested first at a one-sided 0.0125 significance level. If invPFS in the HRD Population is statistically significant then invPFS will be tested in the ITT Population. If both the HRD and ITT Populations reach statistical significance for the primary endpoint, then the first secondary endpoint of OS will be tested at the one-sided 0.0125 significance level in the HRD and ITT Populations for that treatment comparison and testing will continue to the last key secondary endpoint of ORR. Once statistical significance is not achieved for one test, the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure for the comparisons of the rucaparib arm to placebo.

The bicrPFS will be evaluated as a stand-alone secondary endpoint and is not part of the hierarchical step down. The bicrPFS will be used as a supportive analysis to the primary endpoint. The secondary endpoint of DOR will also be evaluated as a stand-alone secondary endpoint and is not part of the hierarchical step down.

**Figure 2 Ordered Step-down Procedure for ATHENA-MONO**




Abbreviations: HRD = homologous recombination deficient; invPFS = progression-free survival as assessed by investigator; ITT = intent-to-treat, ORR = objective response rate; OS = overall survival.

It is anticipated that the data for OS will be immature and thus heavily censored at the time of the ATHENA-MONO treatment unblinding. In order to adjust for multiple analyses of OS at a later stage, a stopping rule will be applied to the interim OS at the time of ATHENA-MONO as detailed in Section 10.2.2. The interim OS at the time of ATHENA-MONO treatment unblinding will still be summarized descriptively, but since it is not the final OS analysis, significance of subsequent secondary endpoint of ORR cannot be claimed until the final OS analysis is performed. The interim OS and ORR will still be summarized in the ATHENA-MONO CSR descriptively.

## 3.5 Stopping Rule, IDMC, and Unblinding

There are no pre-specified stopping rules for the study. There is an IDMC for the ATHENA study, which will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the study, and for monitoring the overall conduct of the clinical study. The IDMC will provide recommendations about the continuation, revision, or termination of the study. Details regarding the IDMC will be documented in a separate IDMC charter.

The sponsor will work with an independent statistician at the time of the ATHENA-MONO read out to maintain the blind for the ATHENA-COMBO comparison and thus only unblind the sponsor to the data and results of ATHENA-MONO (Arm B vs Arm D) comparison as described in this SAP. No further analyses of primary endpoint of invPFS for ATHENA-

MONO are planned beyond the time of treatment unblinding, unless requested by Health Authorities.

The patient, investigator, study staff, and the sponsor study team and its representatives will be blinded to the patients' tumor HRD status and identity of the assigned treatment from the time of randomization until blind break of the ATHENA-MONO comparison. Prior to enrollment, the investigator will receive tissue BRCA mutation results for patients in order to make an informed decision prior to enrolling patients into this study considering the approval of PARPi in current patient populations in certain countries. The sponsor study team and its representatives remained blinded to the BRCA status and subsequent anticancer treatments. If an individual's role on the trial requires information about HRD status or treatment assignment (eg, an individual is involved in emergency unblinding or entry of HRD status for stratification), procedures will be used to ensure all other personnel remain blinded. Study treatment assignment will be available to the investigator upon request for post-study treatment planning. A separate Clovis Oncology blinding plan has been implemented for ATHENA outlining the detail of the blinding process and is used for training with all study personnel and sponsors.

## 3.6 Blinded Independent Central Review

The BICR charter contains the details of the independent central review conducted by the CSP for this study. The independent data review will provide RECIST measurements for each visit for each patient up to the visit cut-off date.

## 3.7 Treatment Effect in Subgroups Based on HRD Classification

Exploratory analyses of the primary endpoint will be performed in order to ensure that the results in the HRD and ITT Populations are not solely driven by the results in the tBRCA or the HRD Population. Thus, subgroup analysis of the primary endpoint of the non-nested subgroups (ie, tBRCA, non tBRCA $LOH^{high}$ , non-tBRCA $LOH^{low}$, and non-tBRCA $LOH^{unknown}$) will be summarized.

# 4 PATIENT DISPOSITION

The following patient disposition will be summarized by treatment arm:

- Number of patients in each analysis population;
- Number of patients that have discontinued oral study drug and the primary reason for discontinuation, for all patients and broken out by those that continued treatment post-radiological progression and those who did not continue treatment post-radiological progression;
- Number of patients that have discontinued IV study drug and the primary reason for discontinuation;
- Number of patients by end-of-treatment status of both Oral and IV study drug; Ongoing with Oral dose, Ongoing with IV, Ongoing with both Oral and IV, or Discontinued both; and
- Number of patients by the end of study status; ongoing or discontinued treatment for oral and IV study drug, withdrew consent, lost to follow-up, death, and still in active long-term follow-up (ie, discontinued both oral and IV treatment, but are still being actively followed for post-progression endpoints and overall survival).

## 4.1 Disposition and Summary of COVID-19 Impact

The number of patients who were ongoing and impacted by COVID-19 will be summarized. This is defined as all patients ongoing, or in Long-term Follow-up starting with visits dated on and after 01 February 2020. The number of tumor scans missed, visits missed, and the number of telehealth visits conducted will also be summarized for both the ITT Population and Safety Population.

# 5 PROTOCOL DEVIATIONS

Major protocol deviations will be identified prior to releasing the treatment codes for primary efficacy analysis in accordance with Clovis SOP CR019 (Identification, Documentation, Management and Review of Protocol Deviations). Patients will not be excluded from any of the analyses due to a major protocol violation. A summary table with the number of patients with major deviations broken down by categories will be provided for both ITT Population and Safety Population. A listing with all the major protocol deviations will also be presented.

# 6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All demographic and baseline characteristics will be summarized by treatment group and overall for HRD, ITT, and Safety Populations. Additional subgroups analyses for the HRD stratification subgroups (ie, tBRCA, nontBRCA LOH$^{high}$ , non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$) may be performed.

## 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, ECOG performance status, and geographic region using the following categorizations:

- Age (years): ≤ 50, 51-60, 61-70, 71-80, 81-90, > 90; and < 65, 64-74, ≥ 75;
- Height (cm): ≤ 75, > 75-100, > 100-125, > 125-150, > 150-175, > 175;
- Weight (kg): ≤ 50, > 50-75, > 75-100, > 100-125, > 125-150, > 150;
- Gender: Female;
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other, or Not Reported;
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown, or Not Reported;
- ECOG performance status: 0, 1;
- Smoking status: Current smoker, Former smoker, never smoked;
- Country; and
- Geographic region (United States/Canada, Europe, Eastern Europe, Latin America, Asia, Australia/New Zealand).

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

## 6.2 Cancer History and Prior Anticancer Treatment, and Disease Burden at Randomization

### 6.2.1 Cancer History and Prior Anticancer Treatment and Surgery

A summary table on the baseline clinical characteristics across patients by treatment and overall will be summarized according to the following:

- Time since cancer diagnosis (months): 0 to 3, > 3 to 6, > 6 to 9, > 9 to 12, > 12;
- Type of ovarian cancer (ie, Epithelial, Primary Peritoneal, Fallopian Tube);
- Cancer histology and FIGO stage at diagnosis;
- Number of prior chemotherapy regimens, and platinum-based regimens;
- Number of cycles of prior chemotherapy regimen, and platinum-based agent;

- Number of patients by administrative setting of front-line regimen (IV only with HIPEC, IV only without HIPEC, IP only with HIPEC, IP only without HIPEC, IV and IP with HIPEC, IV and IP without HIPEC);
- Number of patients with prior bevacizumab use;
- Duration between randomization and the date of first day on the last dose of chemotherapy (in weeks);
- Randomization stratification of disease status (no residual disease vs residual disease);
- Disease status (no residual disease vs residual disease) based on EDC data;
- Randomization stratification of timing of surgery (primary surgery vs interval debulking);
- Timing of surgery (primary surgery vs interval debulking) based on EDC data;
- Best radiological response to first-line treatment (CR, PR, No Disease post-surgery, Inevaluable, or Other);
- Best GCIG CA-125 Response to front-line treatment (Response, No Response, Inevaluable, Other);
- Disease Free with normal CA-125 defined as Best radiological response (CR, No Disease Post-surgery) and CA-125 ≤ ULN (Yes, No)
- Number of prior surgeries (0, 1, 2, > 2);
- Type of surgery (BSO, hysterectomy, partial omentectomy, and full omentectomy and Other); and
- Cytoreductive Surgery Outcome (Complete Resection=R0, microscopic residual < 1 cm, Macroscopic residual ≥ 1 cm, Not applicable).

Descriptive statistics may also be used to summarize these variables.

### 6.2.2 Disease Burden at Randomization

A summary table on the disease burden characteristics across patients by treatment and overall will be summarized according to the following:

- Patients with measurable disease by investigator (ie, target lesions identified by RECIST v1.1);
- Patients with only non-measurable disease by investigator (ie, non-target lesions only identified by RECIST v1.1);
- Patients without any disease by investigator (ie, no target lesions and no non-target lesions identified by RECIST v1.1); and
- Number of patients with CA-125 values within normal limits at baseline based on central laboratory results.

## 6.3 HRD Classification and BRCA Results

A summary table of the HRD classification and BRCA test results by treatment and overall will be summarized. The HRD classification is based on the archival tumor tissue or a screening biopsy tested by FMI. In addition, blood samples will also be collected and tested by an external central laboratory for any germline BRCA mutation. The patients may also have had local BRCA testing with the result entered in the eCRF during Screening. The following test results will be summarized:

- The randomization stratification variables based on HRD status (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, or non–tBRCA LOH$^{unknown}$);
- HRD status (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, or non–tBRCA LOH$^{unknown}$) by central laboratory analysis (FMI);
- BRCA by local testing (BRCA1, BRCA2, or not detected);
- BRCA by central blood testing (BRCA1, BRCA2, or not detected);
- Overall BRCA status from local and central (BRCA1, BRCA2, or not detected); and
- Overall Germline/Somatic status (see Table 2 below for categories).

The tumor tissue-based assay used in this study identifies deleterious mutations in the BRCA1 and BRCA2 genes; however, it does not distinguish between the mutation type of germline or somatic. In order to further explore the mutation type, data from local BRCA test and/or a central blood test of germline BRCA will be used to derive the mutation type according to Table 2 below.

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

| CTA Result | Germline 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 |

[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.

## 6.4 Medical History

The medical history will be summarized for the Safety Population. Medical history events will be classified using the MedDRA classification system version 24.1 or higher. Medical history data will be summarized using frequency tabulations by SOC and PT.

# 7 STUDY DRUG EXPOSURE AND COMPLIANCE

Oral study drug exposure will be summarized for all patients in the Safety Population. The duration of oral study drug exposure 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. For patients that are ongoing at the time of the visit cut-off, the date of the visit cut-off will be used as the end date for oral treatment. The duration will be summarized with summary statistics and by categories (0-6 months, ≥ 6 to 12 months, ≥ 12 – 24 months, ≥ 24 months) for each treatment arm. The oral dose intensity will be summarized and is defined as time normalized actual dose received divided by the starting dose of 600 mg BID.

For oral study drug, the number of patients with at least 1 dose reduction due to a TEAE based on the dosing log will be summarized with frequencies and percentages. Any dose reduction regardless of duration will be summarized. In addition, protocol-specified dose reductions will be broken up by dose level and by reason (ie, AE, non-compliance, or other). That is, the number of patients on each protocol-specified oral dose level will be summarized (ie, 600 mg BID, 500 mg BID, 400 mg BID, 300 mg BID, etc.) in order to assess patients with multiple levels of oral dose reductions. Dose reduction is defined as 3 or more consecutive days at that protocol-specified dose level. The number of patients with at least 1 dose re-escalation will be summarized for each protocol-specified oral dose level from which they escalated.

The number of IV cycles given per treatment arm will also be summarized.

# 8 CONCOMITANT MEDICATIONS

Concomitant medications to oral study drug will be summarized for all patients in the Safety Population. All treatments taken concomitantly with oral study drug will be summarized in frequency tabulations for each randomized treatment group and overall. All treatments will be coded utilizing the WHO Drug Dictionary version 2021MAR01DDE (Enhanced) or later.

Concomitant to oral study drug is defined as all treatments that are either ongoing at the date of the first oral dose or is started prior to the end of the treatment-emergent oral window (ie, within 28 days of date of last dose of oral study drug). A listing of all concomitant treatments will be provided. In addition, a listing of all treatments that are deemed either prior or post of oral treatment will be included in a separate listing. 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 oral study drug then that medication will be classified as concomitant to oral study drug.

# 9 EFFICACY VARIABLES

## 9.1 Primary Efficacy Variable

The primary efficacy variable is invPFS.

## 9.2 Secondary Efficacy Variables Included in the Step Down Analysis

- OS
- ORR by RECIST v1.1 in patients with measurable disease at baseline

## 9.3 Secondary Efficacy Variables Not Included in the Step Down Analysis

- BicrPFS
- DOR by RECIST v1.1 in patients with measurable disease at baseline

## 9.4 Exploratory Efficacy Variables

- PFS of study treatment followed by the subsequent line of treatment (PFS2), defined as the time from randomization to the second event of disease progression or death, as assessed by the investigator
- To evaluate efficacy and safety in the tBRCA subgroup for the comparison of rucaparib vs placebo (invPFS, bicrPFS, OS, ORR, DOR, and safety)
- HRQoL as assessed by the TOI of the FACT-O
- PRO utilizing the EQ-5D
- To explore rucaparib PK in ATHENA-MONO

# 10 EFFICACY ANALYSIS

## 10.1 Primary Efficacy Analysis

The primary efficacy endpoint is PFS as assessed by the investigator (invPFS). The time to invPFS will be calculated in months as the time from randomization to disease progression +1 day, as determined by RECIST v1.1 criteria or death due to any cause, whichever occurs first. Only scans or deaths prior to and on the start of any subsequent anticancer treatment will be used in PFS analysis. Any deaths or progression events occurring within 2 missing expected scan assessments will be included in the analysis. Two missed scans or visits is defined as a duration of 26 weeks (12 × 2 + 2) for the first 3 years and 50 weeks (24 × 2 + 2) thereafter. Events occurring immediately after 2 consecutive missed scans will be censored as below.

Censoring rule: Any patients who do not experience an event of either disease progression or death will be censored on the last on-study tumor assessment prior to start of any subsequent anticancer treatment. Any patient with an event of either disease progression or death following 2 or more missed expected consecutive scans will be censored on the date of the last on-study tumor assessment prior to the gap in scan collection. If a patient does not have any on-study tumor assessments, then the patient will be censored on the date of randomization (ie, Day 1).

The overall tumor assessment date for visits where multiple scans were utilized to make the assessment will be based on the following rule; the scan date showing the disease progression will be used for events where there is disease progression. For censored patients, the later date of the tumor scans within the assessment will be used.

The randomization stratification factors included in the primary analysis of invPFS are:

- HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, or non-tBRCA LOH$^{unknown}$) by central laboratory analysis;
- Disease status post-chemotherapy (residual disease vs no residual disease); and
- Timing of surgery (primary surgery vs interval debulking).

The stratified log-rank test of invPFS between the randomized treatment groups together with a graphical presentation of unstratified invPFS distributions, median invPFS with 95% CI, and event rates will be presented. Furthermore, the probability of being progression free at 6, 12, 18 and 24 months will be summarized by treatment group by using the Kaplan-Meier estimates, both unstratified and stratified, at each time point with 95% CIs using a log-log distribution.

In addition, the primary endpoint will also be analyzed using the stratified Cox proportional hazards model, presenting the hazard ratio with 95% confidence interval between the randomized treatment groups. The stratified log-rank test will be the official test used for the hierarchical testing outlined in Section 3.4.

### 10.1.1 Sensitivity Analyses for PFS

#### 10.1.1.1 Stratification Factors

A sensitivity analysis of invPFS will be performed using the actual supportive data from FMI CTA and EDC to derive the randomization strata groups:

- HRD status based on FMI CTA
- Disease status (no residual disease vs residual disease) based on EDC data; and
- Timing of surgery (primary surgery vs. interval debulking) based on EDC data.

A summary table, broken out by treatment group and overall, with the number of patients that have data that is different between the randomization stratification factors compared to the collected data will also be provided together with a patient listing with details.

#### 10.1.1.2 Censoring Distribution

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

The following sensitivity analyses will be performed:

- **All scans and data:** According to the study protocol, tumor scans were to continue to be performed during follow up for patients who discontinued without a documented disease progression event by RECIST v1.1. As such, a sensitivity analysis will be performed in which all tumor scans or death events will be included for assessment of PFS even if the patient discontinued study treatment or initiated a subsequent anticancer therapy. This is in accordance to the EMA guidelines.[4]
- **Clinical progression or withdrawal:** To evaluate further impact on early treatment discontinuations, a sensitivity analysis will be performed in which patients who discontinued oral study drug due to clinical progression or who withdrew consent from treatment will also be considered events of invPFS on the date of the 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

### 10.2.1 PFS by Blinded Independent Central Review

The secondary endpoint of bicrPFS by RECIST v1.1 is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by BICR, or death due to any cause, whichever occurs first. The time to bicrPFS will be calculated in months as the time from randomization to disease progression +1 day. Only scans or deaths prior to and on the start of any subsequent anticancer treatment will be used in PFS analysis. Any death or progression occurring within two missing expected scan assessments will be included in the analysis. Two missed scans or visits is defined as a duration of 26 weeks (12 × 2 + 2) for the first 3 years and 50 weeks (24 × 2 + 2) thereafter. Events occurring immediately after 2 consecutive missed scans will be censored as below.

Censoring rule: Any patients who do not experience an event of either disease progression or death will be censored on the last on-study tumor assessment prior to start of any subsequent anticancer treatment. Any patients with an event of either disease progression or death following 2 or more missed expected consecutive scans will be censored on the date of the last on-study tumor assessment prior to gap in scan collection. If a patient does not have any

on-study tumor assessments, then the patient will be censored on the date of randomization (ie, Day 1).

The overall tumor assessment date was defined as the latest scan for each visit where multiple scans were utilized to make the overall assessment.

The bicrPFS will be analyzed using the stratified Cox proportional hazards model, presenting the estimated hazard ratio with 95% CI between the randomized treatment groups. In addition, a stratified log-rank test of bicrPFS between the randomized treatment groups together with a graphical presentation of unstratified bicrPFS distributions, median bicrPFS with 95% CI, and event rates will be presented as supportive statistics.

BicrPFS is a stand-alone secondary endpoint and will be summarized for both the HRD and ITT Populations. In addition, bicrPFS may be summarized by the subgroups of patients by HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$ as needed.

### 10.2.2 Overall Survival (Interim and Final)

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

The final OS will be analyzed using the stratified Cox proportional hazards model and a stratified log-rank test. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The stratified log-rank test will be the official test used for the hierarchical testing outlined in Section 3.4.

It is anticipated that the data for OS will be immature and thus heavily censored at the time of the primary endpoint analysis. In order to adjust for multiple analyses of overall survival at a later stage, a stopping rule will be applied. The Haybittle-Peto stopping rule will be applied where any interim (early) overall survival with a p-value < 0.001 can be used to claim superiority.[5,6] This means that a p-value very close to 0.025 two-sided can still be utilized at the final analysis which is projected to be once 70% of the death events has been collected.

For both the interim and final overall survival, the duration of follow-up will be summarized using medians in the following groups of patients for the analysis populations

- In censored patients; Time from randomization date to date of censoring (ie, date of last known to be alive); and
- In all patients; Time from randomization to date of death or the date of censoring (ie, date of last known to be alive) for censored patients.

The time to follow up is defined as time from randomization to the last date known to be alive + 1 day. Kaplan-Meier methodology is used to estimate the median time of follow up for the above patient groups.

### 10.2.3 Objective 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 have measurable target lesions at baseline as assessed by investigator. The confirmed response rate by RECIST v1.1 will be summarized. The confirmed response rate 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 and compared between treatments by using a chi-sqare test of proportions which will be the official test used for the hierarchical testing outlined in Section 3.4. In addition, the frequency and proportion of patients will be summarized based on the below best confirmed response categories:

- CR;
- PR;
- SD;
- PD; and
- Not evaluable

In order to be categorized as a best confirmed response of SD the patient needs to have at least one tumor assessment with SD on or after the start of first protocol specified visit window (ie, Week 16 minus 7 days which is equal to 105 days since randomization). Only tumor scans included for evaluation of the primary endpoint are considered for the ORR endpoint.

### 10.2.4 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 (i.e., CR or PR) by RECIST v1.1 as described in Section 10.2.3. 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 included for evaluation of the primary endpoint are considered for the DOR endpoint.

The DOR will be analyzed using Cox proportional hazards model and a log-rank test. In addition, a graphical presentation of DOR distributions, median DOR with 95% CI, and event rates will be presented.

## 10.3 Exploratory Efficacy Analyses

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

### 10.3.1 Second Event of Progression-free Survival (PFS2)

The second event of progression, 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. The second event will be the disease progression event as reported during the subsequent anticancer follow up. Subsequent anticancer treatments will be collected for all patients every 12 or 24 weeks (± 14 days), until death, loss to follow-up, withdrawal of consent from study, or closure of the study. The subsequent anticancer data with start and stop date and any date of progression will be documented. The date of progression on subsequent anticancer treatments may be a documented event per RECIST guidelines or may be an event of symptomatic/clinical or CA-125 progression. Patients who have not died or had a second event of disease progression will be censored on the date the patient was last known to be alive or last visit. PFS2 will be analyzed using Cox proportional hazards model. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

### 10.3.2 Efficacy for tBRCA in the Monotherapy Treatment Comparison of Arm B (Rucaparib) vs Placebo

The primary and secondary efficacy endpoints for the subgroup of tBRCA patients will be summarized. This subgroup is explored in order to ensure that the results in the HRD and ITT subgroups are not solely driven by the results in the tBRCA subgroup.

### 10.3.3 Health-related Quality of Life as Assessed by the Functional Assessment of Cancer Therapy – Ovarian

PRO utilizing the FACT-O will be assessed at Screening, on Day 1 (Cycle 1 through Cycle 3, and Cycle 5), then every 12 weeks (aligning with CT scans) until treatment discontinuation or until the data cut-off for the primary analysis, whichever comes first. In addition, PRO assessments will be performed at End of Treatment, and at the SFU1 (28-day Safety Follow-up) and the SFU2 (5-month Safety Follow-up) for all patients.

Patients were instructed to complete the instruments on an electronic device before any other scheduled study procedures are performed and dosing occurs (if applicable). Due to COVID-19, the study allowed patients to do telehealth visits and to fill out the questionnaire on paper as well. The PRO data will be scored and summarized in accordance with the scoring manual for the questionnaire. Appendix 1 includes the English version of the questionnaires used with the subscale domains outlined. The FACT-O subscales values and total score together with the TOI will be calculated. A change of at least 10 points in the FACT-O TOI will be considered as clinically relevant and minimally important difference and may be summarized categorically.[7]

Analyses of changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for each subscale, total score and FACT-O TOI. Patients that do not have both a baseline measurement and at least 1 post-baseline measurement will not be included. The final visit is defined as the last assessment within 28 days after date of last

dose of oral study drug for those that discontinued oral treatment or prior to the visit cut-off date for those still ongoing.

For the protocol-specified post-baseline visits; the QoL assessment will be grouped in the following visit windows as described in Table 3 below.

**Table 3 Algorithm for Visit Window of QoL**

| Visits | Visit Window Start Date | Visit Window End Date |
|---|---|---|
| Cycle 2 Day 1 | EDC Cycle 2 Day 1 date - 3 days | EDC Cycle 3 Day 1 date - 4 days |
| Cycle 3 Day 1 | EDC Cycle 3 Day 1 date - 3 days | EDC Cycle 4 Day 1 date + 7 days |
| Cycle 5 Day 1 | EDC Cycle 5 Day 1 date -7 days | EDC Cycle 6 Day 1 date + 7 days |
| Cycle 8 Day 1 | EDC Cycle 8 Day 1 date -7 days | EDC Cycle 9 Day 1 date + 7 days |
| Cycle 11 Day 1 | EDC Cycle 11 Day 1 date -7 days | EDC Cycle 12 Day 1 date + 7 days |
| Cycle 14 Day 1 | EDC Cycle 14 Day 1 date -7 days | EDC Cycle 15 Day 1 date + 7 days |
| Etc…<br>Cycle X Day 1, (where X is every 3 cycles) | EDC Cycle X Day 1 date -7 days | EDC Cycle (X+1) date + 7 days |

If more than one assessment falls within a given visit window, the one that is closest to the actual scheduled EDC visit date will be used. In the case of ties, the assessment prior to the scheduled visit date will be used. The data sets should highlight the value for the patient that was included in the summary table, wherever feasible. The summary tables and graphs will only display data if the number of observations is greater than 10 in each treatment arm.

At a given visit, the change from baseline will be analyzed for the treatment comparisons using an Analysis of Covariance (ANCOVA) with treatment and stratification variables as categorical factors and baseline measurement for the parameter as a continuous covariate. In addition, a graphical presentation of mean changes over time may be presented.

In addition, a repeated measures ANCOVA model may be used to estimate the average treatment effect over the first 12 months and 24 months.

Distribution of item level responses and change from baseline in these item levels for the following 5 questions will be summarized by visit:

From the Physical Well-being questions:

1: I have a lack of energy

2: I have nausea

5: I am bothered by side effects of treatment

7: I am forced to spend time in bed

And from the Functional Well-being questions:

1: I am able to work

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

### 10.3.4 Patient-reported Outcome of EQ-5D-5L

Analyses of changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for the EQ-5D-5L instrument and the EQ VAS. Patients who do not have both a baseline measurement and at least 1 post-baseline measurement will not be included.

The final visit is defined as the last assessment within 28 days after date of last dose of oral study drug for those that discontinued oral treatment or prior to the visit cut-off date for those still ongoing. For the protocol-specified post-baseline visits; the EQ-5D-5L assessment will be grouped in actual scheduled visit windows as described in Table 3. If more than one assessment date falls within a given visit window, the one that is closest to the actual scheduled EDC visit date will be used. In the case of ties, the assessment prior to the scheduled visit date will be used. The data sets will highlight the value for the patient that was included in the summary table, wherever feasible. The summary tables and graphs will only display data if the number of observations is greater than 10 in each treatment arm.

At a given visit, the change from baseline will be analyzed for the treatment comparisons using an Analysis of Covariance (ANCOVA) with treatment and stratification variables as categorical factors and baseline measurement for the parameter as a continuous covariate. In addition, a graphical presentation of mean changes over time may be presented.

### 10.3.5 PRO Patient Disposition and Completion Rate

The following analyses will also be summarized in order to characterize PRO data (eg, FACT-O and EQ-5D-5L) completeness.

PRO patient disposition will be summarized in a table with the cumulative patient disposition by treatment and PRO assessment window for each scheduled post-baseline visit (eg, Cycle 1 Day 1, Cycle 2 Day 1, etc.) . The following categories will be summarized:

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

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

### 10.3.6 PRO Correlation With Adverse Events

The correlation between EQ-5D-5L and FACT-O will be summarized by tabulating the mean EQ-5D-5L subscale score for the mobility, self-care, and usual activities dimension at each cycle broken down by response to FACT-O item GP1 (I have lack of energy) as well as by grade 1, 2, or 3 CTCAE maximum grade of asthenia/fatigue. The mean EQ-5D-5L subscale score of self-care and usual activities at each cycle will be broken down by response to FACT-O item GP2 (I have nausea) as well as by grade 1, 2, or 3 CTCAE maximum grade of nausea.

### 10.3.7 Evaluation of Post-progression Efficacy Endpoints

Following treatment discontinuation, subsequent anticancer treatments will be collected for all patients every 12 or 24 weeks (± 14 days), until death, loss to follow-up, withdrawal of consent from study, or closure of the study. The subsequent anticancer data with start and stop date and any date of progression documented for each regimen will be recorded. The following endpoints will be derived based on these data.

- **Chemotherapy-free interval (CFI),** will be calculated in months as the time since the last dose of the most recent chemotherapy regimen to the date of the first dose of a subsequent chemotherapy, or death due to any cause, + 1 day. Patients without a documented start of a subsequent chemotherapy after study drug will be censored on the date the patient was last known to be alive or last visit.
- **Time to first subsequent anticancer treatment (TFST),** will be calculated in months as the time from randomization to the date of the first dose of the first subsequent anticancer treatment regimen, or death due to any cause, + 1 day. Patients without a documented start date of a subsequent anticancer treatment will be censored on the date the patient was last known to be alive or last visit.
- **Time to second subsequent anticancer treatment (TSST),** will be calculated in months as the time from randomization to the date of the first dose of the second subsequent anticancer treatment regimen, or death due to any cause + 1 day. Patients without a documented start of a second subsequent anticancer treatment will be censored on the date the patient was last known to be alive or last visit.
- **Time to treatment discontinuation of oral dose (TDT),** will be calculated in months as the time from randomization to the date of the last dose of oral treatment + 1 day. Patients still ongoing will be censored at the last visit prior to the visit cutoff.

The same statistical test used for the primary endpoint (ie, stratified log rank test and a stratified Cox proportional model) will be used to compare treatments for this endpoint.

### 10.3.8 Pharmacokinetic Analysis of rucaparib

As an exploratory endpoint, trough ($C_{min}$) concentrations of rucaparib will be summarized with descriptive statistics by cycle in all patients with at least 1 PK sample collected.

## 10.4 Examination of Efficacy in Subgroups

The primary endpoint (invPFS) will be further explored within the ITT Population for the following subgroups:

- The stratification factor used for randomization.
  - HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$);
  - Disease status post chemotherapy (no residual disease vs residual disease); and
  - Timing of surgery (primary surgery vs. interval debulking).
- Age groups (< 65, 65-74, ≥ 75);
- Race (White, Other, Unknown);
- Geographic region (United States/Canada, Europe, Eastern Europe, Latin America, Asia, Australia/New Zealand).
- ECOG (0, ≥ 1)
- FIGO Stage at Diagnosis (III or IV)
- CA-125 at Baseline (≤ ULN or > ULN) using central laboratory
- Prior use of bevacizumab (Yes or No); and
- Surgery outcome (R0 vs other).
- Disease status at baseline;
  - Measurable disease by investigator (ie, target lesions identified by RECIST v1.1);
  - non-measurable disease by investigator (ie, non-target lesions only identified by RECIST v1.1);
  - No disease by investigator (ie, no target lesions and no non-target lesions identified by RECIST v1.1);
- Disease Free with normal CA-125 defined as Best radiological response (CR, No Disease Post-surgery) and CA-125 ≤ ULN (Yes, No)

In addition, primary endpoint of invPFS will be analyzed for the following tBRCA mutation subgroups:

- Mutation: BRCA1 vs BRCA2; and
- Mutation type: Germline, Somatic, or Unknown.

These exploratory subgroup analyses of invPFS will be analyzed using Cox proportional hazards methodology. The hazard ratio from the Cox proportional hazards model will be used to estimate the HR with 95% CIs between the randomized treatment groups. In addition, an interaction test of the subgroup-by-treatment interaction term in the Cox proportional hazards model. All these analyses will be performed using a unstratified model due to smaller sample sizes.

In addition, a log-rank test of invPFS between the randomized treatment groups together with a graphical presentation of invPFS distributions, median invPFS with 95% CI, and event rates will be presented as supportive statistics for these subgroups. Furthermore, the probability of being progression free at 6, 12, 18, and 24 months may be summarized for some of the subgroups by treatment group by using the Kaplan-Meier estimates, at each time point with 95% CIs using a log-log distribution.

# 11 SAFETY ANALYSIS

Only patients who are randomized to Arm B (rucaparib monotherapy) and Arm D (placebo) are included in the Safety Population for ATHENA-MONO. The safety analyses will be presented for the Safety Population presenting the data by each treatment group separately.

Summary tables are based on data that are found to be "on-treatment"/ "treatment-emergent" for the oral study drug as outlined in the below sections. This is regardless of whether these data were "on-treatment"/ "treatment-emergent" for IV study drug.

## 11.1 Adverse Events

AEs will be classified using the MedDRA version 24.1 or higher classification system. The severity of the toxicities will be graded according to the NCI-CTCAE v5.0 or later.[8]

All safety data which are considered treatment-emergent to oral study drug will be summarized. Treatment-emergent to oral study drug: is defined as safety data with an onset date on or after the date of first dose of oral study medication until the date of the last oral study medication plus 28 days. AEs will be considered treatment-emergent to oral study drug 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.

The number and percentage of patients who experience TEAEs to oral study drug will be presented by SOC and PT. Multiple instances of the AEs 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 1 TEAE to oral study drug will also be summarized.

The incidence of TEAEs will be summarized by relationship to either oral or IV 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.

A summary table with the number and percent of patients that fall into each of the AE categories below will be presented for all events, related to oral study drug, and related to IV study drug. In addition, separate tables by SOC and PT will be presented for each of these AE categories:

- All TEAEs;
- Serious TEAEs;
- Grade 3 or greater TEAEs;
- TEAEs that led to death;
- TEAEs that led to oral study drug discontinuation;
- TEAEs that led to IV study drug discontinuation;
- TEAEs that led to discontinuation of both oral and IV treatment;

- TEAEs that led to dose reduction of oral study drug;
- TEAEs that led to oral study drug interruption;
- TEAEs that led to IV study drug interruption;
- TEAEs that led to both oral and IV study drug interruption;
- TEAEs that led to dose reduction or interruption of oral study drug.
- TEAEs that led to dose reduction, interruption, or discontinuation of oral study drug

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 1 TEAE of the given maximum grade will be summarized.

The time to the first TEAE of Anaemia or Haemoglobin decreased, and first TEAE leading to a dose reduction, interruption, and/or discontinuation of oral 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 only 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 will be combined for the following similar terms:

- Anaemia or Haemoglobin decreased;
- Asthenia or Fatigue;
- ALT or AST increased;
- Neutropenia or Neutrophil Count decreased;
- Thrombocytopenia or Platelet count decreased.

In addition to the cumulative incidence tables of AEs, time adjusted AE summaries for the oral treatment study duration will be created. The time adjusted analyses (ie, 100 patient-treated years) of AEs are defined as the number of total events of a certain AE divided by the patient-years. The patient-years is the total sum of all the years the patients in each treatment arm are treated (ie, from the start of first oral dose to date of last oral dose +1 day). The time adjusted analyses will be summarized for the following:

- 100 patient-treated years for all TEAEs;
- 100 patient-treated years for Grade 3 or greater TEAEs; and
- 100 patient-treated years for serious TEAEs.

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 is also summarized.

## 11.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, and serum chemistry. The laboratory values will be presented in standard units. Summary tables and graphical presentations will only include the laboratory values that are deemed to be "on-treatment" to oral study drug as follows: All clinical laboratory values with an onset date on or after the date of first dose of oral study medication until the date of the last oral study medication plus 28 days. The laboratory values collected outside of the on-treatment period for oral study drug will only be presented in the data listings.

For visit-based summaries; the laboratory evaluations that are during the actual scheduled cycle visit (ie, EDC visit structure) will be used, otherwise, any unscheduled laboratory evaluations that are closest to and within the same actual scheduled cycle will be used. The data sets should highlight the value for the patient that was included in the summary table, wherever feasible. The summary tables and graphs will only display data if the number of observations is greater than 10 in each treatment arm.

The summary of laboratory data will include descriptive statistics 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 v5.0 or later) for each lab parameter will be summarized.

Figures of the mean values over time with standard error bars will be presented for key safety laboratory parameters.

This study uses a central laboratory assessment of all safety laboratory data. Local laboratory values that are clinically relevant or support eligibility will be added to the CRFs. All aggregate analyses of data will primarily be done using only the central laboratory data. The local laboratory data will be presented in patient level data listings. However, an additional maximum on-treatment toxicity grade shift from baseline grade may be presented using both local and central laboratory data.

Additional detail regarding clinical laboratory evaluations are provided in Appendix 2.Urinalysis results will be reported in patient level listings.

## 11.3 Vital Signs

The vital signs values will be presented in standard units. Summary tables and graphical presentations will only include the vital signs values that are deemed to be "on-treatment" to oral study drug as follows: all vital signs values with an onset date on or after the date of first dose of oral study medication until the date of the last oral study medication plus 28 days. The vital signs values collected outside of the on-treatment period for oral study drug will only be presented in the data listings.

For visit-based summaries; vital signs evaluated during the actual scheduled cycle visit will be used, otherwise, any unscheduled vital signs evaluations that are closest and within the same actual scheduled cycle will be used. The data sets should highlight the value for the patient that went into the summary table, wherever feasible. The summary tables and graphs will only display data if the number of observations is greater than 10 in each treatment arm.

The summary of vital sign data will include descriptive statistics 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.

## 11.4 ECG

Local reads of ECG were collected at Screening and End of Study.Summaries using descriptive statistics of the observed value and change from baseline to end of study will also be given.

The QT interval was corrected by using both Fridericia's (QTcF) and Bazett's (QTcB) formula. Each patient's maximum QTc intervals will be classified according to the CTCAE V5 grades[8] to the following categories: $< 450$ msec (Normal), $\geq 450$ to $\leq 480$ msec (Grade 1), $> 480$ to $\leq 500$ msec (Grade 2), and $> 500$ msec (Grade 3). In addition, each patient's maximum change from baseline for QTc intervals will be classified into $\leq 30$ msec, $> 30$ to $\leq 60$ msec, and $> 60$ msec (Grade 3). The number and percentage of patients in each classified category will be presented.

## 11.5 Examination of Safety in Subgroups

The following key safety output will be further explored within subgroups based on key intrinsic factors. The key identified safety output are:

- All TEAEs;
- Grade 3 or greater TEAEs;
- Serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of oral study drug;

- TEAEs leading to dose reduction of oral study drug;
- TEAEs resulting in interruption of oral study drug;
- TEAEs resulting in dose reduction or interruption of oral study drug; and
- Shift summary tables from baseline to the maximum on-treatment toxicity grade for each clinical laboratory parameter.

The following subgroups based on key intrinsic factors will be summarized:

- Age groups (< 65, 65-74, ≥ 75; ≥ 65 ; and < 75 years old);
- Race (White, Other, and Unknown); and
- The stratification factor used for randomization of HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$) and the HRD Population.

# 12 DOCUMENT REVISION HISTORY

| Version | Date signed | Description |
|---|---|---|
| **1.0** | 02Dec2021 | Original Version |
| **2.0** | 10Feb2022 | Clarified the test to be chi-square for secondary endpoint of ORR instead of stratified CMH test. Clarified that the log-rank test will be used for the multiplicity testing instead of the Cox proportional hazards model. Administrative changes not affecting the statistical methods. |

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# 14 APPENDICES

## Appendix 1 FACT-O (Version 4)

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

**Physical Well-being (PWB)**

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| 2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| 3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| 4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| 5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| 6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| 7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

**Social/Family Well-being (SWB)**

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| 2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| 3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| 4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| 5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| 6 | I feel close to my partner (or the person why is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it,* | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | *please mark this box ☐ and go to the next section.* | | | | | |
| 7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

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

## Emotional Well-being (EWB)

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| 2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| 3 | I am loosing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| 4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| 5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| 6 | I worry my condition will get worse | 0 | 1 | 2 | 3 | 4 |

## Functional Well-being (FWB)

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I am able to work (include work from home) | 0 | 1 | 2 | 3 | 4 |
| 2 | My work (include work from home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| 3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| 4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| 5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| 6 | I enjoy the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| 7 | I am content with the quality of life right now | 0 | 1 | 2 | 3 | 4 |

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

## Additional Concerns (OCS)

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| 1 | I have swelling in my stomach area | 0 | 1 | 2 | 3 | 4 |
| 2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| 3 | I have control of my bowls | 0 | 1 | 2 | 3 | 4 |
| 4 | I have been vomiting | 0 | 1 | 2 | 3 | 4 |
| 5 | I am bothered by hair loss | 0 | 1 | 2 | 3 | 4 |
| 6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| 7 | I like the appearance of my body | 0 | 1 | 2 | 3 | 4 |
| 8 | I am able to get around by myself | 0 | 1 | 2 | 3 | 4 |
| 9 | I am able to feel like a woman | 0 | 1 | 2 | 3 | 4 |
| 10 | I have cramps in my stomach area | 0 | 1 | 2 | 3 | 4 |
| 11 | I am interested in sex | 0 | 1 | 2 | 3 | 4 |
| 12 | I am concerned about my ability to have children. | 0 | 1 | 2 | 3 | 4 |

The scoring manual for FACT-O is located here: https://www.facit.org/scoring.

The 5 sub scores of the instrument (PWB, SWB, EWB, FWB, and OCS subscale scores) will only be calculated if > 50% of questions that go into the subscale are answered. FACT-O Total Score will only be calculated if > 80% of questions are answered AND none of the component subscale scores (PWB, SWB, EWB, FWB, OCS) are missing. Trial Outcome Index (TOI) will only be calculated if > 80% of questions are answered AND none of the component subscale scores (PWV, FWB, OCS) are missing.

# Appendix 2 Clinical Laboratory Evaluations

## CTCAE Version

The summary of laboratory data includes tables based on NCI-Common Terminology Criteria for Adverse Events (CTCAE), which is a descriptive terminology utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term. In general, CTCAE version 5.0 is used; however, in some cases version 4.03 is substituted as quantitative grading is not available in version 5.0.

The table below lists terms using version 4.03 or a slight modification to version 5.0.

| CTCAE Term | Notes |
|---|---|
| Hyperglycemia<br>Hypophosphatemia<br>Hyponatremia | Version 5.0 is based on clinical observations or interventions initiated that are not available in the clinical database. Version 4.03 is applied. |
| Hyperkalemia<br>Hypernatremia | Version 5.0 is based on a combination of laboratory results and interventions. The logic associated with laboratory results is used. |
| Hypokalemia | Both grades 1 and 2 use <LLN-3.0 mmol/L. Grade 2 additionally requires clinical observations or interventions that are not available in the clinical database. Grade 1 is not used. The range is applied to grade 2. |

## Grading of Central and Local Laboratory Data

The central laboratory provides CTCAE grades according to their lab Tox Grade Report. However, in some instances the Report indicates grading is derived without the use of a baseline result where v5.0 requires use of upper limit of normal (ULN) for normal baseline and increments above baseline for abnormal baseline. Therefore, the CTCAE grading criteria will be applied in a consistent manner across all laboratory assessment using stacked data that includes both central and local results.

## Normal Reference Ranges

A reference range is a set of values that includes upper and lower limits based on a group of otherwise healthy people. The values may depend on age, gender, and specimen type, and can also be influenced by circumstantial situations such as fasting and exercise.

Normal reference ranges for central laboratory assessments are contained within the data provided by the central laboratory. Each of the local laboratories provided normal ranges specific to the laboratory in which the test was done. These local ranges were entered into EDC and applied to results via the lab admin tool.

### Liver Function Tests

Baseline results for four Liver Function Tests (LFTs); Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), and bilirubin will not receive a numeric grade (grade 1-5). They will be categorized in relation to the ULN (eg, ≤ ULN, > ULN-3 × ULN, > 3 × ULN-5 × ULN). Shifts in grade from baseline to maximum on-treatment post-baseline for these events (ALT increased, ALP increased, AST increased, and blood bilirubin increased) will not be summarized.

### Creatinine Clearance

Estimated GFR (eGFR) by Cockcroft-Gault is collected in both central and local laboratory data. These results will be provided in data listings and will not be summarized.

Renal impairment at baseline (creatinine clearance) will be re-calculated using serum creatinine, age and weight using the Cockcroft-Gault formula.

$$\text{Female } CL_{cr} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{[\ 72 \times \text{Serum Creatinine}\ ]} \times 0.85$$

This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL; the calculated units are mL/min.

### CTCAE Grading: Hematology

| CTCAE Description | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Anemia | 100<= AVAL <LLN | 80<= AVAL <100 | AVAL <80 | |
| Lymphocyte count decreased | 0.8<= AVAL <LLN | 0.5<= AVAL < 0.8 | 0.2<= AVAL < 0.5 | <0.2 |
| Lymphocyte count increased | | 4< AVAL <=20 | AVAL >20 | |
| Neutrophil count decreased | 1.5<= AVAL <LLN | 1<= AVAL <1.5 | 0.5<= AVAL <1 | AVAL <0.5 |
| Platelet count decreased | 75<= AVAL <LLN | 50<= AVAL <75 | 25<= AVAL <50 | AVAL <25 |
| White blood cell decreased | 3.0<= AVAL <LLN | 2.0<= AVAL <3.0 | 1.0<= AVAL<2.0 | AVAL <1.0 |

## CTCAE Grading: Chemistry

| CTCAE Description | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Hypoalbuminemia | 30<= AVAL <LLN | 20<= AVAL <30 | AVAL <20 | |
| Alkaline phosphatase increased | If baseline is normal: | | | |
| | ULN< AVAL <=2.5xULN | 2.5xULN< AVAL <=5xULN | 5xULN< AVAL <=20xULN | AVAL >20xULN |
| | If baseline is abnormal: | | | |
| | 2xBASE<= AVAL <=2.5xBASE | 2.5xBASE< AVAL <=5xBASE | 5xBASE< AVAL <= 20xBASE | >20xBASE |
| Alanine aminotransferase increased | If baseline is normal: | | | |
| | ULN< AVAL <=3xULN | 3xULN< AVAL <=5xULN | 5xULN< AVAL <=20xULN | AVAL >20xULN |
| | If baseline is abnormal: | | | |
| | 2xBASE<= AVAL <=2.5xBASE | 2.5xBASE< AVAL <=5xBASE | 5xBASE< AVAL <=20xBASE | >20xBASE |
| Aspartate aminotransferase increased | If baseline is normal: | | | |
| | ULN< AVAL <=3xULN | 3xULN< AVAL <=5xULN | 5xULN< AVAL <=20xULN | AVAL >20xULN |
| | If baseline is abnormal: | | | |
| | 1.5xBASE<= AVAL <=3xBASE | 3xBASE< AVAL <=5xBASE | 5xBASE< AVAL <=20xBASE | >20xBASE |
| Blood bilirubin increased | If baseline is normal: | | | |
| | ULN< AVAL <=1.5xULN | 1.5xULN< AVAL <=3xULN | 3xULN< AVAL <=10xULN | AVAL >10xULN |
| | If baseline is abnormal: | | | |
| | BASE<= AVAL <=1.5xBASE | 1.5xBASE< AVAL <=3xBASE | 3xBASE< AVAL <=10xBASE | >10xBASE |
| Hypocalcemia | 2.0<= AVAL <LLN | 1.75<= AVAL <2.0 | 1.5<= AVAL <1.75 | AVAL <1.5 |
| Hypercalcemia | ULN< AVAL <=2.9 | 2.9< AVAL <=3.1 | 3.1< AVAL <=3.4 | AVAL >3.4 |
| Cholesterol high | ULN< AVAL <=7.75 | 7.75< AVAL <=0.34 | 10.34< AVAL <=12.92 | AVAL >12.92 |
| Creatinine increased | ULN< AVAL <=1.5xULN | 1.5xBASE< AVAL <=3xBASE; 1.5xULN< AVAL <=3xULN | AVAL >3xBASE; 3xULN< AVAL <=6xULN | AVAL >6xULN |
| Hypoglycemia | 3.0<= AVAL <LLN | 2.2<= AVAL <3.0 | 1.7<= AVAL <2.2 | AVAL <1.7 |
| Hyperglycemia | ULN< AVAL <=8.9 | 8.9< AVAL <=13.9 | 13.9< AVAL <=27.8 | AVAL >27.8 |
| Hypokalemia | | 3.0<= AVAL <LLN | 2.5<= AVAL <3.0 | AVAL <2.5 |

| CTCAE Description | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Hyperkalemia | ULN< AVAL <=5.5 | 5.5< AVAL <=6.0 | 6.0< AVAL <=7.0 | AVAL >7.0 |
| Hypomagnesemia | 0.5<= AVAL <LLN | 0.4<= AVAL <0.5 | 0.3<= AVAL <0.4 | AVAL <0.3 |
| Hypermagnesemia | ULN< AVAL <=1.23 | | 1.23< AVAL <=3.30 | AVAL >3.30 |
| Hypophosphatemia | 0.8<= AVAL <LLN | 0.6<= AVAL <0.8 | 0.3<= AVAL <0.6 | AVAL <0.3 |
| Hyponatremia | 130<= AVAL <LLN | | 120<= AVAL <130 | AVAL <120 |
| Hypernatremia | ULN< AVAL <=150 | 150< AVAL <=155 | 155< AVAL <=160 | AVAL >160 |
| Hypertriglyceridemia | 1.71<= AVAL <=3.42 | 3.42< AVAL <=5.7 | 5.7< AVAL <=11.4 | AVAL >11.4 |