# Clinical Study Protocol: CO-338-087
# GOG-3020 / ENGOT-ov45/NCRI/ATHENA

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| **Study Title:** | 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) |
| **Study Number:** | CO-338-087/ GOG-3020/ ENGOT-ov45/NCRI/ATHENA |
| **Study Phase:** | Phase 3 |
| **Product Name:** | Rucaparib (CO-338); Nivolumab (BMS-936558) |
| **IND Number:** | 106,289 |
| **EUDRACT Number:** | [2017-004557-17] |
| **Indication:** | Newly diagnosed, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer |
| **Investigators:** | Multicenter;<br>Lead Investigator: [redacted] |
| **Sponsor Name:** | pharmaand GmbH (pharma&) |
| **Sponsor Address:** | [redacted]<br>[redacted]<br>Phone Number: [redacted] |
| **Responsible Medical Officer:** | [redacted] |

| | Date |
|---|---|
| **Original Protocol:** | 02 March 2018 |
| **Amendment 1** | 05 July 2018 |
| **Amendment 2** | 26 October 2020 |
| **Amendment 3** | 08 September 2021 |
| **Amendment 4** | 29 November 2021 |
| **Amendment 5** | 16 June 2023 |

# PROTOCOL APPROVAL SIGNATURE PAGE

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| **Date:** | 16 June 2023 |
| **Version:** | Amendment 5 |

Reviewed and Approved by:

**Signature:** [redacted]
**Email:** [redacted]
**Title:** [redacted]

[redacted]

[redacted], pharma&

# PROTOCOL ACCEPTANCE FORM

**Protocol:** CO-338-087

**Title:** 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)

**Date:** 16 June 2023

**Version:** Amendment 5

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

| Investigator's Signature | Date (DD-MMM-YYYY) |
|---|---|

Name (printed)

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**Clinical Investigators, Study Sites, and Laboratories:**

This is a multicenter study. Information on investigators, institutions, and laboratories involved in the study are maintained in the clinical study file and can be provided upon request.

# SYNOPSIS

**Sponsor**

pharmaand GmbH (pharma&)

**Name of Finished Product**

Rucaparib tablets;
Nivolumab injection

**Name of Active Ingredient**

Rucaparib camsylate (CO-338);
Nivolumab (BMS-936558)

**Study Title**

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)

**Study Number**

CO-338-087;
GOG-3020;
ENGOT-ov45/NCRI/ATHENA

**Study Phase**

Phase 3

**Rationale**

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes play a critical role in base excision repair (BER).[1] When PARP function and effective BER is impaired, double-stranded deoxyribonucleic acid (DNA) breaks accumulate. In cells deficient in homologous recombination, these breaks cannot be accurately repaired, resulting in synthetic lethality.[2] While mutated breast cancer genes (BRCA)1 and BRCA2 are most commonly associated with homologous recombination deficiency (HRD), other essential homologous recombination repair (HRR) proteins may be mutated or functionally deficient in ovarian cancer. Recently, it has also been determined that measuring genomic loss of heterozygosity (LOH) is a phenotypic approach that can be utilized to identify HRD regardless of underlying mechanism.[3]

The rationale for combining rucaparib, a potent PARP inhibitor, with nivolumab, a programmed death receptor-1 (PD-1) blocking antibody, derives from emerging data that demonstrate an important association between high neoantigen load (increased mutational burden) and high expression of PD-1 and/or its ligand, PD-L1 in ovarian tumors with gene mutations in the HRR pathways compared to ovarian cancers without these mutations.[4-7] BRCA1 and BRCA2 mutations have been reported to increase the number of tumor infiltrating lymphocytes (TILs); BRCA mutations are associated with improved overall survival (OS).[7-9] In addition, internal data (Clovis Oncology, Inc.) indicated a significant association between levels of genomic LOH and tumor mutational burden (TMB). A high TMB increases the likelihood of the development of tumor-specific neoepitopes that could confer clinical benefit from PD-1 blockade. Thus, it is hypothesized that increased DNA

damage by PARP inhibition will increase the number of tumor neoantigens, creating a more antigenic environment in which to stimulate the immune microenvironment.

This study will investigate the safety and efficacy of the combination of the PARP inhibitor, rucaparib, and the PD-1 monoclonal antibody, nivolumab, with the hypothesis that this drug combination may preferentially benefit an HRD-positive ovarian cancer patient population, which in turn may extend progression-free survival (PFS) following standard treatment (surgery and platinum-based chemotherapy) for ovarian cancer in the frontline setting.

**Primary Objective:**

- To evaluate PFS by Response Evaluation Criteria in Solid Tumors (RECIST), as assessed by the investigator (invPFS) using the following separate comparisons:
  - Monotherapy: Arm B (oral rucaparib + intravenous [IV] placebo) vs Arm D (placebo [oral and IV]) in the HRD and intent-to-treat (ITT) sub/populations
  - Combination: Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo) in the ITT Population

**Secondary Objectives:**

- To evaluate PFS by RECIST, as assessed by blinded independent central review (BICR; bicrPFS)
- To evaluate survival benefit
- To evaluate the objective response rate (ORR) and duration of response (DOR), as assessed by the investigator, in patients with measurable disease at baseline
- To evaluate safety

**Exploratory Objectives:**

- To evaluate PFS2 (PFS on the subsequent line of treatment)
- To evaluate the contribution of nivolumab monotherapy vs placebo (invPFS, bicrPFS, OS, ORR, DOR, safety)
- To evaluate the comparison of combination rucaparib + nivolumab vs placebo (invPFS, bicrPFS, OS, ORR, DOR, safety)
- To evaluate efficacy and safety in the tBRCA subgroup for the comparison of rucaparib vs placebo (invPFS, bicrPFS, OS, ORR, DOR, safety)
- To evaluate efficacy and safety in HRD, tBRCA, and PD-L1 subgroups for the comparison of combination vs rucaparib (invPFS, bicrPFS, OS, ORR, DOR, safety)
- 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)
- To evaluate patient-reported outcome (PRO) utilizing the Euro-Quality of Life 5D-5L (EQ-5D-5L)
- To assess mutations in non-tumor BRCA (where tBRCA defines a tumor tissue alteration in BRCA1 or BRCA2) HRR genes as a molecular marker of efficacy
- To assess PD-L1 expression and TMB as molecular markers of efficacy
- To study variants in circulating tumor DNA (ctDNA) as markers of response and resistance

- To characterize pharmacokinetics (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

**Study Design**

This is a randomized, multinational, double-blind, dual placebo-controlled, 4-arm, Phase 3 study evaluating rucaparib and nivolumab as monotherapy and in combination as maintenance treatment following response to front-line treatment (surgery and platinum-based chemotherapy) in newly diagnosed ovarian cancer patients.

The study will enroll patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who achieved a response to their first platinum-based regimen.

This study consists of a Screening Phase, a Treatment Phase, and a Post-treatment Phase.

Screening Phase

All patients will undergo screening assessments within 120 days prior to randomization. Submission of tumor tissue from the cytoreductive surgery (peritoneal cytology alone is not sufficient) will be required prior to enrollment to determine the mutation status of homologous recombination pathway genes, including BRCA1/2. In addition, biomarkers related to response or resistance to immunotherapies will be assessed. Tumor DNA will also be assessed to determine the percentage of the genome with LOH.[3,10-12] Analysis of tumor LOH will allow patients without a BRCA mutation to be classified as non-tBRCA LOH$^{high}$ or non-tBRCA LOH$^{low}$. For the Double-blind Treatment Phase, patients will be stratified into 1 of 4 HRD subgroups (tBRCA, non-tBRCA LOH$^{high}$, or non-tBRCA LOH$^{low}$, or non-tBRCA LOH$^{unknown}$) for randomization based on the results obtained.

Patients must meet all inclusion and exclusion criteria as specified in the protocol.

Enrollment/randomization to study treatment must occur within 8 weeks of the first day of the last cycle of chemotherapy, and study treatment must be initiated within 3 days of enrollment/randomization.

Treatment Phase

The treatment phase will consist of 28-day treatment cycles. In Cycle 1, patients will receive treatment with oral study drug only, beginning on Day 1. Oral study drug will be taken twice a day (BID) continuously thereafter. Dosing with IV study drug will begin on Cycle 2 Day 1 (C2D1); IV study drug will be administered every 4 weeks. Patients will come into the study site for a visit on Day 1 and Day 15 of Cycles 1 and 2, and on Day 1 of every cycle thereafter. A blood sample will be collected from all patients at Cycle 1 Day 1 and stored for subsequent genomic DNA testing and determination of germline status.

Study drug treatment will continue in 28-day cycles until 24 months after initiating oral/IV combination study treatment, disease progression, or unacceptable toxicity, whichever occurs first. Patients will undergo procedures and assessments, including regular safety, PK, and efficacy evaluations, during the entire conduct of the study.

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) relative to C2D1 (the first scan will be 16 weeks after initiation of oral study treatment) for the first 3 years and then every 24 weeks thereafter until objective radiological disease progression, as assessed by the investigator. Patients experiencing disease progression by RECIST v1.1 will be discontinued from treatment and enter follow-up. If the patient has met criteria for radiologic progression by RECIST, but the patient is still receiving benefit from the study drug(s) (eg, patient has mixed radiologic response or is continuing to have symptomatic benefit), according to the investigator, then continuation of treatment will be considered for a maximum cumulative duration of 24 months after initiation of oral/IV combination study treatment. In such cases, the decision to continue receiving treatment with study drug(s) must be documented in source documents, and the patient must provide additional consent prior to continuing treatment with study drug(s). Patients will continue to have all protocol-required assessments specified in the Schedule of Assessments.

Safety and efficacy data will be periodically reviewed by an Independent Data Monitoring Committee (IDMC).

Prior to randomization of patients in the Double-blind Treatment Phase of the study, a minimum of 6 patients may be enrolled into an open-label safety cohort and analyzed for safety after completion of at least 1 cycle of combination therapy. The eligibility criteria and study assessments will be the same for the safety cohort as those described above for the Double-blind Treatment Phase.

Evaluation of a Japanese safety cohort will proceed in the same manner as the initial safety cohort, once the rucaparib monotherapy dose is established in an ongoing Phase 1 study in Japan.

Post-Treatment Follow-up Phase

All patients will be followed for at least 5 months after the last dose of IV study drug treatment. There will be 2 safety 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, the 5-month Safety Follow-up Visit (SFU2) 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 reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals relative to C2D1 for the first 3 years and then every 24 weeks thereafter until objective radiological disease progression by RECIST v1.1, as assessed by the investigator, is documented. An optional tumor biopsy will be collected from patients who experience disease progression/randomized treatment discontinuation and provide appropriate consent.

Patients will also be followed long-term for survival, subsequent treatments, and monitoring for secondary malignancy every 12 weeks (± 14 days) after SFU1 until death, loss to follow-up, withdrawal of consent, or study closure.

**Number of Patients**

Approximately 1000 patients will be randomized in the Double-blind Treatment Phase.

Overall, the double-blind randomization assumes a 4:4:1:1 allocation to treatment with Arm A: oral rucaparib + IV nivolumab (n = 400), Arm B: oral rucaparib + IV placebo (n = 400), Arm C: oral placebo + IV nivolumab (n = 100) and Arm D: oral placebo + IV placebo (n = 100).

At least 6 patients may be enrolled to an open-label safety cohort prior to randomization of patients in the Double-blind Treatment Phase.

A maximum of 500 patients with a deleterious mutation in BRCA1 or BRCA2 (tBRCA) will be randomized.

Patients who withdraw consent from the study or terminate participation prematurely will not be replaced.

**Number of Sites**

This is a multicenter, multinational study. Patients will be enrolled from approximately 290 study sites.

**Inclusion Criteria**

Eligible patients must meet the following inclusion criteria:

1. Have signed an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)-approved informed consent form (ICF) prior to any study-specific evaluation.
2. Be ≥ 18 years of age at the time the ICF is signed (patients enrolled in South Korea, Taiwan, and Japan must be ≥ 20 years of age at the time the ICF is signed).
   a. Patients enrolled in the open-label safety cohort in Japan must be of Japanese ethnicity (ie, both parents are native Japanese and were born in Japan)
3. Have newly diagnosed, histologically confirmed, advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.
4. Completed cytoreductive surgery, including at least a bilateral salpingo-oophorectomy and partial omentectomy, either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking).
5. 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.
   a. A patient with best response of partial response (PR) must have received at least 6 cycles.
   b. Bevacizumab is allowed during the chemotherapy phase, but not during maintenance ie, during therapy directed by this protocol.
6. Have <u>completed</u> first-line platinum-based chemotherapy and surgery with a response, in the opinion of the investigator, defined as no evidence of disease progression radiologically or through rising CA-125 (per Gynecologic Cancer Intergroup [GCIG] guidelines) at any time during front-line treatment; and:
   a. No evidence of measurable disease by RECIST v1.1 (if complete resection/R0 at

primary or interval cytoreductive surgery); or

b. A partial or complete response per RECIST v1.1 (if measurable disease was present after surgery and prior to chemotherapy); or

c. A GCIG CA-125 response (if only non-measurable disease was present after surgery and prior to chemotherapy).

7. Pre-treatment CA-125 measurements must meet criterion specified below:

   If the first value is within upper limit of normal (ULN), the patient is eligible to be randomized and a second sample is not required;

   If the first value is greater than ULN, a second assessment must be performed at least 7 days after the first. If the second assessment is ≥ 15% than the first value, the patient is not eligible.

8. Patient must be randomized within 8 weeks of the first day of the last cycle of chemotherapy.
9. Have sufficient formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 × 4 µm section for hematoxylin and eosin [H&E] stain and approximately 8 to 12 × 10 µm sections, or equivalent) available for planned analyses.
   a. Submission of a tumor block is preferred; if sections are provided, these must all be from the same tumor sample.
   b. Tumor tissue from the cytoreductive surgery is required.
   c. Sample must be received at the central laboratory at least 3 weeks prior to planned start of treatment to enable stratification for randomization.
10. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to randomization:
    a. Bone Marrow Function
       i. Absolute neutrophil count (ANC) ≥ $1.5 \times 10^9$/L
       ii. Platelets ≥ $100 \times 10^9$/L
       iii. Hemoglobin ≥ 9 g/dL
    b. Hepatic Function
       i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 × ULN
       ii. Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome
       iii. Serum albumin ≥ 30 g/L (3.0 g/dL)
    c. Renal Function
       i. Serum creatinine ≤ 1.5 × ULN unless estimated glomerular filtration rate (GFR) ≥ 30 mL/min using the Cockcroft Gault formula
11. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

**Exclusion Criteria**

Patients will be excluded from participation if any of the following criteria apply:

1. Non-epithelial tumors (pure sarcomas) or ovarian tumors with low malignant potential (ie, borderline tumors) or mucinous tumors. Mixed mullerian tumors/carcinosarcomas are allowed.
2. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment.
    a. Patients with a history of malignancy that has been completely treated, with no evidence of active cancer for 3 years prior to enrollment, or patients with surgically-cured low-risk tumors, such as early-stage cervical or endometrial cancer are allowed to enroll.
3. Known central nervous system brain metastases.
4. Any prior treatment for ovarian cancer, other than the first-line platinum regimen, including any maintenance treatment between completion of the platinum regimen and initiation of study drug in this study.
    a. Ongoing hormonal treatment for previously treated breast cancer is permitted. Hormonal maintenance treatment for ovarian cancer is not allowed.
5. Has evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis.
6. Patients with an active, known or suspected autoimmune disease (eg, autoimmune hepatitis). Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
7. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
8. Drainage of ascites during the final 2 cycles of treatment with the platinum regimen.
9. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of study treatment.
10. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at all sites where mandated locally.
11. Any positive test result for hepatitis B and/or known history of hepatitis B infection including patients with undetectable hepatitis B virus (HBV) DNA and inactive carriers; positive test result for hepatitis C antibody (anti-HCV; except if HCV-RNA negative).
12. Pregnant, or breast feeding. All study participants must agree to avoid pregnancy achieved through assisted reproductive technology for the duration of study treatment

and for a minimum of 6 months following the last dose of study drug (oral or IV, whichever is later).

13. Received chemotherapy within 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, Grade 2 anemia with hemoglobin ≥ 9 g/dL, and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug.
14. Non-study related minor surgical procedure (eg, placement of a central venous access port) ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of study drug; in all cases, the patient must be sufficiently recovered and stable before treatment administration.
15. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.
16. Hospitalization for bowel obstruction within 12 weeks prior to enrollment.

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient randomized into the study.

**Enrollment/ Randomization and Study Treatment**

For the Double-blind Treatment Phase, eligible patients will be randomized 4:4:1:1 to the following arms: Arm A: rucaparib + nivolumab (n = 400), Arm B: rucaparib + IV placebo (n = 400), Arm C: oral placebo + nivolumab (n = 100) or Arm D: placebo (oral and IV) (n = 100).

Randomization will occur by a central randomization procedure using interactive response technology (IRT). The following will be included as randomization stratification factors at study entry to ensure treatment groups are balanced:

- 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)
- Timing of surgery (primary surgery vs. interval debulking)

Rucaparib 600 mg, or matching placebo, is administered orally BID (as close to 12 hours apart as possible, preferably at the same times every day) with at least 8 ounces (240 mL) of water starting on Day 1. Oral study drug may be taken with or without food. Rucaparib, or matching placebo, will be provided as 200, 250, and 300 mg (as free base) dose strength tablets.

Nivolumab, or matching placebo, is administered as 480 mg via a 30-minute IV infusion on Day 1 of every 4-week cycle, starting with Cycle 2.

Patients will receive both study drugs for a maximum of 24 months after initiation of oral/IV combination study treatment, or until disease progression by RECIST as assessed by the investigator, unacceptable toxicity, or other reason for discontinuation, whichever occurs first. Treatment interruption or dose reduction of oral study drug are permitted in the

event of unacceptable toxicity. Doses of IV study drug may be interrupted or delayed, but may not be reduced.

Prior to randomizing patients in the Double-blind Treatment Phase of the study, an open-label safety cohort will enroll and evaluate a minimum of 6 patients; patients who provide informed consent and meet all eligibility criteria will participate using the same study assessments as patients enrolled to the Double-blind Treatment Phase. Safety will be evaluated for this cohort after each patient has been dosed with the combination therapy for a minimum of 1 cycle.

Enrollment to a Japanese safety cohort will be conducted in the same manner as the initial safety cohort, for patients of Japanese ethnicity that meet all eligibility criteria, prior to randomizing any patients in Japan. Enrollment to this cohort will be contingent upon the determination of the monotherapy rucaparib dose in Japan.

**Withdrawal Criteria**

A patient must be discontinued from treatment with study drug if any of the following apply:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative.
- Progression of patient's underlying disease by RECIST v1.1 as assessed by the investigator unless patient is still receiving benefit from the study drug(s) according to the investigator, and the patient has provided additional consent.
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient.
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy.

**Efficacy Assessments**

Tumor assessment measurements will be performed at screening, at the end of every 12 weeks of treatment (up to 7 days prior permitted) relative to C2D1 for the first 3 years and then every 24 weeks thereafter until objective radiological disease progression, and as clinically indicated.

Disease assessment will comprise clinical examination and appropriate imaging techniques per RECIST v1.1 (computed tomography [CT] and/or magnetic resonance imaging [MRI] scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST). Other complementary studies (X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. CT/MRI scans of the chest, abdomen, and pelvis performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline. Investigators should perform scans of other anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status. Imaging guidelines provided by the BICR vendor should be followed for the collection of images and the radiological assessment of disease.

Tumor response will be interpreted using RECIST v1.1. Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified based on guidelines outlined in RECIST v1.1. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals (up to 7 days prior permitted) relative to C2D1 for the first 3 years and every 24 weeks thereafter until objective radiologic disease progression by RECIST v1.1, as assessed by the investigator, is documented, or initiating subsequent anticancer treatment.

Blood samples to assess CA-125 will be collected throughout the study and assessed by a central laboratory.

**Safety Assessments**

Safety and tolerability will be assessed based on the following:

- Incidence, type, seriousness, and severity of adverse events (AEs) reported;
- Clinical laboratory investigations (hematology, serum chemistry, urinalysis);
- Vital signs (blood pressure, heart rate, and body temperature);
- 12-lead electrocardiograms (ECGs);
- Physical examinations;
- ECOG performance status.

**Statistical Methods**

**Sample Size**

Approximately 1000 patients will be randomized in a 4:4:1:1 ratio to receive treatment with one 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 $LOH^{unknown}$), disease status (no residual disease vs. residual disease), and timing of surgery (primary surgery vs. interval debulking).

Two separate comparisons of the treatment arms will be evaluated independently, and at different timepoints based on the maturity of the parts of the study:

- Monotherapy: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV])
- Combination: Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo)

The level of statistical significance will be split into 2 so that each of the above comparisons will be made independently at a one-sided 0.0125 (two-sided 0.025) significance level.

The sample size is based on setting the power for each of the 2 independent treatment comparisons at 90% power. The power assumptions are based on the median PFS for patients in Arm A (oral rucaparib + IV nivolumab) from the total patient population (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 [oral rucaparib + IV placebo]) is expected to be about 20 months.

The following table provides the sample size and power for the combination treatment comparison of Arm A (oral rucaparib + IV nivolumab) to Arm B (rucaparib monotherapy) for the ITT Population.

| Group | Hazard Ratio | Cumulative N (4:4) | 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.

The following table provides the sample size and power for the monotherapy treatment comparison of Arm B (rucaparib monotherapy) to Arm D (placebo) for the HRD and ITT sub/populations.

| Group | Hazard Ratio | Cumulative N (4:1) | Number of Events | Median PFS (months) | Power | One-sided Alpha |
|---|---|---|---|---|---|---|
| **HRD** | 0.45 | 205 (164:41) | 123 | 12 vs 26.7 | 90% | 0.0125 |
| **ITT** | 0.60 | 500 (400:100) | 300 | 12 vs 20 | 90% | 0.0125 |

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

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

A minimum of 6 patients will be treated in a small, open-label safety cohort with rucaparib and nivolumab. Additionally, a minimum of 6 patients of Japanese ethnicity will be enrolled into an open-label safety cohort at investigational sites in Japan, contingent upon the recommended rucaparib dose in Japan. These 2 safety cohorts will be evaluated individually after each patient receives a minimum of one cycle of combination therapy.

**Efficacy Analysis**

Primary Efficacy Endpoint

The primary efficacy endpoint for the study is investigator-determined PFS (invPFS) by RECIST v1.1. Investigator-determined PFS is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by the investigator, or

death due to any cause, whichever occurs first.

Only tumor scans prior to the start of any subsequent anticancer treatment are considered for the primary endpoint. The primary endpoint is analyzed using both a stratified log-rank test and a Cox proportional hazard model comparing the treatment groups stratified by the randomization stratification factors (ie, 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]).

The stratified log-rank test will be used to calculate the hazard ratio (HR) between the treatment groups and will be used as the official test for the step-down procedure outlined below.

**Step-down Procedure to Adjust for Multiplicity**

The primary endpoint of invPFS and key secondary endpoints of OS and ORR will be tested among the HRD and ITT sub/populations for the monotherapy comparison and among the ITT Population for the combination comparison, using separate ordered step-down multiple comparison procedures.

That is, for the monotherapy treatment comparison, the invPFS in the HRD subpopulation will be tested first at a one-sided 0.0125 significance level. If invPFS in the HRD subgroup is statistically significant, then invPFS will be tested in the ITT Population. If both the HRD and ITT sub/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 sub/populations for that treatment comparison. If both the HRD and ITT sub/populations reach statistical significance, then testing will continue in an ordered step-down fashion 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 monotherapy treatment comparison.

Enrollment of tBRCA is much lower than originally anticipated in the sample size assumptions in the original protocol. Thus, the monotherapy treatment comparison will start with the HRD analysis population, then ITT Population for the step-down hierarchical testing. The tBRCA subgroup will be an exploratory endpoint for monotherapy treatment, in order to estimate the contribution within the HRD and ITT sub/populations.

For the combination treatment comparison, invPFS in the ITT Population will be tested first at a one-sided 0.0125 significance level. If invPFS is statistically significant, then the first secondary endpoint of OS will be tested at the one-sided 0.0125 significance level in the ITT Population and testing will continue in an ordered step-down fashion to the last key secondary endpoint of ORR. Once statistical significance is not achieved, the statistical significance will not be declared for subsequent analyses in the ordered step-down procedure for the combination comparison in the ITT Population. An exploratory endpoint evaluating efficacy within subgroups based on HRD, tBRCA, and PD-L1 for the combination treatment comparison will be evaluated.

<u>Secondary Efficacy Endpoints</u>

PFS as assessed by BICR review (bicrPFS) by RECIST will be tested as a stand-alone secondary endpoint, outside of the step-down procedure for multiplicity adjustment, due to

it being supportive of the primary endpoint. BicrPFS 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. Only tumor scans prior to start of any subsequent anticancer treatment are included.

OS is defined as the time from randomization to death due to any cause.

Analyses of ORR will be performed in the subgroup of patients with measurable disease at baseline and will be summarized with frequencies and percentages. DOR will be tested as a stand-alone secondary endpoint, outside of the step-down procedure for multiplicity adjustment. DOR is defined as the interval from the first documentation of objective response (RECIST v1.1) to the earlier of the first documentation of disease progression (per RECIST v1.1) or death from any cause.

**Safety Analyses**

All safety analyses will be presented by randomized treatment group for all patients in the safety population (ie, all treated patients). Any patients enrolled in the open-label safety cohorts will be included in this safety analysis population.

Adverse events, clinical laboratory results, vital signs, ECOG performance status, body weight, and concomitant medications/procedures will be tabulated and summarized. Adverse events will be summarized overall and separately for serious adverse events (SAEs), AEs leading to discontinuation/treatment interruptions/dose reductions, AEs leading to death, and NCI CTCAE v5.0 Grade 3 or higher AEs. Body weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum).

**Independent Data Monitoring Committee**

An IDMC will be established to review safety and efficacy data in compliance with a prospective charter. The IDMC will be comprised of 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.

Results from the open-label safety cohort(s) will be shared with the IDMC.

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.

**Steering Committee**

A Study Steering Committee, consisting of selected participating investigators representing Gynecologic Oncology Group (GOG) and the European Network for Gynecological Oncological Trial groups (ENGOT), will meet regularly to advise the sponsor regarding

| |
|---|
| study-related issues, including safety concerns. The Study Steering Committee will participate in a safety review of data from patients enrolled in the safety lead-in cohort(s). |
| **Date of Protocol Amendment 5 Approval**<br>16 June 2023 |

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| | |
|---|---|
| 2QW | twice a week |
| ADP | adenosine diphosphate |
| AE | adverse event |
| AESI | adverse event of special interest |
| AIDS | acquired immunodeficiency syndrome |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BCRP | breast cancer resistance protein |
| BER | base excision repair |
| BICR | blinded independent central review |
| bicrPFS | disease progression according to RECIST v1.1 as assessed by blinded central radiology review, or death from any cause; also known as irrPFS |
| BID | twice a day |
| BRCA1 | breast cancer susceptibility gene 1 |
| BRCA2 | breast cancer susceptibility gene 2 |
| BUN | blood urea nitrogen |
| C2D1 | Cycle 2 Day 1 |
| $C_{av,ss}$ | average nivolumab steady-state exposures |
| CA-125 | cancer antigen 125 |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CL | clearance |
| $CL_{ss}$ | steady-state clearance |
| $C_{max}$ | maximum concentration |
| $C_{max,ss}$ | steady-state maximal concentrations |
| $C_{min,ss}$ | steady-state trough concentrations |
| $CO_2/HCO_3^-$ | bicarbonate |
| CR | complete response |
| CRA | clinical research associate |
| CRO | contract research organization |
| CT | computed tomography |
| ctDNA | circulation tumor DNA |

| | |
|---|---|
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA | cytotoxic T-lymphocyte-associated protein 4 |
| CV% | percent coefficient of variation |
| CYP | cytochrome P450 |
| DDI | drug-drug interaction |
| DILI | drug-induced liver injury |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| DRESS | drug reaction with eosinophilia and systemic symptoms |
| ECG | electrocardiogram |
| ECL | electrochemiluminescent |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| $EC_{50}$ | half-maximal effective concentration |
| EMA | European Medicines Agency |
| ENGOT | European Network for Gynecological Oncological Trial groups |
| EOC | epithelial ovarian cancer |
| EQ-5D-5L | Euro-Quality of Life 5D-5L |
| EU | European Union |
| FACT-O | Functional Assessment of Cancer Therapy - Ovarian |
| FDA | Food and Drug Administration |
| FFPE | formalin-fixed paraffin-embedded |
| FIGO | International Federation of Gynecology and Obstetrics |
| fT3 | free thyroxine |
| fT4 | free triiodothyronine |
| FTC | fallopian tube cancer |
| gBRCA | germline BRCA |
| GBS | Guillain-Barre Syndrome |
| GCIG | Gynecologic Cancer Intergroup |
| GCP | Good Clinical Practice |
| GFR | glomerular filtration rate |
| GOG | Gynecological Oncology Group |
| H&E | hematoxylin and eosin |
| HGSOC | high grade serous ovarian cancer |
| HIPAA | Health Information Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |

| | |
|---|---|
| HRD | homologous recombination deficiency |
| HRQoL | Health-related Quality of Life |
| HRR | homologous recombination repair |
| HuMAb | human monoclonal antibody |
| IB | Investigator's Brochure |
| $IC_{50}$ | half-maximal inhibitory concentration |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IFN | interferon |
| IgG4 | immunoglobulin G4 |
| IMAE | immunotherapy-related adverse event |
| INN | International Nonproprietary Name |
| INR | international normalized ratio |
| invPFS | progression from disease according to RECIST v1.1 as assessed by the investigator, or death from any cause |
| I-O | immune-oncology |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| ITT | Intent-to-treat |
| IUD | intrauterine device |
| IUS | intrauterine system |
| IV | intravenous |
| LDH | lactate dehydrogenase |
| LOH | loss of heterozygosity |
| MATE | multidrug and toxin extrusion transporter |
| mCRPC | metastatic castration-resistant prostate cancer |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MG | myasthenia gravis |
| MRI | magnetic resonance imaging |
| NCI | National Cancer Institute |
| NGS | next-generation sequencing |
| NSCLC | non-small cell lung cancer |

| | |
|---|---|
| OCT | organic cation transporter |
| ORR | objective response rate |
| OS | overall survival |
| PARP | poly (adenosine diphosphate [ADP]-ribose) polymerase |
| PARPi | inhibitor of PARP enzyme |
| PD-1 | programmed death-1 cell surface membrane receptor |
| PD-L1/PD-L2 | ligands of PD-1 |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PFS2 | second event of progression-free survival |
| P-gp | P-glycoprotein |
| PK | pharmacokinetic(s) |
| PMDA | Japanese Pharmaceuticals and Medical Devices Agency |
| PPC | primary peritoneal cancer |
| PPI | proton pump inhibitors |
| PPK | population pharmacokinetics |
| PR | partial response |
| PRO | patient-reported outcome |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| Q4W | every 4 weeks |
| QD | once a day |
| RBC | red blood cell |
| RCC | renal cell carcinoma |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | statistical analysis software |
| sBRCA | somatic breast cancer gene 1 or 2 mutation |
| SCCHN | squamous cell carcinoma of the head and neck |
| SD | standard deviation |
| SFU1 | Safety Follow-up Visit 1 |
| SFU2 | Safety Follow-up Visit 2 |
| SJS | Stevens-Johnson Syndrome |
| SOC | system organ class |
| SOP | standard operating procedure |
| SUSAR | suspected unexpected serious adverse reaction |

| | |
|---|---|
| $t_{1/2}$ | half-life |
| tBRCA | tumor tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA |
| TCGA | The Cancer Genome Atlas |
| TEAE | treatment-emergent adverse event |
| TEN | toxic epidermal necrolysis |
| TIL | tumor infiltrating lymphocyte |
| TOI | trial outcome index |
| TMB | tumor mutational burden |
| TSH | thyroid stimulating hormone |
| UGT | uridinediphosphate-glucuronosyletransferase |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| USPI | United States prescribing information |
| v | version |
| VEGF | vascular-endothelial growth factor |
| $V_{ss}$ | volume of distribution at steady-state |
| WBC | white blood cell |

# 1 INTRODUCTION

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

## 1.1 Background

Globally, ovarian cancer is the seventh most common cancer and the eighth leading cause of cancer death among women, responsible for approximately 150,000 deaths each year.[13] The median age at presentation of epithelial ovarian cancer (EOC) is 60 years. Unfortunately, because of delayed presentation and diagnosis, almost 70% of women with ovarian cancer are diagnosed in the later stage of disease (III/IV), and these women have particularly poor outcomes.[14] Approximately 90% of ovarian tumors are surface epithelial in origin, and the papillary serous histology subtype accounts for approximately 75%, of which the large majority (70%) is high-grade.[15] The site of origin of EOC remains unclear. Some studies suggest that serous EOC and primary peritoneal cancer (PPC) arise from the fallopian tube epithelium; however, other studies suggest an origin within stem cells of the ovarian surface epithelium.[15-18] EOC, PPC and fallopian tube cancer (FTC) behave very similarly and are therefore treated in the same way.

The standard approach to treatment of advanced ovarian cancer is cytoreductive surgery (either at time of diagnosis or interval debulking), with the goal of minimizing residual tumor to no visible residual disease, a major prognostic indicator for improved survival. Six to 8 cycles of platinum and taxane-based chemotherapy is the global standard of care. If initial cytoreduction is not performed, interval debulking surgery is considered. This surgery may be carried out after 3 or 4 cycles of primary chemotherapy, followed by 3 further cycles of chemotherapy. Platinum analogues, such as carboplatin and cisplatin, are the most active agents, mediating their effects through the formation of inter- and intra-strand cross links with deoxyribonucleic acid (DNA).[15,19] Despite a 70% to 80% initial response rate, most women with advanced ovarian cancer will experience disease relapse, usually within 15 months of initial diagnosis.

Maintenance therapy following a response to standard treatment provides an opportunity to extend the disease-free period. Maintenance strategies in ovarian cancer initially focused on the prolonged use of single-agent chemotherapy, anti-angiogenesis agents, hormonal therapy, vaccines, and intraperitoneal chemotherapy. The OCEANS study evaluated carboplatin and gemcitabine with or without bevacizumab as part of the initial treatment and then as maintenance in women with platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer who were in their first relapse following primary chemotherapy.[20] The addition of bevacizumab resulted in a statistically significant improvement in progression-free survival (PFS) (median 12.4 vs. 8.4 months; hazard ratio [HR] = 0.484 [95% confidence interval (CI), 0.388-0.605; log-rank $p < 0.00001$]). The PFS benefit of bevacizumab administered together with chemotherapy followed by single-agent bevacizumab maintenance treatment compared to chemotherapy alone and placebo maintenance was further established in 2 front-line Phase 3 studies, respectively, Gynecological Oncology Group-218 (GOG-218; median PFS 14.1 vs.

10.3 months; HR = 0.717 [95% CI, 0.625-0.824; log-rank p < 0.001])[21] and ICON-7 (median PFS 19.0 vs. 17.3 months, HR = 0.81 [95% CI, 0.70-0.94; log--rank p < 0.004]).[22] Based on these studies, the European Medicines Agency (EMA) approved bevacizumab, in combination with carboplatin and paclitaxel, for front-line treatment of advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III B, III C and IV) epithelial ovarian, fallopian-tube, or primary peritoneal cancer and in combination with carboplatin and gemcitabine, for treatment of first recurrence of platinum-sensitive epithelial ovarian, fallopian-tube or primary peritoneal cancer in women who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF-receptor-targeted agents. Notably, only a study adding bevacizumab to chemotherapy in the recurrent setting (GOG-213) showed an extension of median overall survival (OS) in patients who received bevacizumab combined with chemotherapy treatment (42.2 months) versus the chemotherapy arm (37.3 months; HR = 0.83, p = 0.056). The median PFS benefit in this study was 3.4 months with the addition of bevacizumab to chemotherapy compared to chemotherapy alone (median PFS 13.8 vs. 10.4 months; HR = 0.61 [95% CI, 0.51-0.72, p < 0.0001]).[23]

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor maintenance therapy has also been evaluated as a strategy for improving outcomes in recurrent, second-line and beyond, platinum-sensitive ovarian cancer. Three randomized, double-blind studies have demonstrated statistically significant improvements in median PFS as compared to placebo in the intent-to-treat (ITT) population regardless of breast cancer gene (BRCA[1])1/2 mutation or homologous recombination deficiency (HRD) status.

PARP maintenance was first evaluated in a Phase 2, randomized study, Study 19. This study demonstrated an improved median PFS in those treated with olaparib versus placebo in patients with a BRCA mutation (11.2 vs. 4.3 months; HR 0.18 [95% CI, 0.10-0.31; p < 0.0001]) and the ITT Population (8.4 vs. 4.8 months; HR 0.35 [95% CI 0.25–0.49; p < 0.001]).[24,25] A Phase 3 study of niraparib vs. placebo (NOVA) demonstrated a statistically significant improvement in median PFS, as assessed by blinded independent central review (BICR), in the germline BRCA (gBRCA) cohort (21.0 vs. 5.5 months; HR 0.27 [95% CI, 0.17-0.41; p < 0.001]) and the non-gBRCA cohort (9.3 vs. 3.9 months; HR 0.45 [95% CI, 0.34-0.61; p < 0.001]).[26] A sensitivity analysis of investigator-assessed PFS (invPFS) also showed a PFS benefit in the gBRCA cohort (14.8 vs. 5.5 months; HR 0.27 [95% CI, 0.182-0.401; p < 0.0001]) and the non-gBRCA cohort (8.7 vs. 4.3 months; HR 0.53 [95% CI, 0.405-0.683; p < 0.0001]).[27] ARIEL3, the Phase 3 study assessing rucaparib versus placebo, also demonstrated benefit in this setting with statistically significant improvements in PFS in patients with a BRCA mutation (median PFS 16.6 vs. 5.4 months) and the ITT group (10.8 vs. 5.4 months; Table 1).[28] Analysis of the key secondary endpoint, PFS, as assessed by BICR, were consistent and showed a benefit in the BRCA cohort, as well as the ITT Population in patients treated with rucaparib versus placebo. Results of a randomized, Phase 3 SOLO2 study also showed a significant improvement in median invPFS with

[1] The typical convention is to use italicized names for genes and plain text names for proteins. However, in this document, BRCA mutations which occur at both the gene and protein level are often discussed. Therefore, for enhanced readability, BRCA is written in plain text only throughout this document.

olaparib maintenance vs. placebo in patients with platinum-sensitive ovarian cancer with gBRCA mutations (19.1 vs. 5.5 months; HR 0.30 [95% CI 0.22-0.41; p < 0.0001).[29]

**Table 1. Progression-free Survival per Investigator and per BICR in Primary Analysis Populations in Study CO-338-014**

| Analysis Population | PFS by Investigator Review (Primary Endpoint) | | PFS by BICR (Key Secondary Endpoint) | |
|---|---|---|---|---|
| | Median PFS (months) Rucaparib vs Placebo | Hazard Ratio | Median PFS (months) Rucaparib vs Placebo | Hazard Ratio |
| **Primary Analysis Groups** | | | | |
| tBRCA (rucaparib n = 130; placebo n = 66) | 16.6 vs 5.4 (p < 0.0001)[a] | 0.231 (p < 0.0001)[b] | 26.8 vs 5.4 (p < 0.0001)[a] | 0.201 (p < 0.0001)[b] |
| HRD (rucaparib n = 236; placebo n = 118) | 13.6 vs 5.4 (p < 0.0001)[a] | 0.317 (p < 0.0001)[b] | 22.9 vs 5.5 (p < 0.0001)[a] | 0.336 (p < 0.0001)[b] |
| ITT (rucaparib n = 375; placebo n = 189) | 10.8 vs 5.4 (p < 0.0001) | 0.365 (p < 0.0001)[b] | 13.7 vs 5.4 (p < 0.0001)[a] | 0.354 (p < 0.0001)[b] |
| **Exploratory Analysis of Non-nested Subgroups** | | | | |
| Non-tBRCA LOH+[c] (rucaparib n = 106; placebo n = 52) | 9.7 vs 5.4 (p < 0.0001)[a] | 0.440 (p < 0.0001)[b] | 11.1 vs 5.6 (p = 0.0114)[a] | 0.554 (p = 0.0135) |
| Non-tBRCA LOH-[c] (rucaparib n = 107; placebo n = 54) | 6.7 vs 5.4 (p = 0.0040)[a] | 0.583 (p = 0.0049)[b] | 8.2 vs 5.3 (p = 0.0002)[a] | 0.470 (p = 0.0003) |

Abbreviations: BICR = blinded independent central review (analogous to the term independent radiology review [IRR]); HRD = homologous recombination deficiency; ITT = intent-to-treat; LOH = loss of heterozygosity; PFS = progression-free survival; tBRCA = deleterious tumor alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA.

[a] Stratified log-rank analysis.

[b] Cox proportional hazard model.

[c] LOH+ and LOH- was the terminology used in the ARIEL3 study and is analogous to $LOH^{high}$ and $LOH^{low}$ used in the current ATHENA study.

Despite advances in treatment, including targeted therapies such as anti-angiogenesis agents and PARP inhibitors for advanced treatment settings, there has been little improvement in ovarian cancer outcomes, highlighting a clear need for new and more effective primary treatments for patients with advanced ovarian cancer.[30,31]

### 1.1.1 Rucaparib

Rucaparib is a potent, oral small molecule inhibitor of PARP enzymes (PARPi), including PARP-1, PARP-2, and PARP-3, that play a critical role in base excision repair (BER).[1]

When PARP function is impaired, double-stranded DNA breaks accumulate in the absence of effective BER; in cells deficient in homologous recombination, these breaks cannot be accurately repaired, resulting in synthetic lethality.[2] An analysis of the Cancer Genome Atlas (TCGA), which examined molecular changes associated with high-grade serous ovarian cancer (HGSOC), estimated that approximately 50% of patients with HGSOC have HRD.[4] Approximately, 1 in 4 women with ovarian cancer may have a BRCA mutation.[32] Germline mutations in the BRCA1 and BRCA2 genes (gBRCA) are the strongest known hereditary factors and occur in 18% of all ovarian, fallopian tube, and primary peritoneal cancers.[32-34] These patients carry heterozygous deleterious mutations in their germline DNA and develop tumors when the remaining wild-type functional allele is inactivated (ie, "second hit"). Acquired BRCA1/2 mutations, known as somatic mutations (sBRCA), also account for approximately 6 to 8% of HGSOC patients.[4,32,35]

While mutations in BRCA1 and BRCA2 are gene mutations most commonly associated with HRD, other essential homologous recombination repair (HRR) proteins may be mutated or functionally deficient in ovarian cancer. Over the past decade, it has been determined that patterns of genomic loss of heterozygosity (LOH) can predict HRD.[3] Comprehensive genomic profiling based on next-generation sequencing (NGS) can be utilized to identify non-BRCA patients with HRD. The main advantage of detecting tumor genomic LOH is that it can identify HRD tumors regardless of the underlying mechanisms.[3,12] An analysis of mature data from previous rucaparib clinical studies which enrolled platinum-sensitive patients, suggested that an LOH cut-off of 16% or greater for the BRCA wild-type subgroup provided the optimum discrimination of rucaparib treatment benefit; this group is referred to as LOH-high or the non-tBRCA LOH$^{high}$ subgroup.[28,36] Accordingly, the patients participating in this study with non-BRCA tumors will be categorized into 1 of 3 HRD groups: non-tBRCA LOH$^{high}$ (LOH ≥16%), non-tBRCA LOH$^{low}$ (LOH < 16%), or non-tBRCA LOH$^{unknown}$.

Rucaparib has shown preclinical and clinical activity in cancers associated with a deleterious mutation in BRCA1/2 or other HRR genes and/or genomic LOH.[36,37] The previous Sponsor, Clovis Oncology, Inc., focused clinical development efforts of oral rucaparib on the treatment of cancer associated with HRD, defined by the presence of a deleterious BRCA1 or BRCA2 mutation or other deleterious mutation associated with HRD, and/or high percentage of genome-wide LOH, which is a phenotypic consequence of HRD. Although HRD was predictive of response to rucaparib, activity was also observed in HRD-negative patients, suggesting an incomplete understanding of the biomarkers responsible for PARPi sensitivity.

Rucaparib is approved in the United States (US) for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.[38-40] Rucaparib is additionally approved in the US for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.[38,39] Rucaparib is approved in the European Union (EU) and the United Kingdom (UK) as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy.[40-42]

Summaries of approvals (above) and overviews of data from nonclinical and clinical studies (below) are described in detail in the rucaparib Investigator's Brochure (IB). A summary of the benefit: risk is also provided in the rucaparib IB.

#### 1.1.1.1 Nonclinical Experience

The results from nonclinical studies are consistent with the mechanism of action and pharmacological effects of PARP inhibition.

Pharmacological assessment demonstrated that rucaparib is a potent and selective inhibitor of PARP-1, PARP-2, and PARP-3 and has robust and durable in vitro and in vivo activity in multiple BRCA1/2 mutant cell lines and xenograft models. Rucaparib was also active in a BRCA wild-type model, consistent with in vitro data suggesting that rucaparib is active in cells with other defects in HRR through synthetic lethality. In vitro screens suggested that rucaparib has a limited potential for off-target effects. Safety pharmacology studies suggest that when given orally, rucaparib poses a low risk for causing neurobehavioral and cardiac effects in patients.

In pharmacokinetic (PK) studies, rucaparib demonstrated species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. In vitro data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and dogs. Rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UDP-glucuronosyltransferase 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1), and may inhibit P-gp and BCRP in the gut.

Oral dosing of rucaparib in single and repeat dose toxicity studies in rats and dogs resulted in toxicity to the hematopoietic, lymphopoietic, and gastrointestinal systems. These toxicities were generally both reversible upon recovery and predictive of toxicities observed in patients. Rucaparib was shown to be clastogenic in an in vitro chromosomal aberration assay suggesting potential genotoxicity in humans. Reproductive and development toxicity studies in rat showed that rucaparib caused maternal toxicity and was embryo-toxic. Although no rucaparib related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility.[43-46]

#### 1.1.1.2 Clinical Experience

Rucaparib is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer with and without evidence of HRD. Rucaparib clinical studies have/are evaluating patients with relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer in both the treatment and maintenance settings.

Rucaparib is being evaluated as treatment for patients with metastatic castration-resistant prostate cancer (mCRPC), both as monotherapy and in combination with nivolumab.

Clinical pharmacology studies in patients with advanced solid tumors continue to more fully characterize rucaparib drug-drug interactions, mass balance and drug metabolism, as well as PK in special populations are ongoing.

Additional studies of rucaparib as monotherapy and in combination with other anticancer therapies are planned in ovarian and prostate cancer, as well as other tumor types.

#### 1.1.1.2.1 OVERVIEW OF PHARMACOKINETICS AND DRUG-DRUG INTERACTIONS

Assessment of rucaparib PK in cancer patients showed an approximate dose proportional exposure after once daily (QD) or twice a day (BID) dosing, rapid absorption with $C_{max}$ achieved within 1.5 to 6 hours, and distribution into tissue. The oral bioavailability was 36% and elimination half-life ($t_{1/2}$) ranged from 11 to 29.8 hours. Rucaparib was moderately bound to human plasma proteins in vitro (70%). The steady-state was achieved following 1 week of dosing with rucaparib BID, with approximately 4-fold accumulation.

At a dose of 600 mg BID rucaparib, steady state was achieved after approximately 1 week. A high-fat meal increased the $C_{max}$ and area under the curve $(AUC)_{0\text{-}24h}$ of rucaparib by 20% and 38%, respectively, as compared with that under fasted conditions.

In vitro, rucaparib showed slow enzymatic turnover in human liver microsomes and hepatocytes. Recombinant CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, were able to metabolize rucaparib.

Drug interactions with rucaparib as a substrate were assessed in a population PK (PPK) analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultrarapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyper-inducers) did not significantly impact the steady-state exposure of rucaparib at 600 mg BID. Concomitant administration of strong CYP1A2 or CYP2D6 inhibitors did not significantly impact rucaparib PK. Current smokers had overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play limited role in rucaparib metabolism, and no rucaparib dose adjustment is needed when concomitantly administered with CYP inhibitors.

Concomitant treatment with proton pump inhibitors (PPIs) showed no clinically significant effect on rucaparib PK. No dose modification of rucaparib is required for patients who are receiving concomitant treatment with a PPI.

Results from Study CO-338-044 evaluating potential drug-drug interactions (DDI) with rucaparib, indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on P-gp. Caution should be exercised in the concomitant use of drugs that are substrates of the above CYP enzymes with narrow therapeutic windows.

#### 1.1.1.2.2 OVERVIEW OF EFFICACY

##### 1.1.1.2.2.1 Ovarian Cancer Treatment Indication

On 19 December 2016, the US Food and Drug Administration (FDA) granted accelerated approval for the marketing of rucaparib (Rubraca®) for monotherapy treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥ 2 chemotherapies. The recommended dose of rucaparib is 600 mg BID. The basis for the approval of rucaparib as monotherapy for the treatment of ovarian cancer are the datasets and analyses for patients with EOC, FTC, or PPC comprising the primary efficacy analysis population. The primary efficacy analysis population included 106 patients pooled from the open-label, single-arm Phase 2 studies, Study CO-338-010 (Study 10) Part 2A and Study CO-338-017 (ARIEL2) Parts 1 and 2, with BRCA-mutant ovarian cancer (EOC, FTC, or PPC), who had received ≥ 2 prior chemotherapy regimens, at least 2 of which were platinum-based, and who had received at least 1 dose of 600 mg rucaparib.[47]

The primary outcome measure on which approval was based is investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), with ORR by central independent radiological review conducted as a supportive analysis. ORR by investigator was 53.8%, while ORR by independent review was 41.5%, confirming the results of investigator assessment for this endpoint.[48] Responses were durable, indicated by a duration of response (DOR) by investigator assessment of approximately 9.2 months.

Study CO-338-043 (ARIEL4) was conducted as a confirmatory study comparing rucaparib to chemotherapy in patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥ 2 chemotherapies. Clovis voluntarily withdrew this indication in the US, Europe, UK, and Israel in 2022 based on the detriment in OS observed for patients randomized to rucaparib versus chemotherapy ARIEL4.

##### 1.1.1.2.2.2 Rucaparib as Maintenance Treatment in Ovarian Cancer

Rucaparib monotherapy for treatment of patients with advanced ovarian cancer in the maintenance setting demonstrated significant benefit of rucaparib compared to placebo across primary, secondary, and exploratory endpoints in the randomized, placebo-controlled Phase 3 study, Study CO-338-014 (ARIEL3).[23] In this study, investigator-assessed PFS (invPFS) was the primary efficacy endpoint, with PFS by BICR (bicrPFS) conducted as a key, stand-alone, secondary endpoint. Rucaparib maintenance treatment significantly improved PFS compared with placebo in all primary analysis groups of patients with recurrent ovarian cancer after a complete or partial response to platinum-based therapy (Table 1). Overall, rucaparib as maintenance treatment reduced the risk of progression or death by 63.5% (HR 0.365 [95% CI, 0.295-0.451]; $p < 0.0001$) in the ITT Population, demonstrating a strong treatment effect over placebo. Analysis of non-nested, non-overlapping patient subpopulations indicate that the significant improvement in PFS observed in the ITT Population was not driven only by the HRD or tBRCA (tumor tissue

deleterious alteration in BRCA1 or BRCA2) subpopulations. Nearly half (44.6%) of the ITT patients in the rucaparib group showed benefit at 1 year compared to 8.8% in the placebo group.[28] At 18 and 24 months, 32.0% and 26.0%, respectively, of patients who received rucaparib were still progression-free compared to 5.8% and 2.6% in the placebo group. These investigator-assessed results were confirmed by results of BICR.

The ORR per RECIST v1.1, as assessed by the investigator, was analyzed in the subgroup of patients who had measurable disease (ie, measurable target lesions) at baseline. In the tBRCA population, the confirmed ORR was 15/40 (37.5%) for the rucaparib group and 2/23 (8.7%) for the placebo group (p = 0.0055). In the HRD population, the confirmed ORR was 23/85 (27.1%) for the rucaparib group and 3/41 (7.3%) for the placebo group (p = 0.0031), and in the ITT Population, the confirmed ORR was 26/141 (18.4%) for the rucaparib group and 5/66 (7.6%) for the placebo group (p = 0.0069).

Results of the exploratory endpoint of ORR, along with that of invPFS in the non-nested populations, demonstrated that rucaparib delayed disease recurrence and showed a further response to rucaparib treatment in patients with measurable disease in women with advanced ovarian cancer.

#### 1.1.1.2.3 OVERVIEW OF SAFETY

Results of a recent integrated safety analysis in over 1500 patients with ovarian cancer who received 600 mg BID rucaparib in clinical trials, including ARIEL3, showed that the most common TEAEs reported were primarily mild to moderate (Grade 1 to 2) in severity and include gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, anemia/decreased hemoglobin, ALT/AST increased, decreased appetite, and dysgeusia.[38] The most common TEAEs ≥ Grade 3 include anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin (and associated increase in mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]), increased ALT, increased AST, and increased serum creatinine, most commonly occurring. Decreased platelets, neutrophils, leukocytes, lymphocytes, and increased cholesterol were observed to a lesser extent. The transient elevations in ALT/AST with rucaparib treatment in either the treatment or maintenance settings were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity and generally resolved over time. Furthermore, no cases met Hy's law criteria for drug-induced liver injury (DILI)[49,50], and few patients discontinued rucaparib due to ALT/AST elevations.[28,48] Similarly, elevations in creatinine were self-limiting and stabilized over time. The majority of creatinine elevations were Grade 1 or Grade 2. Elevated serum creatinine levels resolved upon interruption or discontinuation of rucaparib, were not accompanied by changes in blood urea nitrogen (BUN), and did not lead to discontinuation of rucaparib treatment. Increased creatinine with rucaparib treatment is likely due to the potent inhibition by rucaparib of MATE1 and MATE2-K renal transporters (Section 1.1.1.1).

Effects on cardiac channel activity in vitro and a comprehensive assessment of the effects of rucaparib on electrocardiogram (ECG) parameters in cancer patients demonstrated a low risk of cardiac effects by rucaparib.

#### 1.1.1.2.3.1 Safety: Events of Special Interest

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESI), as these events have been observed in patients exposed to cytotoxic chemotherapy (eg, platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, and in some cases a deleterious BRCA mutation, which increases risk for developing cancer(s). Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib.

Adverse events (AEs) of pneumonitis have been reported with PARP inhibitor treatment, including in clinical trials evaluating rucaparib. Currently, however, there is a lack of understanding of a mechanistic link between pneumonitis and PARP inhibitor treatment, and causality assessment is often confounded by lack of a consistent clinical pattern as well as other pre-disposing factors, such as cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy. pharmaand GmbH (pharma&) is seeking to understand whether or not there is a relationship between pneumonitis and rucaparib treatment; thus, pharma& is designating pneumonitis as an AESI to gather data to enable a thorough evaluation and assessment of the event and associated terms specified in Section 8.7.

More information on AESIs experienced by patients in rucaparib clinical studies is provided in the rucaparib IB.

### 1.1.2 Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb; IgG4-S228P) that binds to the programmed death-1 (PD-1) cell surface membrane receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-medicated inhibition of the immune response, including anti-tumor immune response.

Nivolumab (OPDIVO®) is approved as monotherapy and in combination with other therapeutic agents in multiple regions, including the US[51] and EU[52]. Indications include unresectable or metastatic melanoma, adjuvant treatment of melanoma, metastatic non-small cell lung cancer (NSCLC), advanced renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC), and esophageal cancer. In addition, nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma, unresectable pleural mesothelioma, hepatocellular carcinoma (HCC), RCC, and NSCLC, in

combination with cabozantinib for RCC, and in combination with chemotherapy for gastric cancer, gastroesophageal cancer (GEJ), and esophageal adenocarcinoma (excluding EU) in multiple countries, including the US and EU. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies for the treatment of several types of cancer.

Refer to the current OPDIVO® US Prescribing Information (USPI) and European Union (EU) Summary of Product Characteristics (SmPC) for updated indications and recommended dosage.

The approved recommended dose of nivolumab as monotherapy is 3 mg/kg or 240 mg administered intravenously over 60 minutes every 2 weeks.

Overviews of results/data from nonclinical and clinical studies are provided below and described in detail in the nivolumab IB and the current prescribing information for nivolumab (SmPC,[52] USPI,[51] or country-specific label) for more information.

#### 1.1.2.1 Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[53-55] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[56] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD-28, CTLA 4, ICOS, and BTLA.[57] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ), and Bcl-xL. PD-1 expression also has been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice, which develop a variety of autoimmune phenotypes.[58] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab binds to PD-1 with high affinity (half-maximal effective concentration [$EC_{50}$] 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (half-maximal inhibitory concentration [$IC_{50}$] ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA 4, and BTLA.

Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus re stimulation assay with human peripheral blood mononuclear cells, the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV-specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[59]

#### 1.1.2.2 Nonclinical Experience

No mass balance or metabolism studies with nivolumab have been conducted in animals. The expected in vivo degradation of monoclonal antibodies is to small peptides and amino acids via biochemical pathways that are independent of drug metabolism enzymes.

No formal PK drug-drug interaction (DDI) studies have been conducted with nivolumab. Nivolumab is not expected to have any effect on CYP P450 or other drug metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce these types of PK-based drug interactions.

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice a week (2QW) for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.

Administration of nivolumab at up to 50 mg/kg twice 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg. Specifically, increased developmental mortality was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.[60] Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore, nivolumab has the potential to be transmitted from the mother to the fetus.

#### 1.1.2.3 Clinical Experience

The PK, clinical activity, and safety of nivolumab have been assessed in patients with NSCLC, melanoma, clear-cell RCC, classical Hodgkin Lymphoma, urothelial carcinoma, SCCHN, in addition to other tumor types.

##### 1.1.2.3.1 OVERVIEW OF PHARMACOKINETICS

The PK of nivolumab was studied in patients with cancer over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction

(% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance ($CL_{SS}$) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state ($V_{SS}$) was 6.8 L (27.3%), and geometric mean elimination $t_{1/2}$ was 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks (Q2W), and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W.

Population PK (PPK) and exposure-response analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg every 3 weeks (Q3W), and 480 mg every 4 weeks (Q4W) dosing regimens in patients with cancer, in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for patients weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W. Using a PPK model, the overall distributions of nivolumab exposures ($C_{av,ss}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{min1}$) are comparable after treatment with either nivolumab 3 mg/kg or 240 mg Q2W. Following nivolumab 360 mg Q3W and 480 mg Q4W, $C_{av,ss}$ are expected to be similar to those following nivolumab 3 mg/kg or 240 mg Q2W, while $C_{min,ss}$ are predicted to be 6% and ~16% lower, respectively, and are not considered to be clinically relevant. Following nivolumab 360 mg Q3W and 480 mg Q4W, $C_{max,ss}$ are predicted to be approximately 23% and 43% greater, respectively, relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures (median and 90% prediction intervals) following administration of 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W regimens across the 35 to 160 kg weight range are predicted to be maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg nivolumab Q2W dosing regimen.

#### 1.1.2.3.2 OVERVIEW OF EFFICACY

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, classical Hodgkin Lymphoma, small-cell lung cancer, gastric cancer, SCCHN, urothelial cancer, hepatocellular carcinoma, and colorectal cancer. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.

In a small, open-label study conducted in Japan, Hamanishi, et al[61] assessed the safety and anti-tumor activity of nivolumab in 20 patients with platinum-resistant, recurrent, or advanced ovarian cancer. Patients received up to 6 cycles of nivolumab at 1 mg/kg (n = 10) or 3 mg/kg Q2W (n = 10) (4 doses per cycle) or until disease progression. The best ORR by RECIST v1.1 was 15% with 2 patients experiencing a durable complete response, and 4 patients achieving prolonged disease control. The activity of nivolumab was similar to what

has been observed with chemotherapy in the platinum-resistant setting.[62-64] However, the durability of the responses was atypical, and the results were promising in a heavily pretreated difficult to treat patient population. Notably, PD-L1 expression did not significantly correlate with response, highlighting the need to identify other markers that may be associated with activity.

#### 1.1.2.3.3 OVERVIEW OF SAFETY

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. As monotherapy, the most common adverse reactions (≥ 20%) were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, vomiting, and urinary tract infection.[51] The most common treatment-related AEs (≥ 10%) across all studies evaluating monotherapy nivolumab were diarrhea, fatigue, rash, and pruritus (refer to the nivolumab IB).

The nivolumab IB, the current prescribing information for nivolumab (SmPC, USPI, or country-specific label) should be consulted for regarding special warnings and precautions and specific guidance on treatment modifications.

The majority of treatment-related AEs observed with nivolumab treatment of ovarian cancer patients, including hypothyroidism and lymphocytopenia, had been reported in previous clinical studies of nivolumab in other solid tumors.[61] The most frequently observed AEs were those related to thyroid function; nearly all events were Grade 1. The frequency and severity of treatment-related AEs were not different between the 2 dose cohorts.

#### 1.1.2.3.4 IMMUNOGENICITY

Of 2085 patients who were treated with nivolumab 3 mg/kg Q2W and evaluable for the presence of anti-product antibodies, 233 patients (11.2%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in 15 patients (0.7%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-product binding antibody development based on the PPK and exposure-response analyses.

Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

### 1.1.3 PARP Inhibitors and Checkpoint Inhibitors

#### 1.1.3.1 Non-clinical Overview

Recent translational data suggest that ovarian cancer patients with a BRCA mutation may have a preferential response to immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway.[7] BRCA1 or BRCA2 mutant ovarian cancer patients have a higher number of protein coding mutations that can be potentially targeted by the immune system (termed

neoantigens), a higher expression of PD-1 and PD-L1 in intra-tumoral immune cells, and an elevated number of CD3-positive and CD8-positive tumor infiltrating lymphocyctes (TILs).[7] These data suggest that PD-1/PD-L1-targeting immunotherapies may preferentially benefit BRCA1 or BRCA2 mutant ovarian cancer patients. In addition, non-tBRCA patients with HRD that can be identified by a NGS HRD test may well preferentially benefit from PD-1/PD-L1-targeting agents.[36] Published data and internal data (Clovis Oncology, Inc.) have demonstrated a significant association between genomic LOH and protein coding mutations, which provides an estimate of the tumor mutational burden (TMB) that may predict response to immune checkpoint inhibitors.[11]

#### 1.1.3.2 Clinical Overview

The combination of immune checkpoint inhibitors and PARP inhibitors has been recently evaluated in 3 early-phase studies.[8,9,65] In a Phase 1 dose-escalation study of PD-L1 inhibitor, durvalumab, in combination with PARP inhibitor, olaparib, in 12 heavily pretreated participants (10 with ovarian cancer and 2 with triple-negative breast cancer), there were 4 participants with partial response (duration of response ≥ 15 months and ≥ 11 months) and 8 participants with stable disease ≥ 4 months (median, 8 months [4 to 14.5 months]), yielding an 83% disease control rate.[8] The most common treatment-emergent AE with durvalumab plus olaparib was hematologic toxicity, with no dose-limiting toxicity reported at the highest dose combination tested (olaparib 300 mg twice a day [BID] and durvalumab 1500 mg every 4 weeks [Q4W]).

In a Phase 1/1b study, the combination of anti-PD-1 BGB-A317 and PARP inhibitor BGB-290 was generally well tolerated in 43 participants with advanced solid tumors.[65] Liver-related AEs were observed in 12 participants; all events were reversible with or without corticosteroid treatment. Complete or partial response was observed in 11 participants, 4 of whom had confirmed partial response (PR) or complete response (CR); responses were durable and observed in participants with wild-type and mutant gBRCA status. Taken together, these studies have not identified any new safety signals with the combination of a PARP inhibitor and a PD-L1 inhibitor.

Preliminary data from an ongoing Phase 2 study of the combination of durvalumab and olaparib in an unselected population with mCRPC demonstrated that the combination was well-tolerated and there was evidence of durable activity.[9]

## 1.2 Rationale for the Study and Benefit-Risk Assessment

The purpose of this Phase 3 study is to evaluate the PFS of the combination of nivolumab and rucaparib in the front-line maintenance setting of advanced ovarian cancer.

There is a clear and urgent clinical need for novel therapeutic approaches in advanced ovarian cancer. Despite progress in therapy, ovarian cancer remains a major cause of death, with an estimated quarter of a million new cases per year worldwide and only 25% of patients with advanced ovarian cancer surviving long term.[13]

As discussed in Section 1.1, PARP inhibitors, including rucaparib, have demonstrated a clear extension of PFS in patients with platinum-sensitive disease in the second line and beyond

maintenance setting. In addition, the most mature maintenance study conducted with a PARP inhibitor (Study 19) recently showed an increase in median OS in patients treated with olaparib as compared to placebo in the BRCA mutation group (34.9 vs. 30.2 months; HR 0.62 [95% CI, 0.41-0.94; p = 0.025]) and the ITT Population (29.8 vs. 27.8 months, HR 0.73 [95% CI, 0.55–0.96; p = 0.025]) after the third interim analysis of OS.[66] Nivolumab has also shown dramatic durable responses in initial studies of recurrent ovarian cancer, including those with platinum-resistant disease (Section 1.1.2.3.2). Combining rucaparib with nivolumab in the front-line setting provides an opportunity to further extend PFS and to increase the degree of clinical responses and, therefore, has the potential to provide a more efficacious front-line maintenance treatment option.

The preclinical rationale for combining rucaparib with nivolumab is supported by emerging data that demonstrate an association between high neoantigen load and high expression of PD-1/PD-L1 in HRD tumors when compared with homologous recombinant-proficient ovarian cancers.[4-7] BRCA1 and BRCA2 mutations have been reported to increase the number of TILs and are associated with improved OS.[7] In addition, internal data (Clovis Oncology, Inc.) indicate a significant association between genomic LOH and TMB. A high TMB increases the likelihood of the development of tumor-specific neoepitopes that would confer clinical benefit from CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 blockade. Thus, it is hypothesized that increased DNA damage by PARP inhibition will increase the number of tumor neoantigens, creating a more antigenic environment in which to stimulate the immune microenvironment.

Monotherapy oral study drug will be administered in Cycle 1 prior to the initiation of the combination oral and IV study drug administration in Cycle 2 within this study to further explore the hypothesis that priming the TMB will enhance activity of the combination. In addition, this approach provides the opportunity to establish a baseline safety profile of the oral study drug for each patient prior to administering the IV study drug. Overall, the safety profiles of both rucaparib and nivolumab are manageable and generally consistent across completed and ongoing clinical studies. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. A pattern of immune-mediated adverse events (IMAEs) associated with nivolumab has been defined, for which management algorithms have been developed; these are provided in Appendix 7. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (in the case of endocrinopathy) as instructed in these algorithms.

Elevations in ALT, AST, and creatinine are commonly observed in patients receiving rucaparib and typically are observed beginning with Day 15 of the first cycle of treatment with rucaparib. The ALT/AST elevations typically peak after two weeks of dosing and are generally not accompanied by substantial concomitant elevation in bilirubin or alkaline phosphatase. There have been no cases of Hy's law observed across the clinical development program, and based on the data available to date, rucaparib does not appear to be associated with drug induced liver injury. In addition, mean creatinine values increase soon after initiation with rucaparib treatment but subsequently plateau. Creatinine elevation resolves with dose holds of rucaparib and recurs with rechallenge. Rucaparib associated creatinine elevation has not been associated with evidence or reports of permanent renal impairment. The increases in creatinine with rucaparib treatment is likely due to inhibition of MATE1/2K

renal transporters.[48] Elevations in ALT, AST, and creatinine are not typically observed with nivolumab treatment, however elevations in any of these laboratory parameters can be early signs of immune-mediated hepatitis or nephritis. Since Cycle 1 will only include oral study drug, this allows for Cycle 1 laboratory values to be assessed prior to initiation of the oral/IV study drug combination and ultimately should facilitate more accurate attribution to oral or IV study drug so the proper AE management algorithm may be followed.

Additional details on the safety profile of nivolumab and rucaparib, including results from other clinical studies, are also available in the respective drug IBs.

To assure an ongoing favorable risk/benefit assessment for participants enrolled into the present study, the following measures will be employed throughout the conduct of the study:

- Oral study drug administration will begin 28 days (1 cycle) prior to IV study drug administration to explore the hypothesis that priming the TMB with monotherapy rucaparib will enhance the activity in combination with nivolumab. It will also allow the baseline safety profile for oral drug to be established, which will guide appropriate AE management, if needed, during combination therapy.
- Institution of an Independent Data Monitoring Committee (IDMC) to provide independent oversight of safety, study conduct, and efficacy including regular and systematic reviews of safety data by treatment arm.
- Rigorous safety monitoring by the sponsor to ensure participants' safety, including close follow-up of reported safety events, and intensive site and study investigator training/education on the implementation of the nivolumab toxicity management algorithms and toxicity management of the rucaparib and nivolumab combination.
- An open-label safety cohort will be conducted to evaluate the safety of oral rucaparib (600 mg BID) and IV nivolumab (480 mg on Day 1 of every 28-day cycle).
- A Study Steering Committee (consisting of selected participating investigators) will meet regularly to advise the sponsor regarding study-related issues, including safety concerns.

In conclusion, the overall risk-benefit of nivolumab in combination with rucaparib in women with ovarian cancer is deemed acceptable. Detailed information about the known and expected benefits and risks and reasonably anticipated AEs of nivolumab and rucaparib may be found in their respective IBs.

## 1.3 Dose Rationale

### 1.3.1 Dose Rationale for Nivolumab

Nivolumab is currently approved for treatment of various tumors, using regimens that include nivolumab at doses of 240 mg Q2W, 480 mg Q4W, or 3 mg/kg Q2W as a single agent, and at 360 mg Q3W, 1 mg/kg Q3W, 3 mg/kg Q2W, or 3 mg/kg Q3W when used in combination with other therapeutic agents. Refer to the current prescribing information for dosing information.

The nivolumab dose of 480 mg Q4W was selected for this study based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses examining relationships between nivolumab exposures and efficacy and safety responses, using data from studies in multiple tumor types with body weight-normalized dosing (mg/kg). A flat dose of 480 mg Q4W is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provided numerous benefits to participants as they would have increased flexibility between clinical visits.

The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as body weight increased but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK.

Using the PPK and exposure-response models, nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following nivolumab 480 mg Q4W administration and compared to those following nivolumab 3 mg/kg Q2W administration. The overall distributions of average nivolumab steady-state exposures ($C_{av,ss}$) are comparable following administration with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W over a wide range of body weights. Nivolumab 480 mg Q4W administration is predicted to result in approximately 43% greater steady-state peak concentrations ($C_{max,ss}$) compared to nivolumab 3 mg/kg Q2W. Although the $C_{max,ss}$ of nivolumab is expected to be greater following nivolumab 480 mg Q4W compared to nivolumab 3 mg/kg Q2W, the predicted $C_{max,ss}$ following nivolumab 480 mg Q4W is well below the median $C_{max,ss}$ achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level across a wide body range (35 to 160 kg).

Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of AEs due to discontinuation or death, ≥ Grade 3 AEs, and ≥ Grade 2 immunotherapy-mediated AEs (IMAEs) are predicted to be similar following administration of nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. Safety analyses using available data following nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated there were no differences in AE profiles across body-weight groups. Finally, initial clinical evidence demonstrates that, following administration of nivolumab 480 mg Q4W, nivolumab is well tolerated.

Nivolumab 480 mg Q4W is predicted to have approximately 16% lower steady-state trough concentrations ($C_{min,ss}$) compared to nivolumab 3 mg/kg Q2W. While these exposures are predicted to be lower, they are on the flat part of the exposure-response curves and are not predicted to affect efficacy. Exposure-efficacy analyses of multiple PK measures and efficacy endpoints indicated that following administration of nivolumab 480 mg Q4W, efficacy is predicted to be similar to that following administration of nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.

Nivolumab at a dose of 3 mg/kg Q2W has been studied in Japanese patients with ovarian cancer and found to be tolerable and associated with responses (see Section 1.1.2.3.2).[61] In addition, nivolumab at a dose of 240 mg IV over 30 minutes Q2W is being studied in patients with advanced or recurrent ovarian cancer in a randomized Phase 3 study.[67] The ATHENA study will use a 480 mg Q4W regimen for all patients, which was selected based on the equivalence (as described above) to the approved dose of nivolumab in Japan (3 mg/kg Q2W) for 6 indications, including melanoma, lung, and gastric cancers.

Refer to the nivolumab IB for additional details.

#### 1.3.1.1 Rationale for Nivolumab 30-minute Infusion

Long infusion times place a burden on participants and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30-minute duration in participants will diminish the burden, provided there is no change in the safety profile. Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment durations. In Study CA209010 (a Phase 2, randomized, double-blind, dose-ranging study of nivolumab in participants with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1 to 2 and were manageable. An infusion duration of 30 minutes for 360 mg or 480 mg doses of nivolumab is not expected to present safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. Nivolumab 480 mg Q4W and nivolumab 360 mg Q3W infused over 30 minutes are also being investigated in several ongoing clinical studies. Overall, preliminary safety analysis suggests that the safety profile of nivolumab administered IV over 30 minutes at 480 mg Q4W or 360 mg Q3W is consistent with nivolumab 240 mg Q2W or 3 mg/kg Q2W administered IV over 30 or 60 minutes across multiple tumor types with respect to Grade 3 to 4 AEs, serious adverse events (SAEs), AEs leading to discontinuation, and IMAEs including hypersensitivity/infusion reaction IMAEs. There were no new safety concerns identified. For Study CA2099KD, the protocol specifies monitoring and management of safety events including nivolumab-related infusion reactions. In summary, nivolumab 360 mg Q3W or nivolumab 480 mg Q4W infused over 30 minutes is expected to provide a comparable safety profile to that seen with a 60-minute infusion, and is not expected to present additional safety concerns.

### 1.3.2 Dose Rationale for Nivolumab and Rucaparib Combination

The recommended starting dose of rucaparib is 600 mg BID administered orally.[47] Dose modifications should be implemented as described in Section 5.6.

The starting dose for the combination of nivolumab (or IV placebo) plus rucaparib (or oral placebo) in this study will be the same as the monotherapy arms. Rucaparib or matching placebo, will be administered orally at 600 mg BID (as close to 12 hours apart as possible) on a 28-day cycle. Nivolumab, or IV placebo, will be administered at 480 mg via a 30-minute IV infusion on Day 1 of every 28-day cycle, starting with Cycle 2. The mechanisms of action of the 2 agents are different, and their toxicities are not predicted to be cumulative. Extending

the dosing interval of IV study drug to every 4 weeks, as described above, provides a convenience to patients on a 28-day treatment cycle.

Further justification for these doses is provided based on previous early-phase clinical studies of PARP inhibitors plus PD-1/PD-L1 inhibitors as discussed in Section 1.1.3.2. A Phase 1 dose-escalation study of durvalumab in combination with olaparib in pretreated ovarian and triple-negative breast cancer patients was conducted.[8] The dose levels for this combination are also being evaluated in an ongoing Phase 2 study in participants with mCRPC and appears to be well tolerated, with the most common Grade 3/4 AEs also being hematologic toxicity.[9] These studies have not identified any new safety signals when giving PARP inhibitor and an anti-PD-L1 antibody in combination. The maximum tolerated dose (MTD) of the combination of rucaparib and another checkpoint PD-L1 inhibitor, atezolizumab, was recently achieved at the currently-approved dose of each agent (600 mg BID rucaparib and 1200 mg IV on Day 1 every 21 days) in an ongoing Phase 1/2 study (Study WO39409; internal data on file). Further, Study CA2099KD is an ongoing study in patients with prostate cancer to evaluate the combination of rucaparib and nivolumab, using the same doses of each agent that are proposed for this study. In addition, a small open-label safety lead-in will be performed prior to starting the randomized portion of this study. Further, establishment of baseline laboratory values for each patient following monotherapy oral drug and prior to beginning the combination therapy will help guide AE management during administration of the oral/IV combination therapy. The design is described in Section 3.1.3, and the analysis is described in Section 9.9.

Please see Section 5.6 regarding appropriate dose modifications of the study drugs.

## 1.4 Rationale for Duration of Treatment

### 1.4.1 Nivolumab

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary. Accumulating evidence from different clinical studies in different tumor types treated with nivolumab indicates that most of the responses are generally occurring early, with a median time to response of 2 to 4 months.[68-72] A recent analysis in a melanoma study suggests the majority of participants who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment. Furthermore, a limited duration of ipilimumab including only 4 induction doses resulted in long-term survival in participants with metastatic melanoma, with a sustained plateau in survival starting at around year 3.[73] For these reasons, in the current study, treatment with nivolumab (or IV placebo) will be given for up to 24 months after initiation of oral/IV combination study treatment, in the absence of disease progression, unacceptable toxicity, withdrawal of participant consent, or the end of the study, whichever occurs sooner.

### 1.4.2 Rucaparib

Rucaparib (or oral placebo) will be given initially as monotherapy and for up to 24 months in combination with nivolumab, or IV placebo in the absence of disease progression, unacceptable toxicity, withdrawal of participant consent, or the end of the study, whichever occurs sooner. The rucaparib duration of treatment was chosen to align with the duration of treatment for nivolumab (or IV placebo).

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is:

- To evaluate PFS by RECIST, as assessed by the investigator (invPFS) using the following separate comparisons:
  - Monotherapy: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV]) in the HRD and intent-to-treat (ITT) sub/populations
  - Combination: Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo) in the ITT Population

## 2.2 Secondary Objectives

The secondary objectives of this study, using the same comparisons as the primary objective, are:

- To evaluate PFS by RECIST, as assessed by the BICR (bicrPFS)
- To evaluate survival benefit
- To evaluate ORR and DOR, as assessed by the investigator, in patients with measurable disease at baseline
- To evaluate safety

## 2.3 Exploratory Objectives

Exploratory objectives in this study are:

- To evaluate PFS2 (PFS on the subsequent line of treatment)
- To evaluate the contribution of nivolumab monotherapy vs placebo (invPFS, bicrPFS, OS, ORR, DOR, safety)
- To evaluate the comparison of combination rucaparib + nivolumab vs placebo (invPFS, bicrPFS, OS, ORR, DOR, safety)
- To evaluate efficacy and safety in the tBRCA subgroup for the comparison of rucaparib vs placebo (invPFS, bicrPFS, OS, ORR, DOR, safety)
- To evaluate efficacy and safety in the HRD, tBRCA, and PD-L1 subgroups for the comparison of combination vs rucaparib (invPFS, bicrPFS, OS, ORR, DOR, safety)
- 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)

- To evaluate patient-reported outcome (PRO) utilizing the Euro-Quality of Life 5D-5L (EQ-5D-5L)
- To assess mutations in non-tBRCA (where tBRCA defines a tumor tissue alteration in BRCA1 or BRCA2) HRR genes as a molecular marker of efficacy
- To assess PD-L1 expression and TMB as molecular markers of efficacy
- 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

# 3 STUDY DESIGN

## 3.1 Overall Study Design and Plan

This is a randomized, multinational, double-blind, dual placebo-controlled, 4-arm, Phase 3 study evaluating rucaparib and nivolumab in combination and alone as switch maintenance therapy in newly diagnosed ovarian cancer patients who have completed first-line chemotherapy and who had a response.

### 3.1.1 Screening Phase

All patients will undergo screening assessments within 120 days prior to randomization.

The study will enroll patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who achieved either a CR or a PR, defined as RECIST v1.1 PR or a cancer antigen (CA-125) PR by Gynecologic Cancer Intergroup (GCIG) criteria,[74] 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. Prior hormonal therapy for previously-treated breast cancer is permitted.

Screening assessments will include demographics and medical history, prior treatments for serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (and other malignancies, if applicable), prior and current medications and procedures, 12-lead ECG, Eastern Cooperative Oncology Group (ECOG) performance status, central laboratory hematology and serum chemistry, and CA-125 measurement, urinalysis, physical examination, height, weight, and vital signs measurements, adverse events, radiologic assessment by computed tomography (CT) or magnetic resonance imaging (MRI), and a

blood sample for ctDNA analysis. PROs will be collected using the FACT-O and EQ-5D-5L instruments or other collection format, as appropriate. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable to be used as a study procedure only if confirmed to have been standard of care. With the exception of samples for urinalysis, all other samples collected will be analyzed by a central laboratory; a duplicate sample may be collected and analyzed by the local laboratory for immediate eligibility/ treatment decisions.

A patient 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 and other homologous recombination pathway genes, as well as those related to response or resistance to immunotherapies. The degree of tumor LOH will also be assessed for each patient.[3,10-12]

An analysis of mature data from previous rucaparib clinical studies that enrolled platinum-sensitive patients, suggested that a cut-off of 16% or greater for the BRCA wild-type, LOH-high (termed non-tBRCA LOH$^{high}$) subgroup provided the optimum discrimination of rucaparib treatment benefit.[28,36] Accordingly, the patients participating in this study with non-BRCA mutated tumors will be categorized into 1 of 3 HRD groups: non-tBRCA LOH$^{high}$ (LOH ≥ 16%), non-tBRCA LOH$^{low}$ (LOH < 16%), or non-tBRCA LOH$^{unknown}$.

The results from the NGS test will be utilized to stratify patients into one of the above subgroups, or the tBRCA subgroup, for randomization, as follows:

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

The complete results of the NGS-based test, which examines exons of 311 genes as well as introns of 35 genes, will be provided to all patients who opt to receive this information and provide appropriate consent. Tumor tissue results for the BRCA1/2 genes will be provided to patients who consent to receive this information upon availability. Results for the remainder of the gene panel will be provided to consenting patients upon study treatment discontinuation. Results are to be disclosed to consenting patients by the study physician as part of an overall clinical discussion. In the event a mutation associated with hereditary cancer or other syndrome is detected in tumor tissue, the patient may be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines.

Mutations detected in tumor tissue may be somatic or germline; however, the NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients at Cycle 1 Day 1 and stored. Prior to final efficacy analysis, genomic DNA may be subjected to

exploratory analysis in order to determine whether any mutation identified is of germline or somatic origin. This data may be provided to the investigator and/ or consented patient.

The sponsor will remain blinded to all NGS test results (including all tBRCA results), as well as existing BRCA data, with the exception of patients enrolled in the open-label safety cohort(s), until the primary efficacy analysis is conducted.

Enrollment will require sponsor (or designee) review of eligibility, including, but not limited to:

- The details for the front-line platinum-based regimen, including dates administered;
- Details of primary surgery and biopsies taken prior to neoadjuvant treatment (if applicable)
- Documentation supporting a CR by radiographic response or a PR by RECIST/ CA-125 GCIG response to most recent platinum-based treatment;
- Confirmation that sufficient tumor tissue was submitted for HRD stratification for randomization

The protocol eligibility worksheet and associated source documents will be saved in the eTMF for all patients unless retention of source documents is not allowed per local regulations.

### 3.1.2 Enrollment/ Randomization

Enrollment/ randomization to study treatment must occur within 8 weeks of the first day of the last cycle of chemotherapy and is described in more detail in Section 5.4. Study treatment must be initiated within 3 days of randomization.

### 3.1.3 Double-blind Treatment Phase

The Double-blind Treatment Phase will continue in 28-day treatment cycles. The first dose of oral study treatment will be administered on Cycle 1 Day 1 and continue BID throughout the cycle as monotherapy; IV study drug will begin on Cycle 2 Day 1 (C2D1). Details on study drug administration are described in Section 5.5. During the Double-blind Treatment Phase, patients will come into the study site for a visit on Day 1 and Day 15 of Cycles 1 and 2, and on Day 1 of every cycle thereafter. Study treatment will continue until 24 months after initiating oral/IV combination study treatment, disease progression, or unacceptable toxicity, whichever happens first.

During the Double-blind Treatment Phase (continuous 28-day treatment cycles), 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 and for PPK analyses.

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) relative to C2D1 (the first scan will be 16 weeks after initiation of oral study treatment) for the first 3 years 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 (Section 7.5.3.1). Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified based on guidelines outlined in RECIST v1.1. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST v1.1 per the protocol schedule of assessments. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, will be discontinued from treatment and enter follow-up. If the patient has met criteria for radiologic progression by RECIST, but the patient is still receiving benefit from the study drug(s) (eg, patient has mixed radiologic response or is continuing to have symptomatic benefit), according to the investigator, then continuation of treatment will be considered for a maximum cumulative duration of 24 months after initiation of oral/IV combination study treatment (see Section 5.13). Patients will continue to have all protocol-required assessments specified in the Schedule of Assessments (Table 5).

PRO assessment will occur on Day 1 of Cycles 1 through 3, Cycle 5, then every 12 weeks (aligning with tumor assessment scans) until treatment discontinuation or until the data cut-off for the primary endpoint analysis, whichever comes first.

All CT scans (and other imaging, as appropriate) performed during the treatment period and at treatment discontinuation will be collected for BICR.

Patients will be continuously monitored for safety. An IDMC with multidisciplinary representation will evaluate safety in compliance with a prospective charter.

### 3.1.4 End of Treatment

Upon treatment discontinuation, regardless of reason, patients will have an End-of-Treatment Visit. Assessments will include AEs, physical examination, vital signs and weight measurements, central laboratory hematology, serum chemistry, and CA-125 measurement, 12-lead ECG, ctDNA analysis, concomitant medications, therapies and procedures, ECOG performance status, disease status assessment (only if 12 weeks or more since last scan), study drug accountability, and PRO.

### 3.1.5 Open-label Safety Lead-in

Prior to the Double-blind Treatment Phase, a small, open-label safety cohort will be enrolled to assess the safety of the combination of rucaparib (600 mg BID) and nivolumab (480 mg IV on Day 1 of every 28-day cycle, starting with Cycle 2). The eligibility criteria and assessments for these patients will be the same as those described for patients enrolled in the

Double-blind Treatment Phase of the study. The safety cohort will consist of a minimum of 6 patients enrolled at sites from North America and/or Europe. A formal safety review will occur after the safety cohort has enrolled and patients have been treated with the combination for at least 28 days (ie, 1 cycle) and with oral study drug for 2 cycles. The review committee will include external experts and sponsor personnel (see Section 9.9). The data will also be shared with the Independent Data Monitoring Committee (IDMC; see below and Section 8.11). The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review.

The safety cohort will not be enrolled, and the study will proceed directly to the Double-blind Treatment Phase, if, at the time that the first study sites are activated, a minimum of 6 patients have been enrolled in the ongoing Phase 1/2 study in prostate cancer patients (Study CA2099KD [NCT03338790]) with the same rucaparib + nivolumab combination regimen, and the safety evaluation of these patients shows no new safety signals.

Once the evaluation of the safety cohort is complete, the double-blind portion of the study can be opened for randomization in all regions with the exception of Japan. Prior to randomizing any patients in Japan, a safety cohort of at least 6 patients of Japanese ethnicity will be enrolled at investigational sites in Japan. This enrollment is contingent upon determination of a monotherapy rucaparib dose that is currently being evaluated in a Phase 1 dose escalation study (Study CO-338-081) ongoing in Japan. Nivolumab at a dose of 480 mg Q4W will be used in this study and is based on equivalence to the approved dose of 3 mg/kg Q2W in Japan for numerous indications, including melanoma, lung, and gastric cancers. Evaluation of the Japanese safety cohort will proceed in the same manner as the initial safety cohort. Once the evaluation of the Japanese cohort is complete, the double-blind portion of the study can be opened for randomization in Japan.

### 3.1.6 Post-treatment Follow-up Phase

All patients will be followed for at least 5 months after the last IV dose of study treatment. Safety Follow-up Visit 1 (SFU1) should occur 28 days (± 7 days) after last dose of study drug (oral or IV, whichever is later) or can be performed on the date of discontinuation if that date is at least 28 days from the last dose. Assessments will include AEs, physical examination, vital signs and weight measurements, central laboratory hematology, serum chemistry, and CA-125 measurement, ECG, ctDNA analysis (SFU1 only), concomitant medications, ECOG performance status, therapies and procedures, study drug accountability, and PRO. Safety Follow-up Visit 2 (SFU2) should occur approximately 5 months (± 7 days) from the last IV dose of study drug. The same assessments performed at SFU1 will be performed at SFU2; however, chemistry and hematology are only necessary if toxicities are present. If a patient remains on oral study drug after discontinuation of IV study drug, the SFU2 can be performed at the next cycle visit, provided it has been at least 5 months since the last IV dose.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals relative to C2D1 (flexibility with scheduling within 1 week prior to planned imaging date is permitted) for the

first 3 years and every 24 weeks thereafter until objective radiological disease progression by RECIST v1.1 is documented, as assessed by the investigator.

An optional tumor biopsy will be collected from patients who experience disease progression/randomized treatment discontinuation and provide appropriate consent.

Patients will also be followed long-term for survival, subsequent treatments, and monitoring for secondary malignancy every 12 weeks (± 14 days) after SFU1 until death, loss to follow-up, withdrawal of consent, or study closure.

If a patient begins subsequent anticancer therapy, the sponsor will terminate collection of SAEs, with the exception of the AESIs of MDS and AML.

## 3.2 Removal of Patients from Therapy or Assessment

A patient must be discontinued from treatment with study drug if any of the following apply:

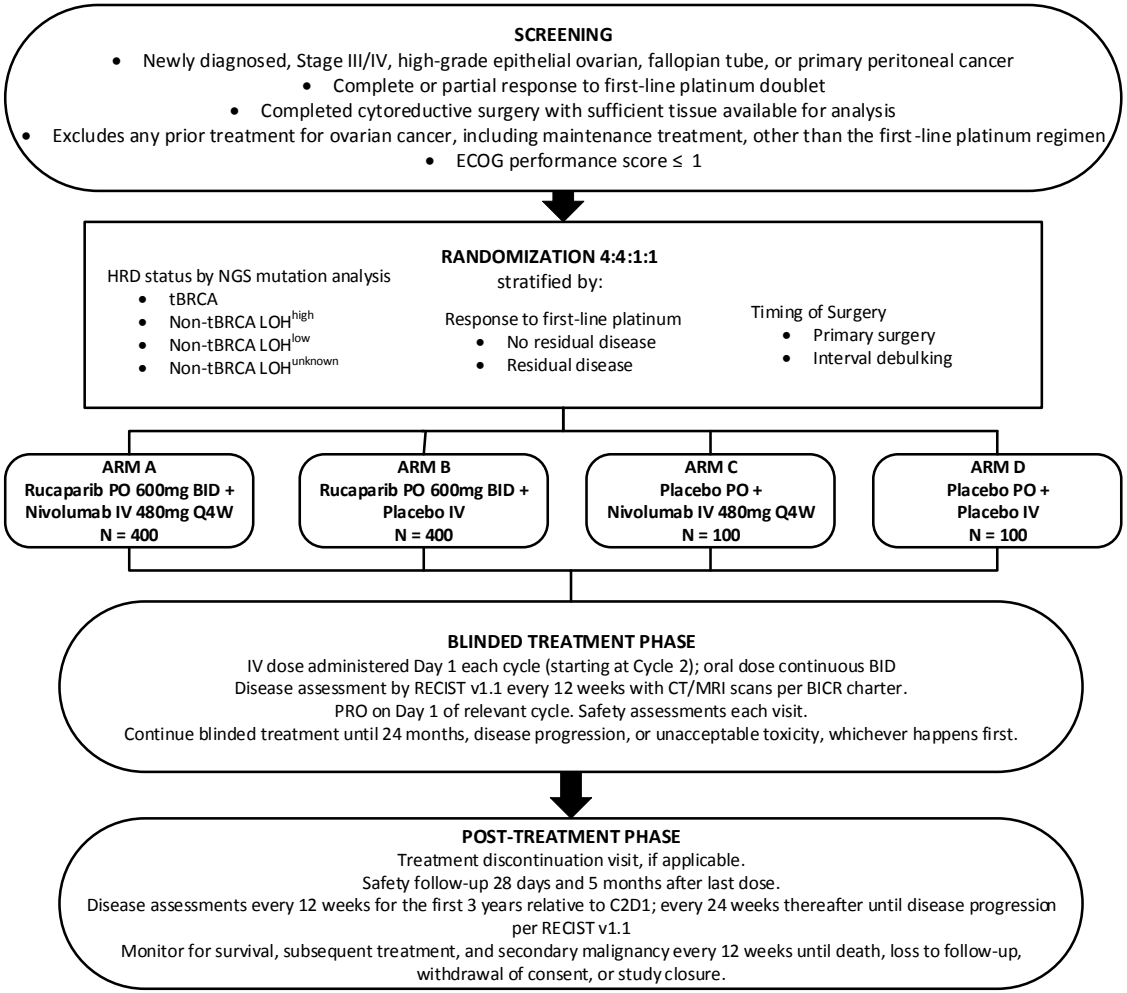
- Consent withdrawal at the patient's own request or at the request of their legally authorized representative.
- Progression of patient's underlying disease by RECIST v1.1 as assessed by the investigator unless patient is still receiving benefit from the study drug(s) according to the investigator, and the patient has provided additional consent.
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient.
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy.

The sponsor may discontinue the trial early for any of the reasons noted in Section 10.6.

## 3.3 Study Schema

The study schema is provided in Figure 1.

## Figure 1. Study Schema




Abbreviations: BID = twice a day; BRCA = breast cancer gene; CA-125 = cancer antigen-125; ECOG = Eastern Cooperative Oncology Group; HRD = homologous recombination deficiency; IDMC = independent data monitoring committee; IV = intravenous; LOH = loss of heterozygosity; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PO = oral; PRO = patient reported outcome; Q4W = every 4 weeks; tBRCA = tumor tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA.

## 3.4 End of Study

The study is monitored on an ongoing basis by an IDMC for the number of PFS events required for the primary endpoint and for safety signals. An unblinding of treatment assignment might be performed when the study is still ongoing if recommended by the IDMC. However, the study is not anticipated to close until all patients are off treatment and sufficient OS follow-up has occurred.

The sponsor may discontinue the study early for any reason as noted in Section 10.6.

Upon formal closure of the study, individual patients who are continuing in long-term follow-up (LTFU) may transition to have their LTFU and scans, if applicable, captured via another mechanism.

## 3.5 Discussion of Study Design

This is a multicenter, randomized, double-blind, dual placebo-controlled study.

Sponsor personnel (with the exception of individuals responsible for clinical supply chain and drug safety personnel), investigator and clinical site staff (except individuals in the pharmacy or authorized designee who are responsible for preparing the IV study drug), and patients will all be blinded to all study treatment to avoid bias in the interpretation of the efficacy and safety results, with the exception of enrollment to the open-label safety cohorts. To avoid bias between treatment arms, patients will be randomized to treatment with active treatment arms or placebo with stratification according to HRD classification and best response to their first-line platinum regimen.

Ovarian cancer patients who have a partial or complete response to front-line treatment, inclusive of surgery and platinum-based chemotherapy, routinely enter a period of active surveillance, with follow-up every 3 months for the first 2 years extending to every 6 months for years 2 to 5 and annually subsequently in the absence of relapse or progression. Several randomized studies have evaluated whether extending the number of platinum cycles during front-line chemotherapy would benefit survival. Eight, 10, and 12 cycles were compared to the standard of 5 or 6 cycles, and no improvement in response or prolongation of survival was established.[75-77] In addition, Copeland et al., showed that weekly paclitaxel given as maintenance after platinum-doublet did not have any effect on OS.[78] The cumulative toxicity and lack of benefit of platinum therapy extended beyond 6 cycles in the first-line setting fails to justify additional cycles beyond standard practice. Patients with PR after completion of standard first-line treatment who are not suitable for bevacizumab (in regions where it is approved in first-line) have the greatest need for improved treatment options. At present there are no proven beneficial treatments that delay progression or improve survival in this patient subgroup. Therefore, the use of a placebo comparator in the proposed study population is justified to objectively test the hypothesis of improved efficacy with the addition of nivolumab + rucaparib in combination, as well as each agent alone, as maintenance treatment in patients who achieve response to frontline treatment with a platinum regimen.

PFS by RECIST will be assessed by the investigator for the primary endpoint (invPFS) and by BICR for the secondary endpoint (bicrPFS).

Ongoing benefit/risk will be assessed regularly by an IDMC that will have access to unblinded datasets (see Section 8.11). A Study Steering Committee, consisting of selected participating investigators representing Gynecologic Oncology Group (GOG), the European Network for Gynecological Oncological Trial groups (ENGOT), and national coordinating investigators from other regions, will meet regularly to advise the sponsor regarding study-related issues, including safety concerns.

Monotherapy oral study drug will be administered in Cycle 1 prior to the initiation of the combination oral and IV study drug administration in Cycle 2 within this study to explore the hypothesis that priming the TMB will enhance activity of the combination. This additionally allows for Cycle 1 laboratory values to be assessed prior to initiation the oral/IV study drug combination, which ultimately should facilitate more accurate attribution to oral or IV study drug so the proper AE management algorithm may be followed.

The small, open-label safety cohort that will enroll preceding randomization into the Double-blind Treatment Phase, was designed to assess the safety of the combination of rucaparib (600 mg BID) and nivolumab (480 mg IV on Day 1 every 28-day cycle, starting with Cycle 2). Evaluation of the full dose of each agent is recommended as the drugs have different mechanisms of action, and the single agent data for rucaparib and nivolumab do not have significant overlapping toxicities.

The safety lead-in provides the opportunity to evaluate the rucaparib + nivolumab combination in an open-label manner with a small subset of patients with the same eligibility criteria and study assessments as those to be enrolled in the Double-blind Treatment Phase. There will be a formal safety review after the open-label safety cohort is enrolled and patients have been treated for at least 28 days of combination treatment (ie, 1 cycle) and 2 cycles of oral study drug; the protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted.

# 4 STUDY POPULATION SELECTION

## 4.1 Number of Patients and Sites

In total, approximately 1000 patients will be randomized in the Double-blind Treatment Phase at approximately 290 study sites. A maximum of 500 patients with a deleterious tBRCA mutation will be enrolled in the Double-blind Treatment Phase. A minimum of 6 additional patients may be enrolled and treated as part of an open-label safety cohort.

## 4.2 Inclusion Criteria

All patients enrolling into the study must meet all of the following inclusion criteria:

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form (ICF) prior to any study-specific evaluation.
2. Be ≥ 18 years of age at the time the ICF is signed (patients enrolled in South Korea, Taiwan, and Japan must be ≥ 20 years of age at the time the ICF is signed).
    a. Patients enrolled in the open-label safety cohort in Japan must be of Japanese ethnicity (ie, both parents are native Japanese and were born in Japan)
3. Have newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.
4. Completed cytoreductive surgery, including at least a bilateral salpingo-oophorectomy and partial omentectomy, either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking).
5. Have received 4 to 8 cycles of first line platinum-doublet treatment per standard clinical practice, including a minimum of 4 cycles of platinum/ taxane combination.
    a. A patient with best response of PR must have received at least 6 cycles.
    b. Bevacizumab is allowed during the chemotherapy phase, but not during maintenance ie, during therapy directed by this protocol.
6. Have completed first-line platinum-based chemotherapy and surgery with a response, in the opinion of the investigator, defined as no evidence of disease progression radiologically or through rising CA-125 (per Gynecologic Cancer Intergroup [GCIG] guidelines) at any time during front-line treatment; and:
    a. No evidence of measurable disease by RECIST v1.1 (if complete resection/R0 at primary or interval cytoreductive surgery); or
    b. A partial or complete response per RECIST v1.1 (if measurable disease was present after surgery and prior to chemotherapy) (Appendix 1); or
    c. A GCIG CA-125 response (if only non-measurable disease was present after surgery and prior to chemotherapy) (Appendix 2).
7. Pre-treatment CA-125 measurements must meet criterion specified below:
    a. If the first value is within upper limit of normal (ULN) the patient is eligible to be randomized and a second sample is not required;

b. If the first value is greater than ULN a second assessment must be performed at least 7 days after the first. If the second assessment is ≥ 15% than the first value the patient is not eligible.

8. Patient must be randomized within 8 weeks of the first day of the last cycle of chemotherapy.
9. Have sufficient formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 × 4 µm section for hematoxylin and eosin [H&E] stain and approximately 8 to 12 × 10 µm sections, or equivalent) available for planned analyses.
   a. Submission of a tumor block is preferred; if sections are provided, these must all be from the same tumor sample.
   b. Tumor tissue from the cytoreductive surgery is required.
   c. Sample must be received at the central laboratory at least 3 weeks prior to planned start of treatment to enable stratification for randomization.
10. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of randomization:
    a. Bone Marrow Function
       ii. ANC ≥ $1.5 \times 10^9$/L
       iii. Platelets ≥ $100 \times 10^9$/L
       iv. Hemoglobin ≥ 9 g/dL
    b. Hepatic Function
       i. AST and ALT ≤ 1.5 × ULN
       ii. Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome
       iii. Serum albumin ≥ 30 g/L (3.0 g/dL)
    c. Renal Function
       i. Serum creatinine ≤ 1.5 × ULN unless estimated glomerular filtration rate (GFR) ≥ 30 mL/min using the Cockcroft Gault formula
11. Have an ECOG performance status of 0 to 1 (Appendix 3).

## 4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Non-epithelial tumors (pure sarcomas) or ovarian tumors with low malignant potential (ie, borderline tumors) or mucinous tumors. Mixed mullerian tumors/carcinosarcomas are allowed.
2. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment.

   a. Patients with a history of malignancy that has been completely treated, with no evidence of active cancer for 3 years prior to enrollment, or patients with surgically-cured low-risk tumors, such as early-stage cervical or endometrial cancer are allowed to enroll.

3. Known central nervous system brain metastases.
4. Any prior treatment for ovarian cancer, other than the first-line platinum regimen, including any maintenance treatment between completion of the platinum regimen and initiation of study drug in this study.
   a. Ongoing hormonal treatment for previously treated breast cancer is permitted. Hormonal maintenance treatment for ovarian cancer is not allowed.
5. Has evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis.
6. Patients with an active, known or suspected autoimmune disease (eg, autoimmune hepatitis). Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
7. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
8. Drainage of ascites during the final 2 cycles of treatment with the platinum regimen.
9. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of study treatment.
10. Known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at all sites where mandated locally.
11. Any positive test result for hepatitis B and/or known history of hepatitis B infection including patients with undetectable hepatitis B virus (HBV) DNA and inactive carriers; positive test result for hepatitis C antibody (anti-HCV; except if HCV-RNA negative).
12. Pregnant, or breast feeding. All study participants must avoid pregnancy achieved through assisted reproductive technology for the duration of study treatment and for a minimum of 6 months following the last dose of study drug (oral or IV, whichever is later).
13. Received chemotherapy within 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version [v]5.0) Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, Grade 2 anemia with hemoglobin ≥ 9 g/dL, and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug.

14. Non-study related minor surgical procedure (eg placement of a central venous access port) ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of study drug; in all cases, the patient must be sufficiently recovered and stable before treatment administration.
15. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.
16. Hospitalization for bowel obstruction within 12 weeks prior to enrollment.

## 4.4 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion. In addition, due to inclusion criteria #4, requiring at least a bilateral salpingo-oophorectomy and partial omentectomy, women of child-bearing potential will not be randomized in this study.

All study participants must avoid pregnancy achieved through assisted reproductive technology for the duration of study treatment and for a minimum of 6 months following the last dose of study drug (oral or IV, whichever is later).

## 4.5 Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolling into the study.

# 5 STUDY TREATMENT(S)

## 5.1 Description of Treatment(s) and Storage

For the Double-blind Treatment Phase, eligible patients will be randomized 4:4:1:1 to the following 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: placebo (oral and IV) (n = 100).

For the open-label safety cohort(s), patients will receive open-label oral rucaparib + IV nivolumab combination treatment.

### 5.1.1 Investigational Drug Product – Rucaparib or Placebo

Rucaparib camsylate (also known as CO-338; formerly known as PF-01367338 and AG-014447) is an oral formulation. Rucaparib tablets for oral administration will be supplied to the study sites by the sponsor. A brief description of rucaparib is provided below in Table 2, with details in the Pharmacy Manual.

**Table 2. Description of Rucaparib Tablets**

| | |
|---|---|
| Drug Name: | Rucaparib |
| INN: | Rucaparib |
| Formulation: (strengths expressed as free base) | Tablet; film coated; 200 mg (blue, round, debossed with C2), 250 mg (white, diamond shape, debossed with C25), 300 mg (yellow, oval, debossed with C3) |
| How Supplied: | 200 mg, 250 mg, and 300 mg (as free base) strength tablets in 60 count bottles. Patients may receive one or more strengths. |
| Storage Conditions: | 15–30°C (59–86°F). |

Placebo tablets will be identical in appearance to the rucaparib tablets.

### 5.1.2 Investigational Drug Product – Nivolumab or Placebo

Nivolumab, also referred to as BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains (molecular weight: 146 kDa). A brief description of nivolumab is provided below in Table 3, with details in the Pharmacy Manual.

**Table 3. Description of Nivolumab for Injection**

| | |
|---|---|
| BMS Number: | BMS-936558 |
| INN | Nivolumab |
| Other names: | Opdivo, BMS-936558, MDX1106, ONO-4538, anti-PD-1 |
| How Supplied | 10 mg/mL concentrate for solution for infusion as 100 mg/10 mL single dose glass vials |
| Storage Conditions: | 2–8°C (36–46°F). Protect from light and freezing. |

Placebo infusion, once prepared for administration, will be identical in appearance to the nivolumab (refer to Section 5.2.2).

## 5.2 Packaging and Labeling

### 5.2.1 Rucaparib or Placebo Tablets

All study drug tablets (rucaparib or placebo) are provided in 60-count bottles and should be stored in the provided containers between 15° and 30° C (59 and 86° F). Patients will be dispensed one or more strengths depending on their current dose of rucaparib/placebo. The number of bottles of each strength dispensed will be sufficient to supply 28-days treatment per cycle, including a small overage.

For the Double-blind Treatment Phase, study drug containers containing rucaparib tablets or placebo will be labeled in a blinded way according to national regulations for investigational products. Details with respect to packaging and labeling of study drug tablets are described in the pharmacy manual.

### 5.2.2 Nivolumab or IV Placebo

Nivolumab will be supplied by the sponsor as a 10 mg/mL solution.

The vials and outer carton will be labeled according to national regulations for investigational products.

The solution will be diluted for administration as an infusion in sodium chloride 9 mg/mL (0.9%) solution or glucose 50 mg/mL (5%).

The placebo for nivolumab infusion will be an infusion of sodium chloride 9 mg/mL (0.9%) solution or glucose 50 mg/mL (5%). Details regarding placebo infusion may be found in the pharmacy manual.

Both active and placebo infusions will be prepared by an unblinded pharmacist or authorized designee in order to maintain the blind to the patients, investigator and other study/site personnel during the Double-blind Treatment Phase. Infusions will be labeled in a blinded way.

## 5.3 Blinding/Masking of Treatments

With the exception of the safety lead-in, every attempt will be made to maintain the treatment blind throughout the study.

Active and placebo tablets will be identical in appearance and supplied in identical containers. The medication labeling will ensure that no staff member or patient will be able to identify whether the tablets are placebo or contain active medication. Patients will take the equivalent number of active or placebo tablets according to the treatment assignment and scheduled dose.

The IV solution (nivolumab or placebo) will be prepared by the unblinded pharmacist or authorized designee), as described in the Pharmacy Manual, such that the IV solutions will be identical in appearance and supplied in identical IV bags for administration.

With the exception of the unblinded pharmacist or authorized designee, the investigator, study site personnel, clinical research organization (CRO) staff, and sponsor personnel will not have access to the randomization scheme during the study except in the case of an emergency.

In the event of a medical emergency, an individual patient's treatment assignment may be unblinded using interactive response technology (IRT). The module to unblind treatment assignment is accessible only to specific authorized study personnel. AEs per se are not a reason to break the treatment code. Unblinding should only occur for medical emergencies that require explicit knowledge of the treatment administered in order to determine the next course of action. The IRT vendor operates a 24-hour/365 day helpline as a back-up in the rare event the electronic system in unavailable when unblinding is required (refer to IRT Manual).

Only for the safety lead-in will unblinded data be evaluated. Once the Double-blind Treatment Phase has commenced, the study will not be unblinded for overall safety evaluation. If the blind is broken, the reason and when and how the blind was broken will be documented.

## 5.4 Method of Assigning Patients to Treatment Groups

For the Double-blind Treatment Phase, eligible patients will be randomized 4:4:1:1 to the following 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),
- Arm D: Oral placebo + IV placebo (n = 100).

Randomization will occur by a central randomization procedure using an IRT. The following will be included as randomization stratification factors at study entry to ensure treatment groups are balanced:

- 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)
- Timing of surgery (primary surgery vs. interval debulking)

Prior to randomization in the Double-blind Treatment Phase, an open-label safety cohort will be evaluated. A second safety cohort may follow for patients of Japanese ethnicity. Patients who provide informed consent and meet all eligibility criteria would be eligible to participate in these safety cohorts.

## 5.5 Preparation and Administration of Protocol-specified Treatment

The investigator or designee will be responsible for distributing oral study drug to all patients, and the unblinded pharmacist or authorized designee will be responsible for preparing the IV study drug for all patients.

Study drug (ie, rucaparib/placebo and nivolumab/placebo) will be assigned by the IRT according to the patient's randomization assignment. The IRT will manage all study drug supplied by the sponsor. The system should be accessed to record each dispensation of study drug, both oral and IV, according to the patient's randomized treatment. Guidelines for the use of the IRT will be provided to study sites.

Rucaparib and nivolumab will be dispensed by IRT for the open-label safety lead-in portion of the study.

### 5.5.1 Rucaparib/Oral Placebo

Rucaparib 600 mg, or matching placebo, is administered orally BID (as close to 12 hours apart as possible, preferably at the same times every day) with at least 8 ounces (240 mL) of water starting on Day 1. Study drug (tablets) may be taken with or without food. Tablets should be swallowed whole without crushing or chewing. Oral study drug will be provided as 200, 250, and 300 mg (as free base) dose strength tablets. If a patient vomits after dosing, the dose will not be made up; the patient will take their next dose at the regularly scheduled interval.

Each treatment cycle of oral study drug is 28 (± 3) days, and treatment will begin on Day 1 of Cycle 1. Patients will be provided a sufficient quantity of study drug to last until Day 1 of the next treatment cycle. Patients will be instructed to bring their study drug tablets and all containers (empty, partially used, and/or unopened) to the next scheduled visit for reconciliation by site personnel.

### 5.5.2 Nivolumab/IV Placebo

Nivolumab, or matching placebo, is administered IV as a 480 mg via a 30-minute IV infusion on Day 1 of every 28-day cycle, starting on Cycle 2. IV study drug infusion should be prepared as specified in the Pharmacy Manual. Refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information.

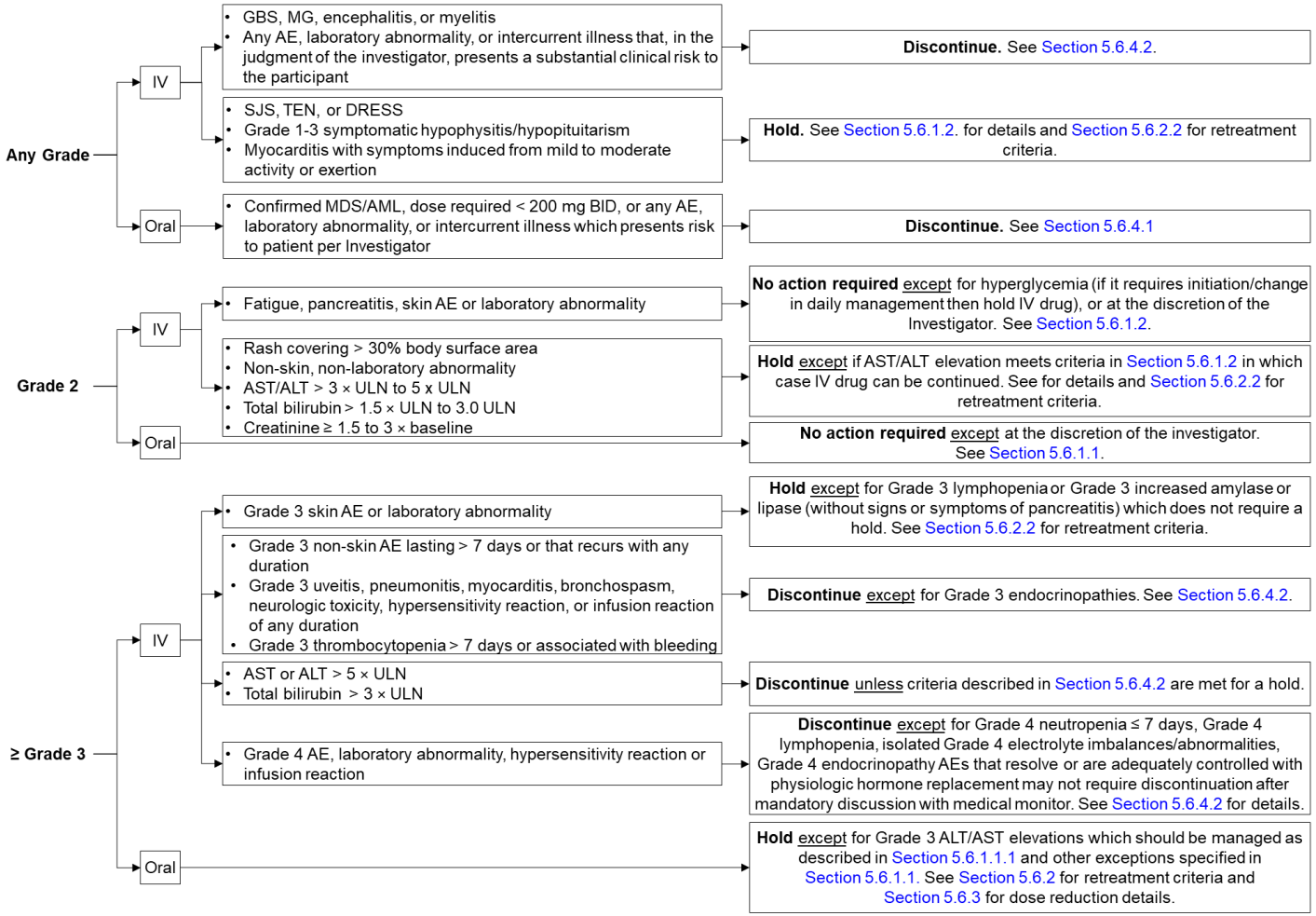
## 5.6 Dose Modification Criteria

Doses of oral study drug, and/or IV study drug, may be interrupted or delayed for toxicity and other protocol specified criteria. Dose reductions are permitted for oral study drug but not for IV study drug. The assessment for delay or discontinuation should be made separately

for the oral study drug (rucaparib or placebo) and the IV study drug (nivolumab or placebo); however, if toxicity is considered related to all study drugs or if the investigator is unable to determine which study drug is the cause of the AE, then all study drugs in the combination should be delayed and/or discontinued. Dose delay criteria also apply for the placebo of each agent, given the blinded nature of this study. Treatment may be prematurely discontinued due to withdrawal of consent, unacceptable toxicity, disease progression, completion of treatment cycles, or termination of the study, whichever occurs first.

An integrated summary of dose modification guidance by CTCAE Grade v5.0 for events related to IV and/or oral drug is provided below in Figure 2. In addition to the guidance summarized, a dosing delay of > 14 days or > 8 weeks (2 or more consecutive cycles) with oral or IV drug, respectively, requires discontinuation except if approved by the study medical monitor/designee. More detail is provided in Section 5.6.1 (treatment delay and/or interruption), Section 5.6.2 (re-treatment criteria), Section 5.6.3 (dose reduction), and Section 5.6.4 (study drug discontinuation). Please also refer to Appendix 8: AE Criteria for Delay, Resume and Discontinue of Nivolumab.

## Figure 2. Integrated Dose Modification Guidance for Events Related to IV and/ or Oral Drug by CTCAE Grade (CTCAE v5.0)




Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; BID = twice a day; CTCAE = Common Terminology Criteria for Adverse Events; DRESS = drug reaction with eosinophilia and systemic symptoms; IV = intravenous; MDS = myelodysplastic syndrome; SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis.

### 5.6.1 Treatment Delay and/or Interruption

#### 5.6.1.1 Rucaparib/Oral Placebo

Treatment with oral study drug should be held if any of the following are observed:

- Grade 3 or 4 drug-related hematologic toxicity
- Grade 3 or 4 drug-related non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines).
  - Grade 3 or Grade 4 ALT/AST elevations should be managed as described in Section 5.6.1.1.1.
- At the discretion of the investigator, oral study drug may be interrupted or continued if new or worsening unexplained pulmonary symptoms suggestive of pneumonitis (including, but not limited to, dyspnea) occur and while evaluation to rule out pneumonitis or confirm such a diagnosis as well as etiology are ongoing; these events should be managed as described in Section 5.7.2.
- In addition, and at the discretion of the investigator, the dose of oral study drug may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

##### 5.6.1.1.1 ALT/AST ELEVATIONS

- Grade 4 ALT/AST elevations: hold oral study drug until values have improved to Grade 2 or better, then resume oral study drug with a dose reduction. Monitor liver function tests weekly for 3 weeks after oral study drug has been restarted.
- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:
  - Monitor liver function tests weekly until improvement to ≤ Grade 2.
  - Continuation of oral study drug with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN and alkaline phosphatase is < 3 × ULN.
  - If patient has Grade 3 ALT/AST and continues on oral study drug, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and improvement to ≤ Grade 2 will be required before oral study drug can be resumed, either at the current dose or at a reduced dose.
- ALT or AST > 3 × ULN AND bilirubin > 2 × ULN (suspected DILI).[49]
  - While treatment is interrupted, the patient should be evaluated for the presence of confounding factors including malignant disease in the liver, coadministration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, oral study drug must be permanently discontinued.

- Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin. See Section 8.9.

#### 5.6.1.2 Nivolumab/IV Placebo

IV study drug administration should be held for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue and pancreatitis
- Grade 2 drug-related creatinine (≥ 1.5-3.0 × baseline; > 1.5-3.0 × ULN) or Grade 3 drug-related creatinine (> 3.0 × baseline; > 3.0-6.0 × ULN) abnormalities
  - Baseline is defined as the creatinine value obtained prior to dosing the IV drug on C2D1, or first dose of IV drug, whichever is later

    **Note**: Elevated creatinine is frequently observed with rucaparib monotherapy. Rucaparib is a potent inhibitor of MATE1 and MATE2-K transporters, which are involved in active secretion of creatinine. Rucaparib-mediated creatinine elevation occurs early in treatment (Day 15 of Cycle 1), and is not typically accompanied by elevations in urea (blood urea nitrogen [BUN]). Creatinine elevation resolves with dose holds of rucaparib and recurs with rechallenge. Rucaparib associated creatinine elevation has not been associated with evidence or reports of permanent renal impairment.
- Drug-related AST, ALT, and/or bilirubin abnormalities with the range of AST or ALT > 3 × and ≤ 5 × ULN or total bilirubin > 1.5 × and ≤ 3 × ULN, regardless of baseline value
  - For participants with the above range of AST or ALT elevations with onset during dosing of the first cycle of oral study drug, IV study treatment hold is not required if AST/ALT elevations begin to resolve before the next scheduled infusion and toxicity is considered to be mainly related to oral study treatment. If the patient has an existing such elevation, and a subsequent AST/ALT increase of more than 20% is observed following infusion of IV study drug, the next IV study drug administration will be held and, if further increase is observed, the Hepatic Adverse Event Management Algorithm will be followed (see Appendix 7). If AST or ALT or total bilirubin elevations are considered mainly related to IV drug, IV drug dosing may resume when laboratory values return to baseline. IV drug should be discontinued at concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, regardless of baseline value.
  - For participants with ALT or AST elevations > 3 × ULN or total bilirubin > 1.5 × ULN regardless of baseline value that begin after Cycle 3, the Hepatic Adverse Event Management Algorithm will be followed (see Appendix 7).

    **Note**: Rucaparib may cause transient AST and/or ALT elevations (without increased total bilirubin) at Cycle 1, Day 15 that begin to resolve by Day 29, even with continued rucaparib dosing.
- Grade 2 or 3 colitis or diarrhea

- Grade 3 pancreatitis with symptoms. Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay
- Grade 2 rash covering > 30% body surface area or Grade 3 drug-related skin AE. Suspected Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)
- Endocrinopathies met the following criteria:
  - Grade 2 adrenal insufficiency.
  - Grade 2 or 3 hyperglycemia requiring initiation or change in daily management.
  - Grade 1-3 hypophysitis/hypopituitarism that is symptomatic and also associated with corresponding abnormal lab and/or pituitary scan.
  - Grade 2 or 3 hyperthyroidism or hypothyroidism.
- Grade 2 uveitis.
- Grade 2 neurological (other than Guillain-Barre Syndrome [GBS], myasthenia gravis [MG], encephalitis, or myelitis).
- Any grade of encephalitis or myelitis. After workup for differential diagnosis, (ie, infection, tumor-related), if it is not drug related, then dosing may resume when AE resolves.
- Myocarditis with symptoms induced from mild to moderate activity or exertion.
- Other Grade 3 drug-related AE with first occurrence lasting ≤ 7 days.
- Grade 3 drug-related laboratory abnormality (not listed above), with the following exceptions:
  - Grade 3 lymphopenia or Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay.
  - Grade 3 thrombocytopenia > 7 days or associated with bleeding requires for dose discontinuation.
  - AST, ALT, and/or total bilirubin elevations with a range of AST or ALT > 5 × ULN or total bilirubin > 3 × ULN, regardless of baseline value, will require dose delay or discontinuation. (See Section 5.6.4.2)*
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require dose hold should be re-evaluated weekly or more frequently if clinically indicated and resume dosing during the next scheduled dosing window (Cycle X, Day 1 ± 3 days) after re-treatment criteria are met (Section 5.6.2).

Please refer to Appendix 8: AE Criteria for Delay, Resume and Discontinue of Nivolumab.

### 5.6.2 Retreatment Criteria

#### 5.6.2.1 Rucaparib/Oral Placebo

For patients who meet treatment interruption guidelines in Section 5.6.1, treatment with oral study drug should be held until the toxicity improves to ≤ CTCAE Grade 2. Twice a day dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, treatment should be interrupted, then resumed at a reduced dose following improvement of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted (Table 4); however, the investigator should consult with the sponsor's medical monitor before reducing to 300 mg BID.

If any blood hematology parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. For management of anemia, please refer to Section 5.7.1.

#### 5.6.2.2 Nivolumab/IV Placebo

Participants may resume treatment with IV study drug when the drug-related AE(s) improve to Grade ≤ 1 or resolve to baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue and pancreatitis.
- Participants who are suspected with SJS, TEN, or DRESS may resume treatment if SJS, TEN, or DRESS are ruled out and rash reduces to ≤ 10% body surface area.
- For participants with elevated AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the study medical monitor.
- Participants with Grade 2 uveitis may resume treatment if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If patient requires oral steroids for uveitis, then permanently discontinue study drug.
- For visual complaints, patients should be referred to an ophthalmologist following the guidance in Section 7.1.10 of the nivolumab Investigator's Brochure.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the study medical monitor.

Participants with Grade 2 neurological (other than GBS, MG, encephalitis, or myelitis) may resume when AE resolves to baseline

If the criteria to resume treatment are met, the patient should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is withheld past the window period of the next scheduled timepoint per protocol to ensure adequate recovery from the adverse event or tapering of immunosuppression, the dosing should continue to be withheld until the subsequent scheduled timepoint.

If treatment is withheld > 8 weeks from the last dose (2 or more consecutive IV drug cycles missed), the subject must be permanently discontinued from study therapy, except as specified in Section 5.6.4.2.

Please refer to Appendix 8: AE Criteria for Delay, Resume and Discontinue of Nivolumab.

### 5.6.3 Dose Reduction

There will be no dose modifications permitted for IV study drug.

#### 5.6.3.1 Rucaparib/Oral Placebo

The dose reduction steps for oral study drug are presented in Table 4.

Dose escalation upon improvement of toxicity to ≤ CTCAE Grade 1 is permitted at the discretion of the investigator.

Dose modifications must be recorded for each patient in the appropriate section of the electronic case report form (eCRF).

**Table 4. Oral Study Drug Dose Reduction Steps**

| Starting Dose | 600 mg BID |
|---|---|
| Dose Level: – 1 | 500 mg BID |
| Dose Level: – 2 | 400 mg BID |
| Dose Level: – 3[a] | 300 mg BID |

Abbreviation: BID = twice a day.

[a] Consult with sponsor's medical monitor before reducing to dose level 3. Further dose reduction may be possible but requires consultation with the sponsor's medical monitor.

### 5.6.4 Study Drug Discontinuation

Rucaparib/oral placebo and/or nivolumab/IV placebo should be discontinued according to the criteria specified below. The decision to discontinue each agent may be made independently of one another. However, if the toxicity is considered related to all study drugs or if the

investigator is unable to determine which study drug is the cause of the AE, then both oral and IV study drug must be discontinued.

#### 5.6.4.1 Rucaparib/Oral Placebo

Oral study drug should be permanently discontinued for any of the following:

- If a participant continues to experience drug-related toxicity despite dose reduction steps to 200 mg BID or if dosing with oral study drug is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, with the following exceptions:
  - Dosing delay > 14 days may be allowed if approved by the study medical monitor/designee. Prior to re-initiating treatment in a participant with a dosing delay lasting > 14 days, the study medical monitor/designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Confirmed MDS/AML.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued oral study treatment dosing.

#### 5.6.4.2 Nivolumab/IV Placebo

Nivolumab/IV placebo should be permanently discontinued for any of the following:

- Any Grade of GBS, MG and drug-related encephalitis and myelitis
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or that recurs with any duration, with the following exceptions laboratory abnormalities, drug-related uveitis, pneumonitis, myocarditis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, myocarditis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
    - AST, ALT, or total bilirubin elevations with AST or ALT > 5 × ULN or total bilirubin > 3 × ULN, regardless of baseline value, requires dose delay or discontinuation*

      *In most cases of such AST or ALT elevation, IV study drug will be permanently discontinued. For participants with such AST or ALT elevations after the start of IV dosing, but on a background of previous elevations on the

first cycle of oral study drug, IV study drug hold is required, but discontinuation is not required, if AST/ALT elevations begin to resolve before the next scheduled infusion, and toxicity is considered to be mainly related to oral study treatment, after the investigator discusses the case with the study medical monitor. Levels will be monitored every 3 days; if they continue to rise more than 20%, the Hepatic Adverse Event Management Algorithm will be followed (see Appendix 7). Treatment with IV drug may be resumed if levels return to an ALT and ALT < 5 × ULN, and total bilirubin < 3 × ULN. If AST or ALT or total bilirubin elevations are considered mainly related to IV drug, and the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy. IV drug dosing may resume when laboratory values return to baseline.

- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events that do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance and adrenal insufficiency, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after mandatory discussion with and approval from the study medical monitor/designee.
- Grade 3 or 4 hypersensitivity reaction or infusion reaction. Please refer to Section 5.9 on Treatment of Related Infusion Reactions
- Any event that leads to delay in dosing lasting > 8 weeks (2 or more consecutive IV drug cycles missed) from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 8 weeks (2 or more consecutive IV drug cycles missed) from the previous dose that occur for non-drug-related reasons may be allowed if approved by the study medical monitor/designee.

  Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks (2 or more consecutive IV drug cycles missed), the study medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued IV study drug dosing.

Please refer to Appendix 8: AE Criteria for Delay, Resume and Discontinue of Nivolumab.

## 5.7 Management Algorithms for Oral Study Drug

### 5.7.1 Management of Anemia

If anemia CTCAE Grade ≥ 3 occurs and persists for > 14 days, or a dependence upon blood transfusions occurs, then weekly complete blood counts are recommended until resolution of the anemia to ≤ Grade 1. If after 42 days of treatment interruption anemia has not improved to Grade ≤ 1, a referral to a hematologist and analysis of the bone marrow according to institutional standard practice is recommended.

Refer to Sections 8.3 and 8.7 of the protocol for additional information regarding classification and reporting of MDS or AML as an AESI.

### 5.7.2 Management of New or Worsening Pulmonary Symptoms Suggestive of Pneumonitis

If new or worsening unexplained pulmonary symptoms suggestive of pneumonitis (including, but not limited to, dyspnea) occur, or a deterioration of pulmonary function is observed, and/or radiologic abnormality is detected in the lungs, and this occurs in the absence of any clear diagnosis, a diagnostic workup (including high resolution CT scan) in consultation with a pulmonologist should be performed in order to rule out pneumonitis. During this time, treatment with oral study drug may be interrupted or continued per investigator discretion. The contribution of IV study drug should also be assessed independently.

Following investigation, if pneumonitis is not confirmed, treatment with oral study drug may be resumed/continued as deemed appropriate by the investigator and in accordance with the study protocol directions for management of AEs. All confirmed events of pneumonitis should be treated as appropriate per medical judgement and institutional guidelines. If the event resolves and retreatment with oral study drug is being considered, please consult the study medical monitor. Re-treatment with oral study drug may be resumed at the current or a reduced dose, if appropriate.

Refer to Sections 8.3 and 8.7 of the protocol for additional information regarding classification and reporting of pneumonitis (and similar events) as an AESI.

## 5.8 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an I-O agent in this protocol. Early recognition and management of AEs associated with I-O agents may

mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

The above algorithms are found in Appendix 7 of this protocol.

## 5.9 Treatment of Infusion-related Reactions

Since nivolumab contains only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (v5.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

**For Grade 1 symptoms**: (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional IV study drug administrations.

**For Grade 2 symptoms:** (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or

acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study treatment will be administered at that visit.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before IV study drug infusion. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used

**For Grade 3 or 4 symptoms:** (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

## 5.10 Interruption of Study Drug for On-study Procedures

In the case where a patient must undergo a procedure or surgery after the start of dosing (eg, ileostomy or colostomy reversal), management of oral and IV drug should proceed as follows:

Oral drug should be held for 3-4 days (5x half-life) prior to planned procedure, and resumed once the patient has fully recovered, in the opinion of the investigator.

IV drug may be continuously administered, at the discretion of the investigator. If possible, the procedure should be planned as close to the mid-way point of the cycle as possible (Week 2 of a 4-week cycle), and no less than 1 week before or after an IV drug administration. If the procedure must occur within 1 week of a scheduled IV drug

administration, the investigator should hold IV drug during that cycle, and restart once the patient has sufficiently recovered.

## 5.11 Treatment Compliance

### 5.11.1 Rucaparib/Oral Placebo Treatment Compliance

Documentation of dosing will be recorded in a study specific dosing diary provided by the sponsor (or designee). Dosing noncompliance is defined as a patient missing > 14 days of medication in a 28-day window for 2 consecutive visits for a nonprotocol-specified reason. The sponsor may require patients meeting noncompliance criteria to discontinue study treatment. Study-site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose. Patients (or legally authorized representative) will be instructed to keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next scheduled clinic visits. A compliance check and tablet count will be performed by study personnel during clinic visits. Additional details regarding study drug dispensation and return can be found in the pharmacy manual.

Every effort should be made to ensure patients return to the clinic with their study drug containers/unused study drug at the end of each cycle of treatment. Study site personnel should conduct a verbal review of dosing with the patient and document the discussion in the patient's medical record. This may serve as source documentation for the purpose of entering dosing data on the appropriate eCRF.

### 5.11.2 Nivolumab/IV Placebo Treatment Compliance

Each dose of IV study drug will be prepared by an unblinded pharmacist or authorized designee and transferred to a blinded infusion set. The infusion will then be monitored by the investigator or study coordinator. Treatment compliance will be monitored by drug accountability, and any preparation of infusion deviations (eg, infusion less/greater than 30 min) will be recorded on the patient's eCRF.

## 5.12 Accountability of Protocol-specified Treatment

Study personnel will maintain accurate records of study drug receipt, dispensation, use, return, destruction, and reconciliation for study drugs provided by the sponsor. The IRT will be used to manage study drug inventory at all sites. In order to function properly, the system will require real-time entry of study drug receipt, dispensation, destruction, etc. by study personnel at the study site.

The site is responsible for the return or destruction of study drug supplied by the sponsor. Authorization to destroy study drug at the site that has not been dispensed to a patient (eg, expired study drug), must be requested from the sponsor prior to destruction. All study drug containers must be accounted for prior to their destruction at the study center, according to institutional procedures for disposal of hazardous materials. Unused study drug product

and containers should be destroyed on-site if possible. If destruction on site is not possible, supply should be returned to the drug depot, following the sponsor's instructions.

During the course of the study and at completion of the study, the number of study drug units and containers received, dispensed, returned, and destroyed must be recorded and reconciled. Additional details regarding study drug accountability can be found in the pharmacy manual.

## 5.13 Treatment of Study Drug Beyond Disease Progression

Patients will receive study drug until confirmed radiologic disease progression as assessed by investigator using RECIST Version 1.1 criteria, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up, death, or withdrawal of consent.

If a patient receiving study drug has met criteria for confirmed radiologic disease progression by RECIST Version 1.1 criteria, but the patient continues to derive clinical benefit per the investigator, then continuation of treatment will be permitted. In such cases, the investigator's decision to continue treatment should be documented in the source documents and the patient must provide additional consent prior to continuing treatment with study drug. Clinical scenarios where continuation of study drug after radiographic progression may be considered include 1) a patient for whom radiographic progression develops slowly while disease-related symptoms remain well controlled, 2) a patient who experiences progression in a site of disease that is unlikely to adversely affect prognosis (eg, enlargement of a solitary lymph node), or 3) a patient with general disease control but limited progression in sites of disease that can be managed with local therapies such as surgery or radiation. Patients continuing to receive study drug will continue to have all protocol-required assessments as described in Section 7.

Continuation of randomized treatment will be considered for a maximum cumulative duration of 24 months after initiation of oral/IV combination study treatment.

# 6 PRIOR AND CONCOMITANT THERAPY

Drug-drug interactions between nivolumab and rucaparib are unlikely (see Section 1.1.2.2).

Patients who have received prior treatment for ovarian cancer, other than the front-line platinum regimen, including any treatments in the maintenance setting, are not eligible to participate in this study; ongoing hormonal treatment for previously treated breast cancer is permitted. Patients who have received prior treatment with a PARP inhibitor including IV or oral rucaparib or a PD-1/ PDL-1 targeting agent are not eligible to participate in this study.

All procedures performed (eg, thoracentesis, etc.) during the study must be documented on the eCRF.

## 6.1 Supportive Care

During the study, supportive care (eg, antiemetics; analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures. Supportive care must be recorded for each patient in the appropriate section of the eCRF.

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered per standard of care and according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

## 6.2 Radiotherapy

Palliative radiotherapy on lesions not considered target lesions for tumor evaluation is permitted during the study. Treatment with study drug should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation related toxicity.

## 6.3 Anticancer or Experimental Therapy

No other anticancer therapies (including chemotherapy, radiation, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study with the exception of palliative radiotherapy and hormonal treatment. Prior treatment with such excluded anticancer therapies must have been completed > 14 days prior to the first dose of study drug.

## 6.4 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo CYP interaction study (CO-338-044), rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used in patients on rucaparib taking concomitant medicines that are sensitive substrates of CYP1A2, CYP2C9, and/or CYP3A (Appendix 4). Selection of an alternative concomitant medication is recommended.

Although in vitro rucaparib metabolism is mediated by CYP3A4, results from Study CO-338-107 showed that concomitant use of the strong CYP3A4 inducer enzalutamide had no clinically significant effect on rucaparib PK.

### 6.4.1 Transporter Inhibitors, Inducers, and Substrates

Based on the results from Study CO-338-095, rucaparib has no clinically significant effect on the PK of oral rosuvastatin, a sensitive BCRP substrate.

## 6.5 Anticoagulants

Rucaparib is a weak inhibitor of CYP2C9 in vivo. Caution should be exercised in patients receiving rucaparib and concomitant warfarin (Coumadin). Patients taking warfarin should have INR monitored regularly per standard clinical practice.

## 6.6 Immunosuppressive Agents

Immunosuppressive agents are prohibited, with the exception of inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, in the absence of active autoimmune disease. Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded.

## 6.7 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF.

Rucaparib marginally increased digoxin AUC by 20%. Caution should be exercised for patients receiving rucaparib and requiring concomitant medication with digoxin. Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice.

Rucaparib marginally increased the $C_{max}$ and mildly increased the AUC of oral contraceptives (ethinylestradiol and levonorgestrel). No clinically meaningful DDIs are expected for concomitant use of oral contraceptives and rucaparib.

In vitro, rucaparib is a potent inhibitor of MATE 1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib.

## 6.8 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Oral and/or IV contrast should be used whenever possible and appropriate, and rectal contrast should only be considered in patients with peritoneal disease. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated GFR < 30 mL/min/1.73 $m^2$) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator and the standard set by the local IEC.

## 6.9 General Restrictions

Photosensitivity has been observed in patients treated with rucaparib. Patients should avoid spending time in direct sunlight because they burn more easily during treatment with rucaparib. When outdoors, patients should use typical precautions such as applying sunscreen (sun protection factor 50 or greater) and/or covering exposed skin with clothing and wearing a hat and sunglasses.

# 7 STUDY PROCEDURES AND METHODS

## 7.1 Schedule of Assessments

Table 5 summarizes the procedures and assessments to be performed for all patients. Study procedures and assessments should be performed as close to the scheduled time as possible, but within ± 3 days of the scheduled time unless otherwise stated.

Table 6 summarizes the timing of collection of PK and immunogenicity samples.

Imaging guidelines provided by the BICR vendor should be followed for the collection of images and the radiological assessment of disease.

All serum chemistry, hematology, serology testing, tumor tissues (screening and optional sample at the time of disease progression/randomized treatment discontinuation), CA-125, PK samples, and all study required blood samples will need to be sent to central laboratories for processing. Please refer to study laboratory manuals for detailed collection and shipment requirements.

## Table 5. Schedule of Assessments for All Patients

| Procedure[a] | Screening Phase | | | Randomization[b] | Treatment Phase 28-day cycles ± 3 days | | | Post-Treatment Follow-up Phase | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-Randomization | | | | Cycles 1 & 2 | | Cycles 3+ | | | |
| | Day -120 to Day-1 | Day -28 to Day -1 | Day -14 to Day -1 | | Day 1 | Day 15 | Day 1 | End of Treatment | Safety Follow-up (×2)[c] | Long-term Follow-up |
| Informed Consent[d] | X | | | | | | | | | |
| Medical/Oncology History[e] | X | | | | | | | | | |
| Tumor Tissue Sample (central lab)[f] | X | | | | | | | | | |
| Physical Examination, Height[g], Weight | | X | | | X | | X | X | X | |
| Vital Signs[h] | | X | | | X | X | X | X | X | |
| 12-lead ECG[i] | | X | | | | | | X | X | |
| Prior/Concomitant Medications/Procedures | | X | | | X | X | X | X | X | |
| Disease/ Tumor assessments[j] | | X | | | | | X[k] | X[l] | X[l] | X[l] |
| Patient-reported outcome (TOI FACT-O, EQ-5D-5L)[m] | | X | | | X | | X | X | X | |
| ECOG Performance Status | | X | | | X | X | X | X | X | |
| Hematology (central lab)[n] | | | X | | X | X | X | X | X[c] | |
| Serum Chemistry[o] including Hep B and C testing (central lab, non-fasting) | | | X | | X | X | X | X | X[c] | |
| Urinalysis[p] | | | X | | | | | | | |
| CA-125 Measurement (central lab)[q] | | | X | | X | | X | X | X | X |

## Table 5. Schedule of Assessments for All Patients (cont.)

| Procedure[a] | Screening Phase | | | Randomization[b] | Treatment Phase | | | Post-Treatment Follow-up Phase | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cycles 1 & 2 | | Cycles 3+ | | | |
| | Pre-Randomization | | | | | | | | | |
| | Day -120 to Day-1 | Day -28 to Day -1 | Day -14 to Day -1 | | Day 1 | Day 15 | Day 1 | End of Treatment | Safety Follow-up (×2)[c] | Long-term Follow-up |
| Randomization to Study Treatment | | | | X[r] | | | | | | |
| Blood Sample for g/sBRCA status (central lab) | | | | | X[s] | | | | | |
| Blood Sample for ctDNA Analysis (central lab)[t] | | X | | | X | | X | X | X | |
| Oral Study Drug Dispensation[b] | | | | | X[b] | | X | | | |
| IV Study Drug Administration[u] | | | | | X[u] | | X | | | |
| Adverse Events[v] | (X) | (X) | (X) | | X | X | X | X[v] | X[v] | X[v] |
| Blood Sample for PK (central lab) | Refer to Table 6 for sampling schedule | | | | | | | | | |
| Blood Sample for Immunogenicity (central lab) | Refer to Table 6 for sampling schedule | | | | | | | | | |
| Post-Treatment Tumor Tissue Biopsy (central lab, OPTIONAL; consent required) | | | | | | | | X[w] | | |
| Subsequent Treatments, Secondary Malignancy Monitoring, and Overall Survival[x] | | | | | | | | | X | X |

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine transaminase; AML = acute myeloid leukemia; ANC = absolute neutrophil count; AST = aspartate transaminase; BICR = blinded independent central radiology review; BUN = blood urea nitrogen; CA-125 = cancer antigen-125; $CO_2/HCO_3^-$ = bicarbonate; CR = complete response; CT = computer tomography; ctDNA = circulating tumor deoxyribonucleic acid; C2D1 = Cycle 2 Day 1; eCRF = electronic case report form; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = Euro-QoL 5D-5L; FACT-O = Functional Assessment of Cancer Therapy – Ovarian; fT3 = free triiodothyronine; fT4 = free thyroxine; QoL= quality of life; Hct = hematocrit; HIV = human immunodeficiency virus; Hep B and C = hepatitis B and C; Hgb = hemoglobin; HIV = human immunodeficiency virus; HRD = homologous recombination

## Table 5. Schedule of Assessments for All Patients (cont.)

deficiency; IRT = interactive response technology; IV = intravenous; gBRCA = germline breast cancer gene; GCIG = Gynecologic Cancer Intergroup; GFR = glomerular filtration rate; LDH= lactate dehydrogenase; LOH = loss of heterozygosity; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; RBC= red blood cell count; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SFU1 = Safety Follow-up Visit 1; SFU2 = Safety Follow-up Visit 2; T3 = triiodothyronine; T4 = thyroxine; tBRCA = tumor tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA; TOI = trial outcome index; TSH= thyroid stimulating hormone; ULN = upper limit of normal; WBC = white blood cell; WOCBP = women of child bearing potential.

[a] = The study visit window in the treatment phase is ± 3 days, unless noted otherwise for a particular assessment. Study visits should take into account the subject's investigational product supply. Only 1 cycle of oral study drug will be dispensed to the subject on Day 1 of each cycle.

[b] = First dose of oral study drug in Cycle 1 should be administered within 3 days of enrollment/randomization. Study treatment continues in 28-day cycles (± 3 days) until 24 months after initiation of oral/IV combination study treatment, disease progression, or unacceptable toxicity, whichever happens first.

[c] = Patients must be followed for at least 5 months after last IV dose of study treatment. Safety Follow-up Visit 1 (SFU1) should occur 28 days (±7) from the last dose of study drug (oral or IV, whichever is later) or can be performed on the date of discontinuation if that date is at least 28 days from last dose. Safety Follow-up Visit 2 (SFU2) occurs approximately 5 months (± 7) from last IV dose of study drug. Chemistry and hematology are only necessary at SFU2 if toxicities are present. Both follow up visits should be conducted in person. If a patient remains on oral study drug after discontinuation of IV study drug, the 5-month Safety Follow-up Visit can be performed at a cycle visit, provided it has been at least 5 months since the last IV dose.

[d] = Consent may be completed outside the 120-day screening window as consent does not expire. Reconsent is not required if outside the screening window. The screening period begins with the first study-specific procedure, performed outside standard of care, and only after consent for study participation has been provided.

[e] = Patient's medical record must include prior treatments received, dates of administration, date of progression and how assessed, and radiology reports. BRCA1/2 mutation status and if germline or somatic, if known, will also be recorded on the appropriate eCRF. Medical history should be updated within 3 days of the first dose of study drug.

[f] = Adequate tumor tissue samples must be provided to enable determination of HRD status for randomization, determination of HRD status prior to final analysis (if required. The sample from primary surgery should be provided as well as a core biopsy sample prior to neoadjuvant treatment, if applicable. Submission of a tumor block and tumor content ≥ 30% is strongly preferred. Sample must be submitted to the central laboratory **at least 3 weeks prior to planned start of treatment** in order to enable stratification for randomization.

[g] = Height at screening only.

[h] = Vital signs (blood pressure, pulse, and temperature) to be taken predose on drug administration days, after the patient has been resting for at least 5 min.

[i] = Heart rate, PR, QRS, QT, QTc, and rhythm. Investigator to review results and assess as normal or abnormal (clinically significant or not clinically significant). ECGs to be repeated throughout the study as clinically indicated, at the Treatment Discontinuation Visit, and at both SFUs 1 (28-day post-treatment discontinuation) and 2 (5-month post-IV treatment discontinuation).

[j] = Disease assessments to consist of clinical examination and appropriate imaging techniques per RECIST (CT and/or MRI scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST). Other complementary studies (X-ray, PET, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. CT/ MRI scans of the chest, abdomen, and pelvis performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline. All study-related scans should be submitted to the BICR vendor for central read.

## Table 5. Schedule of Assessments for All Patients (cont.)

[k] = Tumor scans to be performed every 12 calendar weeks (a 7-day window prior is permitted) relative to Cycle 2 Day 1 (C2D1) for the first 3 years and every 24 weeks thereafter until objective radiological disease progression. Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

[l] = To be performed every 12 weeks (within 7 days prior is permitted) relative to C2D1 for the first 3 years and every 24 weeks thereafter until investigator-assessed radiologic disease progression by RECIST v1.1 or initiating subsequent anticancer treatment for any patient who discontinued from study treatment for reason other than disease progression or death. Tumor scans at the End-of-Treatment Visit are only required if it has been 12 weeks or more since the last scan.

[m] = The TOI FACT-O and EQ-5D-5L assessments must be completed prior to other scheduled study procedures and dosing (if applicable) 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 the End-of-Treatment Visit, at the SFU1 (28-day post-treatment discontinuation) and the SFU2 (5-month post-IV treatment discontinuation) for all patients.

[n] = Includes RBC and parameters (Hgb, Hct, MCV, MCH, MCHC) and reticulocyte count, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a central laboratory. A duplicate sample may be collected and analyzed by the local laboratory for immediate eligibility/treatment decisions.

[o] = Includes total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, ALP, ALT, AST, total cholesterol, glucose, sodium, potassium, magnesium, chloride, $CO_2/HCO_3$, calcium, phosphorus, LDH, folic acid (first 6 cycles only), TSH, Free T3, Free T4 at screening; TSH, with reflexive fT3 and fT4 if TSH is abnormal on treatment. If pancreatitis is suspected clinically, serum lipase and amylase should be analyzed. Blood will be analyzed by a central laboratory. A duplicate sample may be collected and analyzed by the local laboratory for immediate eligibility/treatment decisions. Tests for hepatitis C antibody and hepatitis B surface antigen are required at screening. Testing for HIV must also be performed at screening if mandated locally by a given site.

[p] = Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings abnormal based on investigator's judgment, perform microscopic evaluation to assess abnormal findings. Urinalysis to be repeated as clinically indicated.

[q] = CA-125 measurement should be performed at screening and on Day 1 of every subsequent cycle, at treatment discontinuation, in follow-up, and as clinically indicated. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging.

[r] = Randomization to study treatment must occur within 8 weeks following a patient's first day of the last cycle of chemotherapy and oral study treatment must begin within 3 days of randomization. Randomization will occur by a central randomization procedure using an IRT. Patients will be stratified based on 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).

[s] = If sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter.

[t] = Screening, Day 1 of Cycle 1 through Cycle 6 and at the same time as radiological imaging thereafter, and at the End of Treatment Visit and Safety Follow-up. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging.

[u] = First dose of IV study drug occurs C2D1. Study treatment continues on Day 1 every 28-day cycle until 24 months after initiation of oral/IV combination study treatment, disease progression, or unacceptable toxicity, whichever happens first.

## Table 5. Schedule of Assessments for All Patients (cont.)

[v] = AEs, SAEs, and AESIs that occur after first administration of study drug through to 28 days after last dose of oral or IV study drug, whichever occurs later, and AEs/SAEs assessed as related to IV drug that occur up to 5 months after the last IV dose of study drug will be recorded. In addition, AEs that were related to a screening procedure will also be recorded. Section 8 includes the details of reporting AEs, SAEs, and AESIs. Ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed to resolution or stabilization. After the 28-day (oral) or 5-month (IV) windows, only SAEs considered as potentially study-drug related (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) regardless of causality, will be recorded. If a patient discontinues from treatment and begins a subsequent anticancer therapy, the sponsor will terminate collection of SAEs, with the exception of the AESIs of MDS and AML.

[w] = An optional tumor biopsy may be collected from patients at time of disease progression/randomized treatment discontinuation. Additional consent is required. Refer to the central Laboratory Manual for detailed sample collection and handling instructions.

[x] = All patients discontinued from treatment, regardless of reason, should be followed for subsequent treatments, secondary malignancy, and survival every 12 weeks (± 14 days) after SFU1 (28-days after the last dose of study drug) until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone. Diagnosis of any secondary malignancy requires appropriate documentation (ie, laboratory and/or pathology reports) and should be reported as specified in Section 8.7.

## Table 6. Pharmacokinetic and Immunogenicity Sample Collections

| Study Day (Cycle, Day)[a] (1 Cycle = 28 days) | Time (Event) | Time (Relative to Start of Infusion) | Pharmacokinetic Blood Sample for Nivolumab | Immunogenicity Blood Sample for Nivolumab | Pharmacokinetic Blood Sample for Rucaparib[b] |
|---|---|---|---|---|---|
| C2D1 | (Predose)[c] | 00:00 | X | X | X |
| | (EOI)[d] | 00:30 | X | | |
| C3D1 | (Predose)[c] | 00:00 | X | | X |
| C4D1 | (Predose)[c] | 00:00 | | | X |
| C6D1 | (Predose)[c] | 00:00 | X | X | X |
| CXD1: Every 4 cycles after C6 D1 (ie, C10D1, C14D1, etc.) | (Predose)[c] | 00:00 | X | X | |
| Safety Follow-up Visits 1 & 2 (28 days and 5 months, respectively, from the treatment discontinuation during the Treatment Phase or at 24 months after initiation of oral/IV combination study treatment) | NA | NA | X | X | |

Abbreviations: C = cycle; D = day; EOI = end of infusion; IV = intravenous; NA = not applicable; PK = pharmacokinetic; SFU1 = Safety Follow-up Visit 1; SFU2 = Safety Follow-up Visit 2.

[a] = If a participant discontinues study drug treatment during the sampling period (ie, prior to 24 months after initiation of oral/IV combination study treatment), all subsequent CXD1 samples will be inapplicable, but samples will be collected on the 28-day SFU1 and the 5-month SFU2 for nivolumab PK and immunogenicity analysis.

[b] = PK samples for rucaparib are to be collected approximately 12 hours after the last dose, but prior to the next dose (ie, within 1 hour). If dosing is held for toxicity or any other reason, PK sample should still be collected at the end of treatment Cycles 1, 2, 3, and 5.

[c] = All predose samples for nivolumab should be taken (preferably within 30 minutes) prior to the start of nivolumab infusion. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[d] = EOI-nivo: **EOI samples should be collected immediately (preferably within 5 minutes) prior to stopping nivolumab infusion**. If the end of infusion is delayed, the collection of the EOI samples should be delayed accordingly. Please ensure accurate collection of time/date of sample collection. EOI samples may not be collected from the same IV access as drug was administered.

## 7.2 Informed Consent

The investigator or their designee shall discuss with each patient the nature of the study and its requirements. To participate in the study, informed consent must be obtained from each potential patient prior to any study activities. The information on the IRB/ ERC-approved consent form should be translated and communicated in the language the patient (or legally authorized representative) can understand. A separate consent form may be used for tissue testing.

Analysis of tumor tissue for a deleterious BRCA1/2 mutation (germline or somatic) will be performed using the Foundation Medicine's NGS test (germline/somatic status will not be differentiated as such in the test report). These results will be provided to patients who consent to receive this information. In the event a BRCA1/2 alteration is identified in tumor tissue, the patient may be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If mutations other than BRCA1/2 are identified by the NGS test, they will also be provided to patients who consent to receive this information when they discontinue from treatment.

Additionally, patients participating in the optional tumor tissue biopsy at the time of radiographic disease progression/randomized treatment discontinuation must provide additional consent for this procedure.

All procedures and assessments are to be completed within ± 3 days of the scheduled time unless otherwise stated.

## 7.3 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to randomization within the allowable windows of time as indicated below. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable to be used as a study procedure only if confirmed to have been standard of care. Screening procedures may be repeated if the findings/results are considered invalid or not representative of the patient's baseline medical status. When screening procedures are repeated, the rationale should be documented in the source file.

Consent may be completed outside the 120-day screening window as consent does not expire. Reconsent is not required if outside the screening window. The screening period begins with the first study-specific procedure, performed outside standard of care, and only after consent for study participation has been provided.

### 7.3.1 Within 120 Days Prior to Randomization

- Medical/oncology history, including demographic information (birth date, race, gender, etc.), smoking status, and oncology history, including date of diagnosis for epithelial ovarian, primary peritoneal, or fallopian tube cancer (and other malignancy, if applicable), prior surgeries/treatments received for cancer, dates of treatment

administration, best response achieved, radiology reports, and BRCA1/2 mutation status (if known);

- FFPE archival tumor tissue or screening biopsy sample. Sufficient archival FFPE tumor tissue (enough for 1 × 4 µm section for H&E and approximately 8 to 12 × 10 µm sections [unstained], or equivalent) is required for study participation per inclusion criteria #9. In addition to this minimum requirement, it is highly desirable to have additional 4 × 4 µm sections and 2 × 10 µm sections for other planned analyses. Refer to Section 7.5.7.1 for more information and to the central Laboratory Manual for detailed sample handling instructions.
  - Tumor tissue from the cytoreductive surgery must be provided.
  - Tumor tissue from a pre-treatment biopsy should be provided, if available, for patients treated with neoadjuvant chemotherapy (a core biopsy is preferred).
  - Submission of a tumor block preferred; if sections are provided, these must all be from the same tumor sample.
  - Tumor content ≥ 30% is strongly preferred for successful genomic scarring/LOH analysis. At a minimum, the tumor BRCA status is required. If LOH status is unknown in patients without BRCA mutations, enrollment is permitted, but attempts will be made to obtain additional tissue to enable an LOH result for final analysis.
  - Sample must be submitted to the central laboratory **at least 3 weeks prior to planned start of treatment** in order to enable stratification for randomization.
- AE monitoring (only record if related to screening procedures).

### 7.3.2 Up to 28 days Prior to Randomization

- PRO collected using the TOI FACT-O, and EQ-5D-5L instruments or other collection format, as appropriate (complete before other procedures);
- Physical examination by body system, including height and weight;
- Vital signs (blood pressure, pulse, and body temperature);
- 12-lead ECG;
- Prior and concomitant medications, any surgical/ medical procedures, and update medical history;
- Disease/tumor assessment: assessments should consist of clinical examination and appropriate imaging techniques per RECIST v1.1 (CT scans and/or MRI scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1). Other complementary studies (X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow lesions throughout the clinical study;
- ECOG performance status (Appendix 3);
- Blood sample for ctDNA analysis; and
- AE monitoring (only record if related to screening procedure).

- Optional collection of pre-treatment core biopsies from patients who have measurable disease and disease that is accessible for biopsy, after chemotherapy is completed and prior to initiating study drug as outlined in this protocol. If a biopsy was recently performed as standard of care prior to this patient consenting to this study, or after study informed consent but outside the 28-day screening window, this may be acceptable with advance approval from the sponsor.

### 7.3.3 Up to 14 days Prior to Randomization

- Hematology: includes red blood cell count (RBC) and parameters (hemoglobin, hematocrit, MCV, MCH, and mean corpuscular hemoglobin concentration [MCHC]) and reticulocyte count, white blood cell count (WBC) and differential (with ANC), and platelet count;
- Serum chemistry: includes total protein, albumin, creatinine, or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, glucose, sodium, potassium, magnesium, chloride, bicarbonate ($CO_2/HCO_3^-$), calcium, phosphorus, lactate dehydrogenase (LDH), folic acid, and total cholesterol. Also, thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4) at screening; TSH with reflexive fT3 and fT4 if TSH is abnormal on treatment. *Note: fasting is not required*;
- Serology serum for hepatitis B surface antigen and hepatitis C antibody (screening only). Note: testing for HIV must also be performed at screening if mandated locally by a given site;
- Urinalysis (performed on freshly voided clean sample): includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings;
- CA-125 measurement (Appendix 2);
- Update medical history; and
- AE monitoring (only record if related to screening procedure).

### 7.3.4 Up to 3 days Prior to First Dose of Study Drug

- Update medical history; and
- AE monitoring (only record if related to screening procedure).

## 7.4 Treatment Phase

### 7.4.1 Day 1 of Cycle 1

The following procedures/assessments will be completed before study drug is administered:

- PRO using the TOI FACT-O and EQ-5D-5L instruments or other format, as appropriate;
- Physical examination;
- Weight;
- Vital Signs;
- Concomitant medications and procedures;
- ECOG performance status (Appendix 3);
- Hematology;
- Serum chemistry (fasting is not required);
- CA-125 measurement;
- Blood sample for ctDNA analysis;
- Blood sample for determining germline/somatic BRCA status (Cycle 1 only; if sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter);
- Dispensation of oral study drug;
- AE monitoring.

Oral study drug (rucaparib or oral placebo) will be dispensed to the patient in sufficient quantity to last until the next treatment cycle. Patients will ingest oral study drug BID at about the same times every day, as close to 12 hours apart as possible. Patients may take study drug with or without food (with a regular meal or within 30 minutes after a regular meal). Patients will record dosing information in their dosing diary.

Patients will be instructed to refrain from taking their morning daily dose of study drug at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

### 7.4.2 Days 15 of Cycle 1 and 2

The following procedures will be completed:

- Vital Signs;
- Concomitant medications and procedures;
- ECOG performance status (Appendix 3);
- Hematology;

- Serum chemistry (fasting is not required);
- AE monitoring.

Patients will ingest oral study drug (rucaparib or placebo) BID at about the same times every day, at close to 12 hours apart as possible. Patients may take study drug with or without food. Patients will record dosing information in their dosing diary. Patients will be instructed to refrain from taking their morning daily dose of study drug at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

### 7.4.3 Cycle 2 Day 1

The following procedures/assessments will be completed before study drug is administered:

- PRO using the TOI FACT-O and EQ-5D-5L instruments or other format, as appropriate;
- Physical examination;
- Weight;
- Vital Signs;
- Concomitant medications and procedures;
- ECOG performance status (Appendix 3);
- Hematology;
- Serum chemistry (fasting is not required);
- CA-125 measurement;
- Blood sample for ctDNA analysis;
- Blood sample for determining germline/somatic BRCA status (Cycle 1 only; if sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter);
- PK samples for nivolumab prior to and after the IV infusion (see Table 6 and Section 7.5.6);
- Immunogenicity sample for nivolumab prior to the IV infusion (see Table 6 and Section 7.5.6);
- Plasma PK sample for rucaparib (prior to first dose taken that day) (see Table 6 and Section 7.5.6);
- Administration of IV study drug;
- Dispensation of oral study drug;
- AE monitoring.

Oral study drug (rucaparib or oral placebo) will be dispensed to the patient in sufficient quantity to last until the next treatment cycle. Patients will ingest oral study drug BID at

about the same times every day, as close to 12 hours apart as possible. Patients may take study drug with or without food (with a regular meal or within 30 minutes after a regular meal). Patients will record dosing information in their dosing diary.

Patients will be instructed to refrain from taking their morning daily dose of study drug at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

### 7.4.4 Day 1 of Cycles 3 and Beyond

The following procedures will be completed:

- Physical examination;
- Weight;
- Vital signs;
- Concomitant medications and procedures;
- Disease assessment/tumor scans every 12 calendar weeks (within 7 days prior is permitted) relative to C2D1 for the first 3 years and every 24 weeks thereafter until objective radiological disease progression;
- PRO, using the TOI FACT-O and EQ-5D-5L instruments or other format, as appropriate, at Cycle 3, Cycle 5, and then every 12 weeks, to coincide with disease assessment/tumor scans (perform before other assessments that day) until treatment discontinuation or until the data cut-off for the primary analysis, whichever comes first;
- ECOG performance status (Appendix 3);
- Hematology;
- Serum chemistry (fasting is not required);
- CA-125 measurement;
- Blood sample for ctDNA analysis (Day 1 of Cycle 1 through Cycle 6, and at the same time as radiological imaging thereafter);
- PK samples for nivolumab prior to the IV infusion at Cycle 6 and every 4 cycles thereafter while IV study drug continues (see Table 6 and Section 7.5.6);
- Immunogenicity sample for nivolumab prior to the IV infusion at Cycle 6 and every 4 cycles thereafter while IV study drug continues (see Table 6 and Section 7.5.6);
- Administration of IV study drug;
- AE monitoring;
- Plasma PK samples for rucaparib (prior to the first dose of study drug taken this day; Cycle 3 and Cycle 4 only; see Section 7.5.6).

Oral study drug (rucaparib or placebo) will be dispensed to the patient in sufficient quantity to last until the next clinic visit; for Cycles 3 and 4, oral study drug can be resumed after the PK sample is collected. Patients may take study drug with or without food. Patient will record dosing information in their dosing diary.

Patients will continue dosing with study drug at home with or without food, taking doses BID at about the same times every day. Patients will record dosing information in their dosing diary.

### 7.4.5 Post-treatment Follow-up Phase

#### 7.4.5.1 End of Treatment

Upon treatment discontinuation, regardless of the reason, patients will have an End-of-Treatment Visit as soon as feasible. The following procedures will be performed:

- PRO using the TOI FACT-O and EQ-5D-5L instruments or other format, as appropriate;
- Physical examination;
- Weight;
- Vital signs;
- 12-lead ECG;
- Concomitant medications and procedures;
- Tumor scans (using the same methodology as was used at screening and only if it has been 12 weeks or more since last scan) if reason for treatment discontinuation was other than disease progression based on radiologic assessment;
- ECOG performance status (Appendix 3);
- Hematology;
- Serum chemistry (fasting is not required);
- CA-125 measurement;
- Blood sample for ctDNA analysis;
- AE monitoring;
- Optional tumor tissue biopsy collection at time of disease progression/randomized treatment discontinuation (requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the central Laboratory Manual for detailed sample handling instructions.

#### 7.4.5.2 28-day Safety Follow-up (Safety Follow-up Visit 1 [SFU1])

The procedures to be performed for all patients 28 (± 7) days after the last dose of study drug (oral or IV, whichever is later) are listed below.

- PRO collected using the TOI FACT-O and EQ-5D-5L instruments or other format, as appropriate;
- Physical examination;
- Weight;
- Vital signs;
- 12-lead ECG;
- ECOG performance status (Appendix 3);
- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans should continue to be performed at 12-week intervals (up to 7 days prior permitted) relative to C2D1 for the first 3 years and every 24 weeks thereafter until radiologic disease progression by RECIST v1.1, as assessed by the investigator, is documented;
- Blood sample for ctDNA analysis should be collected at the same time as radiological imaging;
- CA-125 measurement should be performed at the same time as radiological imaging;
- Hematology;
- Serum chemistry (fasting is not required);
- PK sample for nivolumab (see Table 6 and Section 7.5.6);
- Immunogenicity sample for nivolumab (see Table 6 and Section 7.5.6);
- AE monitoring;
- Concomitant medications and procedures.

#### 7.4.5.3 5-month Safety Follow-up (Safety Follow-up Visit 2 [SFU2])

The procedures to be performed for all patients 5 calendar months (± 7 days) after the last dose of IV study drug are listed below. If a patient remains on oral study drug after discontinuation of IV study drug, the 5-month Safety Follow-up Visit can be performed at a cycle visit, provided it has been at least 5 months since the last IV dose.

- PRO collected using the TOI FACT-O and EQ-5D-5L instruments or other format, as appropriate;
- Physical examination;
- Weight;
- Vital signs;
- 12-lead ECG;
- ECOG performance status (Appendix 3);

- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans should continue to be performed at 12-week intervals (up to 7 days prior permitted) relative to C2D1 for the first 3 years and every 24 weeks thereafter until radiologic disease progression by RECIST v1.1, as assessed by the investigator, is documented;
- Blood sample for ctDNA analysis should be collected at the same time as radiological imaging;
- CA-125 measurement should be performed at the same time as radiological imaging;
- Hematology (only required if toxicities are present);
- Serum chemistry (fasting is not required) (only required if toxicities are present);
- PK sample for nivolumab (see Table 6 and Section 7.5.6);
- Immunogenicity sample for nivolumab (see Table 6 and Section 7.5.6);
- AE monitoring;
- Concomitant medications and procedures.

### 7.4.6 Long-term Follow-up (LTFU)

Patients who complete the Safety Follow-up Visit(s) after the last dose of study treatment will continue in long-term follow-up as described below.

- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans should continue to be performed at 12-week intervals (up to 7 days prior permitted) relative to C2D1 for the first 3 years and every 24 weeks thereafter until radiologic disease progression by RECIST v1.1, as assessed by the investigator, is documented;
- CA-125 measurement should be performed at the same time as radiological imaging;
- Subsequent treatments, secondary malignancy monitoring, and OS information will be collected for all patients every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent from study, or closure of the study, starting 12 weeks after SFU1. Follow-up can be performed via the telephone. Diagnosis of any secondary malignancy requires appropriate documentation (ie, laboratory and/or pathology reports) and should be reported as indicated in Section 8.7;
- SAEs assessed as potentially related to study drug, and AESIs of MDS and AML irrespective of causality, are to be reported as specified in Section 8.7;
- SAEs unrelated to IV drug do not need to be captured after the 28-day follow-up visit/period. Only those related or possibly related to IV drug should be captured until the 5-month SFU2.

## 7.5 Methods of Data Collection

### 7.5.1 Medical History and Demographic/ Baseline Characteristics

Basic demographic and baseline characteristics will be collected during screening. In addition to the evaluation of a patient's medical history in terms of study eligibility, all relevant medical conditions will be documented on the appropriate eCRF. Events that occur after signing of informed consent but prior to initiation of study drug, unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF.

The patient's entire oncology history will be collected on the appropriate eCRF including date of diagnosis for epithelial ovarian, primary peritoneal, or fallopian tube cancer (and other malignancy, if applicable), prior surgeries/ treatments received for cancer, dates of treatment administration, best response achieved, date of progression and how assessed, radiology reports, and BRCA1/2 mutation status and if gBRCA or sBRCA (if known).

### 7.5.2 Prior and Concomitant Medication Assessments

Medications being used by the patient will be recorded as prior medications during screening from Days -28 to -1, and as concomitant medications following receipt of the first dose of study drug through the completion of the 28-day Safety Follow-up Visit. Any concomitant medication given for AEs related to IV drug up to 5 months after IV treatment discontinuation will also be recorded. Medications information will be entered in the appropriate eCRF after it is obtained at each study visit.

Following treatment discontinuation, subsequent anticancer treatments will be collected for all patients every 12 or 24 weeks (± 14 days), to coincide with tumor assessments, until death, loss to follow-up, withdrawal of consent from study, or closure of the study. With the exception of the 28-day and 5-month Safety Follow-up Visits, follow-up can be performed via the telephone.

### 7.5.3 Efficacy Evaluations

#### 7.5.3.1 Disease/ Tumor Assessments

Tumor assessment measurements will be performed at screening, at the end of every 12 weeks of treatment (up to 7 days prior permitted) relative to C2D1 for the first 3 years and every 24 weeks thereafter until objective radiological disease progression. If C2D1 visit did not occur, the first on-study scan should occur 16 weeks after C1D1. Tumor assessments should be performed at the time of treatment discontinuation if the reason for discontinuation was other than radiologically confirmed disease progression and it has been ≥ 12 weeks since the last assessment. In addition, tumor assessments should be made as clinically indicated. Also see Section 6.8.

Disease assessment will comprise clinical examination and appropriate imaging techniques per RECIST v1.1 (CT and/or MRI scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST). Other complementary studies (X-ray, PET, and ultrasound) may be performed if required. If a site can document that the CT performed as part of a

PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements. All sites of disease should be followed, and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. CT/MRI scans of the chest, abdomen, and pelvis performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline. Investigators should perform scans of other anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status. Imaging guidelines provided by the BICR vendor and should be followed for the collection of images and the radiological assessment of disease.

Tumor response will be interpreted using RECIST v1.1. Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals (up to 7 days prior permitted) relative to C2D1 for the first 3 years and every 24 weeks thereafter until objective radiologic disease progression by RECIST v1.1, as assessed by the investigator, is documented, or initiating subsequent anticancer treatment.

Copies of CT scans (and other imaging, as appropriate) will be collected from all patients for BICR. Refer to imaging charter from BICR vendor.

#### 7.5.3.2 Tumor Markers

Blood samples to assess CA-125 will be collected at screening, on Day 1 of Cycle 1, at the start of every cycle thereafter, at treatment discontinuation, and as clinically indicated. All CA-125 tests will be performed by a central laboratory.

For patients that are in LTFU and continuing to have disease assessments, CA-125 values should be assessed by a local laboratory, if feasible, at the time of radiological imaging.

### 7.5.4 Safety Evaluations

#### 7.5.4.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. During the screening period, unless otherwise required by local regulations, SAEs which are related to protocol-mandated assessments will be reported. Once enrolled and study drug is administered, patients will be monitored for all AEs/SAEs/AESIs during study participation and until 28 days after the last dose of oral study drug and 5 months after the last dose of IV study drug, whichever occurs

later. After the 28-day (oral) or 5-month (IV) window, only SAEs assessed as potentially related to study drug (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML irrespective of causality, need to be reported. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution or stabilization or until loss to follow-up. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (v5.0) and recorded on the eCRF.

If a patient begins subsequent anticancer therapy, the sponsor will terminate collection of SAEs, with the exception of the AESIs of MDS and AML.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 8.

#### 7.5.4.2 Clinical Laboratory Investigations

With the exception of urinalysis samples, all other samples collected will be analyzed by a central laboratory; a duplicate sample may be collected and analyzed by the local laboratory for immediate eligibility/ treatment decisions. If a patient has a known, clinically significant laboratory abnormality and/or associated symptoms that would require AE management or interruption of the IV study drug, either central or local laboratory tests should be analyzed prior to each administration of an IV drug infusion. The panels of laboratory tests to be performed are shown below:

**Hematology:** RBC and parameters (hemoglobin, hematocrit, MCV, MCH, and MCHC) and reticulocyte count, WBC and differential (with ANC), and platelet count will be assessed for all patients at screening, during treatment at each study visit, and at the Treatment Discontinuation Visit, 28-day SFU1, and at the 5-month SFU2, if toxicities are present. Hematology results must be reviewed by the investigator before the start of study drug and ongoing at times testing occurs. Additional and more frequent tests may be performed at the investigator's discretion.

**Clinical Chemistry:** total protein, albumin, creatinine or estimated GFR using the Cockcroft-Gault formula or institutional standard formula, BUN or urea, total bilirubin, ALP, ALT, AST, LDH, glucose, sodium, potassium, magnesium, chloride, bicarbonate ($CO_2$,/$HCO_3^-$), calcium, phosphorus, TSH, Free triiodothyronine (T3; fT3); Free thyroxine (T4, fT4) at screening; TSH with reflexive fT3 and fT4 if TSH is abnormal on treatment, folic acid (first 6 cycles only), and total cholesterol will be assessed for all patients at screening, during treatment at each study visit, and at the Treatment Discontinuation Visit, 28-day SFU1, and at the 5-month SFU2, if toxicities are present. Fasting is not required before blood sampling. If pancreatitis is suspected clinically, serum lipase and amylase should be analyzed. Serum chemistry results must be reviewed by the investigator before the start of treatment with study drug and ongoing at times testing occurs.

In addition to the clinical chemistry assessments above, serology serum for hepatitis C antibody and hepatitis B surface antigen should be performed at screening. Testing for HIV must also be performed at screening if mandated locally by a given site.

**Urinalysis:** performed locally on a freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on the investigator's judgment, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at screening only, but may be conducted at other times as clinically indicated.

Laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow-up to the abnormalities, will be documented on the eCRF as an AE. Refer to Section 8.5 for guidelines on reporting of abnormal laboratory values as AEs.

#### 7.5.4.3 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature and will be taken after the patient has been resting for at least 5 minutes during screening, at study visits during the Treatment Phase, and at the Treatment Discontinuation Visit.

#### 7.5.4.4 12-Lead Electrocardiogram

For all patients, local 12-lead ECGs will be taken at screening (within 28 days prior to first dose of study drug), at End-of-Treatment Visit, and at both SFU1 and SFU2.

The following will be measured or calculated: heart rate, PR, QRS, QT, QTc, and rhythm. The investigator or qualified designee will review the ECGs locally and assess the results as normal or abnormal (clinically significant or not clinically significant).

If it is clinically indicated, ECGs can be performed at other times during the study.

#### 7.5.4.5 Body Weight and Height

Height will be measured during the Screening Visit only. Weight will be measured per institutional guidelines during screening, on Day 1 of each cycle, and at the Treatment Discontinuation Visit.

#### 7.5.4.6 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Complete physical examinations will be performed during screening and at End of Treatment. Physical examinations at study visits during the Treatment Phase will be limited as appropriate.

#### 7.5.4.7 ECOG Performance Status

ECOG performance status (Appendix 3) will be assessed during screening, at study visits during the Treatment Phase, and at End of Treatment. The ECOG performance status should

be assessed by the same study personnel at each visit, if possible. For eligibility purposes, patients with borderline ECOG performance status should be considered carefully to avoid enrolling patients who may have significant impairment.

### 7.5.5 Patient-reported Outcomes

PRO utilizing the TOI FACT-O and EQ-5D-5L instruments (see Appendix 5 and Appendix 6) 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 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 will complete the assessments on an electronic device or other format (ie, paper form), as appropriate, before any other scheduled study procedures are performed and dosing occurs (if applicable).

### 7.5.6 Pharmacokinetic and Immunogenicity Evaluations

Samples for nivolumab and rucaparib PK and immunogenicity assessments will be collected for all patients, as described in Table 6. For nivolumab, corresponding serum samples designated for either PK or immunogenicity assessments may also be used for either of those analyses, if required (eg, insufficient sample volume to complete testing).

#### 7.5.6.1 Rucaparib Pharmacokinetic Sample Collection

For all patients, plasma samples are to be collected for trough level PK analysis of oral study drug within 1 hour before the morning dose on Day 1 of Cycle 2, 3, 4, and 6. Plasma samples are to be collected approximately 12 hours after the last oral dose, but prior to the next oral dose (ie, typically within 1 hour prior to dosing). If oral dosing is held for toxicity or any other reason, plasma samples for PK should still be collected at the end of treatment Cycles 1, 2, 3, and 5.

A central laboratory will be used for bioanalysis of plasma rucaparib concentration measurement. Please refer to the central Laboratory Manual for details on collection and processing of blood PK samples.

#### 7.5.6.2 Nivolumab Pharmacokinetic Sample Collection

All time points are relative to the start of IV treatment administration. All on-treatment time points are intended to align with days on which IV treatment is administered. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the IV dose is subsequently delayed, then an additional pre-dose sample should not be collected.

Blood samples should be drawn from a site other than the nivolumab/IV placebo infusion site (ie, contralateral arm) on days of infusion. All samples collected pre-dose should be collected just prior to the administration from the contralateral arm (ie, the arm not used for the

infusion). If the nivolumab/IV placebo infusion was interrupted, the interruption details will also be documented on the eCRF. Blood samples will be processed to collect serum and stored preferably at -70°C (samples may be stored at -20°C up to 2 months). Further details of PK sample collection and processing will be provided to the site in the central Laboratory Manual. Serum concentration analyses for nivolumab will be performed by validated bioanalytical method(s).

#### 7.5.6.3 Nivolumab Immunogenicity Assessments

Samples for nivolumab immunogenicity assessment will be collected from all patients receiving nivolumab/rucaparib, active or placebo, as described in Table 6.

The serum samples will be analyzed for anti-nivolumab drug antibody (ADA) by validated immunoassays. Samples with a positive ADA response may also be analyzed for neutralizing ADA response to nivolumab. The immunogenicity (and corresponding drug exposure) data from these samples will be reported as part of a participant's overall immunogenicity assessment. Selected serum samples may be analyzed by an exploratory method that measure nivolumab or detect ADA for technology exploration purposes; exploratory results will not be reported. Further details of immunogenicity sample collection and processing will be provided to the site in the central Laboratory Manual.

### 7.5.7 Biomarker Analysis

#### 7.5.7.1 Biomarker Analysis – Tumor Tissue

A sufficient quantity of tumor tissue from the cytoreductive surgery must be provided during the screening process and submitted **to the central laboratory directly at least 3 weeks prior to the planned randomization** for determination of HRD status. This tumor tissue is required for HRD stratification for randomization and for additional biomarker testing described below. If the patient received neoadjuvant chemotherapy, a pre-treatment core biopsy should also be provided, if available.

Sufficient quantity of tumor tissue must be confirmed by central laboratory testing in these patients during the study.

Sufficient archival FFPE tumor tissue (enough for 1 × 4 µm section for H&E and approximately 8 to 12 × 10 µm sections [unstained], or equivalent) is required for study participation per inclusion criteria #9. In addition to this minimum requirement, it is highly desirable to have an additional 4 × 4 µm sections and 2 × 10 µm sections for other planned analyses. In addition to determining HRD status, gene expression profiling on extracted RNA will be analyzed to classify tumors into gene expression molecular subtypes, which have been shown to associate with patient survival in HGSOC.[79] Refer to the central Laboratory Manual for details. The tumor tissue sample must be of adequate quality (at least 20% tumor content [≥ 30% is strongly preferred] with a minimum of 80% nucleated cellular content), or a new sample must be acquired.

Optional pre-treatment core biopsies may be taken from patients who have measurable disease and disease that is accessible for biopsy, after chemotherapy is completed and prior to initiating study drug as outlined in this protocol.

A tumor tissue biopsy sample from the time of disease progression/randomized treatment discontinuation until the start of the next treatment is optional; patients must provide additional consent for this optional tumor tissue biopsy sample. If disease progression is caused by appearance of a new lesion(s), the lesion(s) should be prioritized for the optional biopsy. Detailed sample handling instructions are located in the central Laboratory Manual.

The tumor specimens will be sequenced using Foundation Medicine's NGS-based test, which examines a panel of cancer-related genes, including BRCA1/2 and other homologous recombination pathway genes, and assesses the percentage of genomic LOH. The goal is to assess mutations in these genes as molecular markers for predicting response or resistance to the combination of rucaparib and nivolumab. The NGS-based test will also enable assessment of TMB as a molecular marker for efficacy.

In addition, immunohistochemistry staining of the tumor specimen will be performed to assess protein expression of immune-related markers, such as PD-L1, as a molecular marker for efficacy.

#### 7.5.7.2 Biomarker Analysis – ctDNA

Blood samples will be collected during screening, before dosing on Day 1 of Cycles 1 to 6, at the time of radiologic imaging, and at treatment discontinuation from all patients entered in the study for plasma ctDNA analysis. Sample collection details will be provided in the central Laboratory Manual.

These samples will be used for ctDNA profiling to assess alterations in genes that may be associated with response and resistance to the combination of rucaparib and nivolumab.

#### 7.5.7.3 Biomarker Analysis - Genomic DNA from Blood

A blood sample for genomics analysis will be collected at Cycle 1 Day 1 from all patients for determination of germline status of mutations identified using NGS testing. Results may be provided to patients who consent to receive this information upon availability of this information. Sample collection details will be provided in the central Laboratory Manual.

#### 7.5.7.4 Additional Research

The patient will have the option to provide additional consent to allow the sponsor to retain residual samples for future unspecified research.

# 8 ADVERSE EVENT MANAGEMENT

## 8.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a non-leading question (eg, "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE). Symptoms reported spontaneously by the patient during the physical examination would also qualify as an AE (and hence documented on the AE eCRF, instead of the physical examination eCRF, which is reserved for physical signs or findings).

## 8.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (or, occurs after informed consent is given and prior to dosing if the SAE is related to a study procedure) that:

- Results in death. Any event resulting in death during the reporting period (from date of first dose of study drug through 28 days after last dose of oral drug or IV study drug, whichever occurs later) must be treated as an SAE and reported as such. In addition, any event resulting in death that occurs more than 28 days after last dose of oral or IV study drug that is considered treatment-related should be reported as an SAE. An event related to a study procedure that occurs after informed consent, but prior to dosing that results in death must also be reported as an SAE;
- Is life-threatening (patient is at immediate risk of death from the event as it occurred);
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization;
- Results in persistent or significant disability/ incapacity;
- Results in a congenital anomaly or birth defect; or
- Is an important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical

intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

## 8.3 Definition of an Adverse Events of Special Interest

AESIs (serious or nonserious) are defined as AEs of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted.

Details on the sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to the sponsor within 24 hours of knowledge of the event (see Section 8.7 for reporting instructions).

## 8.4 Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/ or convenience situations (eg, respite care);
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward);
- Overdose of either study drug or concomitant medication unless associated with an SAE. However, the event should still be captured as a nonserious AE on the appropriate eCRF page;
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an AE or SAE; and
- Events that meet the SAE criteria (as outlined in Section 8.2) and occur after informed consent but before the first dose of study drug, which are considered unrelated to protocol-mandated screening procedures.

## 8.5 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in laboratory values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality;
- intervention for management of the abnormality is required; or
- at the discretion of the investigator should the abnormality be deemed clinically significant.

## 8.6 Pregnancy or Drug Exposure During Pregnancy

Pregnancy is an exclusion criterion. In addition, due to inclusion criteria #4, requiring at least a bilateral salpingo-oophorectomy and partial omentectomy, women of child-bearing potential will not be randomized in this study.

All study participants must avoid pregnancy achieved through assisted reproductive technology, for the duration of study treatment and for a minimum of 6 months following the last dose of study drug (oral or IV, whichever is later).

## 8.7 Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

Events that occur after signing of informed consent but prior to initiation of study drug, unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF; however, events are to be reported as SAEs if serious and related to a protocol-mandated procedure during this time. Any AE (serious or non-serious) that occurs after first dose of study drug through 28 days after receiving the last dose of oral or IV study drug, whichever occurs later, will be recorded on the AE eCRF. Additionally, only AEs that are related to IV drug that occur between 28 days and 5 months after the last dose of IV drug will be recorded on the AE eCRF.

After the 28-day reporting window following discontinuation of randomized treatment, only SAEs assessed as potentially related to study drug should be reported.

After the 28-day or 5-month reporting window after discontinuation of randomized treatment, AESIs of MDS and AML, irrespective of causality, should be reported.

- AESIs of pneumonitis or similar events should only be reported up to, but not beyond, the SFU1 (28-days after the last dose of rucaparib). After this period, only events considered serious and related to study drug should be reported as SAEs (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia), if considered to be related to study drug.

Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 8.8.

In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis, if appropriate. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

SAEs and AESIs that occur during the study or within 28 days after receiving the last dose of oral study drug or 5 months after receiving the last dose of IV study drug, whichever is later, whether or not related to study drug, must be reported immediately (ie, **within 24 hours** of knowledge of the event or additional information for a previously-reported event) to the sponsor/SAE designee. The contact information for reporting of SAEs/AESIs can be found on the SAE/ AESI Reporting Form.

### 8.7.1 Onset Date of Adverse Events

The onset date is the date that the event or the signs/symptoms attributed to the event started.

### 8.7.2 Resolution Date of Adverse Events

The resolution date is the date that the event or the signs/symptoms attributed to the event resolved or resolved with sequelae or it is the date when the patient has reached a new baseline if the event is not expected to resolve.

### 8.7.3 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, v5.0 grading scale.[80]

Severity is not the same as Serious.

For AEs not covered by NCI CTCAE, the severity will be characterized as mild, moderate, severe, life-threatening, or fatal according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities;
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities;
- Severe events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required;
- Life-threatening events require urgent intervention to prevent death; or
- Fatal events are events that lead to the patient's death.

### 8.7.4 Causal Relationship of Adverse Events to Study Drug

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge with the study drug.

| | |
|---|---|
| Not Related to Study Drug | • An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.)<br>• It does not follow a reasonable temporal sequence from administration of the study drug.<br>• It does not follow a known pattern of response to study drug<br>• It does not reappear or worsen when study drug is restarted.<br>• An alternative explanation is likely, but not clearly identifiable. |
| Related to Study Drug | • An AE that is difficult to assign to alternative causes.<br>• It follows a strong or reasonable temporal sequence from administration of study drug.<br>• It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient.<br>• It follows a known response pattern to study drug<br>• It is confirmed with a positive rechallenge or supporting laboratory data. |

### 8.7.5 Outcome and Action Taken

The investigator will record the action taken and outcome for each AE according to the following criteria:

**Action Taken with Study Drug (note all that apply)**

- None
- Dose reduced/delayed
- Study drug temporarily interrupted
- Study drug permanently discontinued
- Other (specify)

**Outcome**

- Recovered
- Recovered with sequelae
- Recovering/ Resolving/ Improving
- Ongoing
- Death
- Lost to follow-up

## 8.8 Follow-Up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 28 days after the last dose of oral study drug or 5 months after the last dose of IV study drug, whichever occurs later. Any SAEs, AESIs, and treatment-related Grade 3/4 AEs must be followed until resolution or stabilization, or until lost to follow-up. After the 28-day (oral) or 5-month (IV) window, only SAEs assessed as potentially related to study drug (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML irrespective of causality, should be reported. AESIs of pneumonitis or similar events should only be reported up to, but not beyond, SFU1.

## 8.9 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria,[49] must be reported as SAEs (see Section 8.10 for reporting details).

Potential drug induced liver injury is defined as:

1. ALT or AST elevation > 3 × ULN

AND

2. Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of ALT/AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

## 8.10 Regulatory Aspects of Serious Adverse Event and Adverse Events of Special Interest Reporting

All SAEs and AESIs, regardless of relationship to study drug, must be reported to the sponsor/ SAE designee **within 24 hours** of knowledge of the event, during the study through 28 days after receiving the last dose of oral study treatment and 5 months after receiving the last dose of IV study treatment, whichever occurs later, according to the procedures below. After the 28-day window, only SAEs considered to be potentially treatment-related (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report. **The Serious Adverse Event (SAE)/Adverse Events of Special Interest (AESI) Report Form must be used for reporting SAEs and AESIs. The contact information for reporting of SAEs and AESIs can be found on the SAE/ AESI Reporting Form.**

The sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the FDA, according to 21 Code of Federal Regulations (CFR) 312.32; to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA); to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other applicable regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

The sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

## 8.11 Independent Data Monitoring Committee

No formal efficacy interim analyses are planned.

An IDMC will be established to review safety and efficacy data in compliance with a prospective charter. The IDMC will be comprised of medical 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 responsibilities, authorities, and procedures will be documented in the IDMC charter, which will be endorsed and signed by the IDMC prior to the first data review meeting.

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 HRD subgroups (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$)

Results from the open-label safety cohort(s) will be shared with the IDMC.

Following data review, the IDMC will recommend continuation, revision, or termination of the study and/or continuing or halting enrollment into a particular subgroup. The IDMC may recommend that the study be stopped for futility if the data indicate that the invPFS benefit will very likely not be achieved and/or there is excessive toxicity observed in the rates of serious and/or Grade 3 and 4 AEs.

The IDMC will meet at least semi-annually after sufficient data has been collected. The IDMC chairperson may convene formal IDMC meeting if there are safety concerns. The sponsor can also request an IDMC review of safety data.

Details regarding the IDMC will be documented in a separate committee charter.

# 9 PLANNED STATISTICAL METHODS

## 9.1 General Considerations

All safety analyses will be summarized for all patients who received at least 1 dose of protocol-specified 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. If estimable, 50th (median) percentile with the 95% CI will be summarized for each randomized treatment group. The stratified hazard ratio from the log-rank test and 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.

All data will be used to their maximum possible extent but without any imputations for missing data. Unless otherwise specified, baseline is defined as the last measurement on or prior to the first day of study drug administration.

All statistical analyses will be conducted with the statistical analysis software (SAS®) System, Version 9.4. Further details around the statistical analyses planned in this study will be outlined in the Statistical Analysis Plan (SAP).

## 9.2 Determination of Original Sample Size

### 9.2.1 Determination of Sample Size in Original Protocol

Up to approximately 1000 patients will be randomized in a 4:4:1:1 ratio to receive treatment with one 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$^{unknown}$), disease status (no residual disease vs residual disease), and timing of surgery (primary surgery vs. interval debulking).

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

1. Arm A (oral rucaparib + IV nivolumab) vs Arm B (oral rucaparib + IV placebo)
2. Arm A (oral rucaparib + IV nivolumab) vs Arm D (placebo [oral and IV])
3. Arm B (oral rucaparib + IV placebo) vs 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 the total patient population (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) [oral 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 sub/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 sub/populations.

| Group | Hazard Ratio | Cumulative N (4:4) | 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 deficiency (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 sub/populations. The power associated with comparison 2 of Arm A (rucaparib + nivolumab) to Arm D (placebo) is assumed to be higher than for 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 deficiency (tBRCA + non-tBRCA LOH$^{high}$);
ITT = intent-to-treat; PFS = progression free survival; tBRCA = tumor tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA.

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

A minimum of 6 patients may be treated in a small, open-label safety cohort with rucaparib (600 mg BID) and nivolumab (480 mg IV on Day 1 of every 28-day cycle). A minimum of 6 patients of Japanese descent may be enrolled into an open-label, safety cohort at investigational sites in Japan, contingent upon the recommended rucaparib dose in Japan. These 2 safety cohorts will be evaluated individually after each patient receives a minimum of one cycle of combination therapy.

### 9.2.2 Changes to Sample Size Assumptions as of Implementation of Protocol Amendment 2

The first patient was randomized in August 2018, and randomization is expected to close the third quarter of 2020. Based on the recently established standard of care of PARPi monotherapy in the front-line maintenance setting,[81,82] 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 timepoints based on the maturity of the parts of the study, in order to evaluate both rucaparib monotherapy and rucaparib in combination with nivolumab:

- Monotherapy: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV])
- Combination: 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 frontline maintenance setting (SOLO1 study),[81] 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 analysis subpopulation, then ITT Population for the step-down hierarchical testing and the tBRCA population 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.[82] 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<br>18 vs 36 months | 90% | 0.008 |
| | HRD | 340 (270:68) | 230 | HR 0.60,<br>15 vs 25 months | 90% | 0.008 |
| | ITT | 500 (400:100) | 340 | HR 0.65<br>12 vs 17 months | 90% | 0.008 |
| **Amendment 2** | HRD | 205<br>(164:41) | 123 | HR 0.45[82]<br>12 vs 26.7 months | 90% | 0.0125 |
| | ITT | 500 (400:100) | 300 | HR 0.60[82]<br>12 vs 20 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.

The power assumption for the combination treatment comparison is still set at 90% power for both HRD and ITT sub/populations as per 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 and ITT sub/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.

### 9.2.3 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 sub-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, as shown in Section 9.2.2 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.

## 9.3 Analysis Populations

**Intent-to-treat (ITT) Population:** The ITT Population will consist of all randomized patients. This includes all patients randomized into any of the 4 HRD classifications (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 one dose of protocol-specified treatment.

## 9.4 Patient Disposition

Patient disposition will be summarized using frequency counts and the corresponding percentages. The number of patients in each analysis population, number of patients discontinued, and the primary reason for discontinuation will be summarized.

## 9.5 Demographics and Baseline Characteristics

All demographic (eg, age, race, and ethnicity as allowed by local regulations) and baseline characteristics will be summarized for the safety population.

The following variables will be summarized with frequency tabulations:

- Time since diagnosis (months): > 12 to 24, > 24
- Baseline laboratory parameters: graded based on CTCAE
- Molecularly defined subgroups based on HRD and TMB and other definitions as appropriate.
- Best response to most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST v1.1 with normalization of CA-125] or PR [defined as partial radiologic response by RECIST v1.1 and/or a GCIG CA-125 response]). All responses require that CA-125 be < ULN.

Descriptive statistics may also be used to summarize the continuous variables.

## 9.6 Efficacy Analyses

### 9.6.1 Primary Efficacy Analyses

The primary efficacy endpoint for the study is investigator-determined PFS (invPFS) by RECIST. Investigator-determined PFS is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by the investigator, or death due to any cause, whichever occurs first. Only scans or deaths prior to or on the start of any subsequent anticancer treatment will be used in PFS analysis. Any death or progression event

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 patients with an event of either disease progression or death directly following 2 or more missing 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 stratification factors included in the primary analysis of invPFS will be as follows:

- 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)
- Timing of surgery (primary surgery vs. interval debulking)

The primary endpoint is analyzed using stratified Cox proportional hazard model and log-rank test comparing the treatment groups stratified by the randomization stratification factors, ie, HRD classification (tBRCA, non-tBRCA LOH$^{high}$, non-tBRCA LOH$^{low}$, and non-tBRCA LOH$^{unknown}$), disease status (no residual disease versus residual disease), and timing of surgery (primary surgery vs. interval debulking). The log-rank test will be the official test used for evaluating primary endpoint significance in the step-down procedure.

In addition, a 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 as supportive statistics.

#### 9.6.1.1 Step-down Procedure to Adjust for Multiplicity

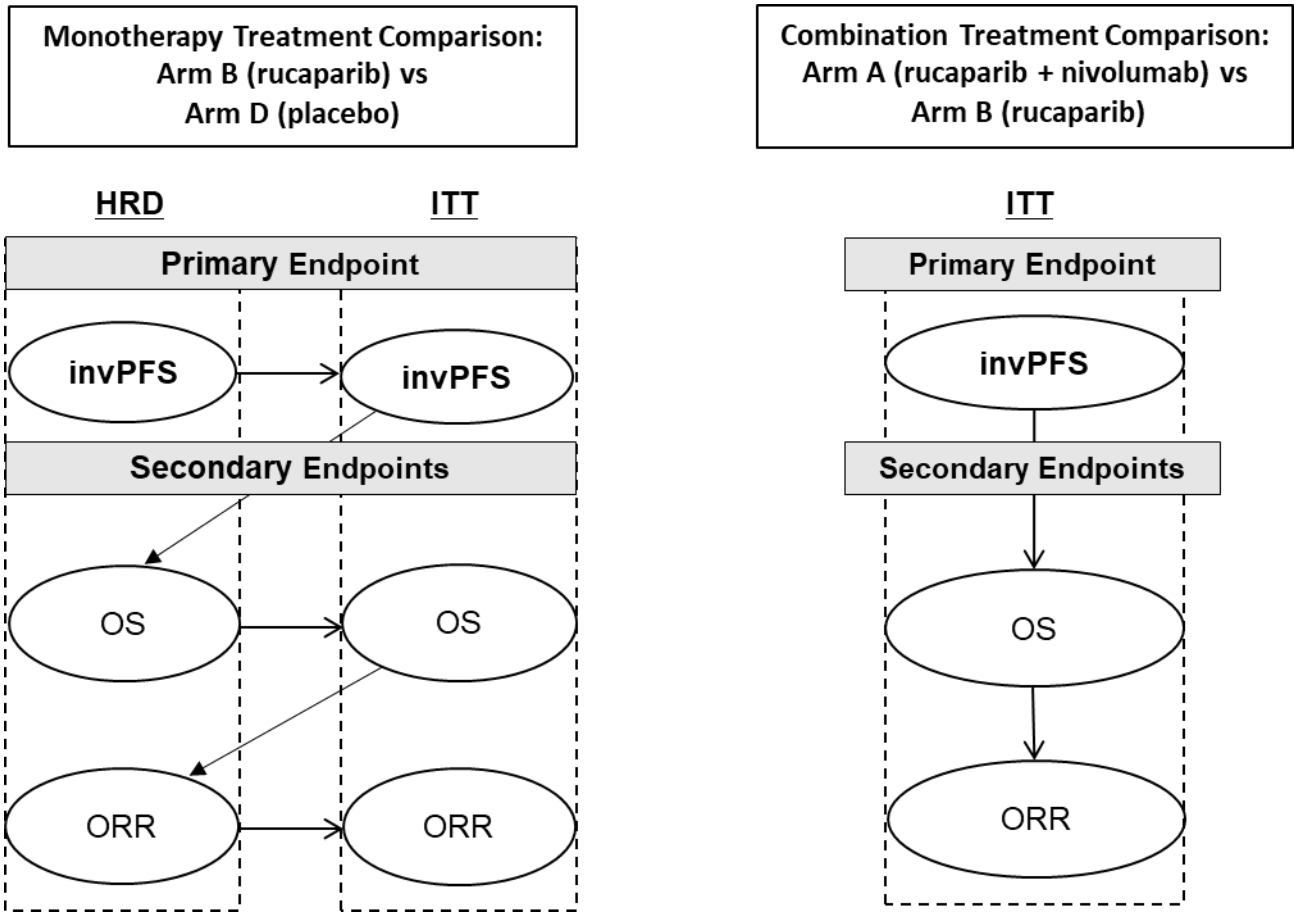
The primary endpoint of invPFS and key secondary endpoints of OS and ORR will be tested among the HRD and ITT sub/populations for the monotherapy comparison and among the ITT Population for the combination comparison, using separate ordered step-down multiple comparison procedures, as shown in Figure 3.

That is, for the monotherapy treatment comparison, the invPFS in the HRD subpopulation will be tested first at a one-sided 0.0125 significance level. If invPFS in the HRD subgroup is statistically significant, then invPFS will be tested in the ITT Population. If both the HRD and ITT sub/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 sub/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 monotherapy treatment comparison.

For the combination treatment comparison, the invPFS in the ITT Population will be tested first at a one-sided 0.0125 significance level. If invPFS is statistically significant, then the first secondary endpoint of OS will be tested at the one-sided 0.0125 significance level 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, the statistical significance will not be declared for subsequent analyses in the ordered step-down procedure for the combination comparison in the ITT Population.

**Figure 3. ATHENA Statistical Design**




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

### 9.6.2 Secondary Efficacy Analysis

The following secondary efficacy endpoints are included in the step-down procedure as outlined in Section 9.6.1.1:

1. Overall survival
2. Investigator determined ORR per RECIST

The following secondary efficacy endpoints are stand alone and are not included in the step-down procedure (ie, no multiplicity adjustment):

- PFS according to RECIST as assessed by BICR
- Investigator determined DOR per RECIST

#### 9.6.2.1 Progression-free Survival as Assessed by BICR

Progression-free survival (PFS) as assessed by BICR (bicrPFS) by RECIST 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. Only tumor scans prior to start of any subsequent anticancer treatment are included. Any death or progression event 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 patients with an event of either disease progression or death following 2 or more missing 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).

#### 9.6.2.2 Overall Survival

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

#### 9.6.2.3 Investigator determined ORR per RECIST

Analyses of ORR will be performed in the subgroup of patients with measurable disease at baseline and will be summarized with frequencies and percentages. The best ORR will be evaluated both as a single time point evaluation and requiring confirmation.

#### 9.6.2.4 Duration of Response

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. Duration of response is defined as the interval from the first documentation of objective response (RECIST v1.1) to the earlier of the first documentation of disease progression (per RECIST v1.1) or death from any cause. Any patients with an ongoing response will be censored on the date of the last post-baseline scan.

## 9.7 Safety Analyses

All safety analyses will be summarized by randomization treatment group or safety cohort and pooled for all patients.

Safety endpoints are incidence of AEs, clinical laboratory abnormalities, and dose modifications.

Data from all patients who receive at least 1 dose of study drug will be included in the safety analyses. AEs, clinical laboratory results, vital signs, ECG results, ECOG performance status, body weight, and concomitant medications/ procedures will be tabulated and summarized.

### 9.7.1 Adverse Events

AEs will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v5.0 later. Only treatment-emergent adverse events (TEAEs) will be collected: TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until 28 days after the last dose of oral study drug or 5 months after the last dose of IV study drug, whichever occurs later.

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

Separate tables will be presented as follows:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs;
- Serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study drug;

- TEAEs resulting in interruption/delay of study drug; and
- TEAEs resulting in dose reduction of study drug.

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

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

### 9.7.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will be presented in SI units. The on-treatment period will be defined as the onset date on or after the date of first dose of study drug until 28 days after the last dose of oral study drug or 5 months after the last dose of IV study drug, whichever occurs later. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include shift tables based on CTCAE for shifts in grade from baseline to maximum, minimum, and last value during the on-treatment period.

Supporting laboratory data including normal ranges and abnormal laboratory flags will be provided using by-patient listings. Separate listings will be produced for clinically significant laboratory abnormalities (ie, those that meet Grade 3 or 4 criteria according to CTCAE).

### 9.7.3 Vital Sign Measurements

The on-treatment period will be defined as the onset date on or after the date of first dose of study drug until 28 days after the last dose of oral study drug or 5 months after the last dose of IV study drug, whichever occurs later. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

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

## 9.8 Pharmacokinetic Analysis

### 9.8.1 Rucaparib Pharmacokinetic Analysis

In all patients with at least one PK sample collected, the trough plasma rucaparib PK data ($C_{min}$) and summary statistics (N, mean, SD, minimum, median, max, CV%]) will be reported.

The PK data may be further analyzed by a PPK approach. The post hoc estimated exposures will be used for exposure-response analyses of selected efficacy and safety endpoints if the data permit. The PPK and the exposure-response analyses may be presented separately from the main clinical study report.

### 9.8.2 Nivolumab Pharmacokinetic Analysis

The nivolumab concentration versus time data obtained in this study will be combined with data from other studies in the clinical development program to develop a PPK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab to determine measures of individual exposure (such as steady-state peak, trough and time-averaged concentration). PK drug-drug interaction between nivolumab and other component drugs will be studied by a PPK approach. Model-determined exposures will be used for exposure response analyses of selected efficacy and safety endpoints if the data permit. The PPK analysis will be presented separately from the main clinical study report.

## 9.9 Interim Analysis

### 9.9.1 Open-label Safety Cohort

A formal safety review will occur after the safety lead-in cohort has enrolled and patients have been treated with the combination for at least 28 days. The review committee will include external experts and sponsor personnel. The external experts will include, but not be limited to, the Coordinating PIs of the study [redacted] the Principal Investigator(s) who enrolled and treated the respective patients, and key members of the Steering Committee. Sponsor reviewers will include the medical monitor, Chief Medical Officer, Head of Pharmacovigilance, and the study Biostatistician. The data will also be provided to the IDMC. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review.

Evaluation of the Japanese safety cohort will proceed in the same manner as the initial safety cohort. Once the evaluation of the Japanese cohort is complete, the double-blind portion of the study can be opened for randomization in Japan.

### 9.9.2 Double-blind Treatment Phase

No formal efficacy interim analyses for early stopping are planned.

An IDMC will meet regularly to review the efficacy and safety data from this study (see Section 8.11).

# 10 STUDY ADMINISTRATION

## 10.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; ICH E6 (R2); FDA regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki. The ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations (CFR), Title 21, Part 50 (21CFR50) and applicable local requirements.

### 10.1.1 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to concerned regulatory agencies for approval prior to the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each investigator must complete a Form FDA 1572 (or equivalent) and provide the completed form according to written instructions to the sponsor (or designee). Each investigator must submit to the sponsor (or designee) financial disclosure information according to national law and/or local regulations.

US-generated data will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The trial will be registered on www.clinicaltrials.gov, EudraCT, and other applicable trial registry systems as appropriate.

### 10.1.2 Institutional Review Board or Independent Ethics Committee Approval

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IEC/ IRB. This also applies to protocol amendments.

The sponsor will supply relevant data for the investigator to submit the study protocol and additional study documents to the IEC/ IRB. The principal investigator will submit the study protocol for review and approval by an IEC/ IRB, according to national law and/or local regulations, and will provide the IEC/ IRB with all appropriate materials.

Verification of the IEC's/ IRB's unconditional approval of the study protocol and the written ICF will be transmitted to the sponsor. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

No patient will be admitted to the study until appropriate IEC/ IRB approval of the study protocol has been received, the investigator has obtained the signed and dated ICF, and the sponsor is notified.

The principal investigator will submit appropriate reports on the progress of the study to the IEC/ IRB at least annually in accordance with applicable national law and/ or local regulations and in agreement with the policy established by the IEC/ IRB and sponsor.

The IEC/ IRB must be informed by the principal investigator of all subsequent study protocol amendments and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

## 10.2 Patient Information and Consent

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed ICFs from all patients participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

The ICF, prepared by the investigator with the assistance of the sponsor, must be approved along with the study protocol by the IEC/ IRB and be acceptable to the sponsor.

The patient must be provided with the patient information and ICF consistent with the study protocol version used and approved by the relevant IEC/ IRB. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/ or relatives, guardians, or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator concerned. Both the patient and the person explaining the study and with whom the patient can discuss the informed consent will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original ICF will be filed in the investigator file unless otherwise agreed.

## 10.3 Patient Confidentiality

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient identifiers such as initials, year of birth, and an identification code (ie, not names) should be recorded on any form submitted to the sponsor and the IRB/ IEC. The investigator must record all screened and enrolled patients in the eCRF. The investigator must maintain a list with the identity of all treated patients, but not intended for use by the sponsor.

The investigator agrees that all information received from the sponsor or designee including, but not limited to, the IB, this protocol, eCRFs, the protocol specified treatment, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure of confidential patient information to any

unauthorized party or otherwise into the public domain. The investigator will notify pharma& (contact@pharmaand.com) within 24 hours of a security event that impacts or has the potential to impact confidentiality, integrity, or availability study data.

## 10.4 Study Monitoring

On behalf of the sponsor, a CRO or contract monitor will contact and visit the investigator at the study center prior to the entry of the first patient (unless the sponsor or the CRO has worked with the center recently, in which case this initial visit maybe waived) and at appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit. Visits may also be conducted by sponsor personnel.

Where applicable, if the sponsor or their representatives are not able to come to the study center, patient study data may be reviewed by them remotely, in conformity with the applicable institutional guidance and local regulations. The site staff may place relevant medical records with personal identifiers removed into a secure computer system for the sponsor or their representative to view, allow them to view these records during a video conference and/or provide them direct access to patient's electronic medical records. This review would occur in a manner that protects the confidentiality of study patient data. Whether a patient's medical records are reviewed at the study center or remotely, their identity and medical records will be kept secure during this process. Remote review of patient study data should not be carried out if adequate data protection, including data security and protection of personal data even if pseudonymized, is not ensured. Further details will be provided in the study training materials.

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (ie, the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (ie, source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the investigator file.

## 10.5 Case Report Forms and Study Data

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be

completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the eCRF should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Medidata RAVE, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

## 10.6 Study Termination and Site Closure

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

The sponsor reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study;
- Evidence has emerged that, in the opinion of the sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical;
- The stated objectives of the study are achieved; or
- The sponsor discontinues the development of rucaparib.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented.

## 10.7 Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/ IRB must be informed of all amendments and give approval prior to their implementation. The sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines.

## 10.8 Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, drug accountability records,

correspondence with the IEC/IRB and the sponsor, and other study-related documents. The investigator should have control of all essential documents generated by the site. Source documents must be maintained, ALCOAC used. Any changes to source data should be traceable.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor or its designees. The investigator should have control of and continuous access to the eCRF data.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of the sponsor. Copies of original documents should fulfill the requirements for certified copies. Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in writing of the new responsible person and/or the new location. The sponsor will inform the investigator, in writing, when the trial-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

## 10.9 Quality Control and Assurance

The sponsor will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

### 10.9.1 Changes to the Protocol and Deviations

The investigator may not deviate from the protocol unless necessary to eliminate immediate hazards to the patient. A deviation may result in the patient having to be withdrawn from the study and rendering that subject nonevaluable. Any deviation must be documented in the source documents and reported to the sponsor.

If changes to the study are required, they must be provided in a formal protocol amendment having been approved by an appropriate IRB/IEC.

### 10.9.2 Study Site Training and Ongoing Monitoring

Each investigator and the site personnel for this study will be trained by the sponsor and/ or a designee (ie, a CRO) on the design, conduct, procedures, and administrative aspects of this study. This may include, but is not limited to, on-site training, Investigator Meeting(s), and/ or tele/ videoconferencing. Training may be ongoing as refresher, to address specific items, or to introduce changes in the study.

In accordance with Code of Federal Regulations 21 CFR 312.56, ICH GCP and local regulations, the clinical monitor will periodically inspect via direct access to records, all eCRFs, study documents, medical records (office, clinic, or hospital) for patients in this study (anonymity is to be preserved), research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the investigator must inform the sponsor of these restrictions before initiation of the study.

### 10.9.3 Direct Access to Source Data/ Documents for Audits and Inspections

The investigator site is to maintain a record of locations of essential documents and study source documents. Members of the sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written standard operating procedures (SOPs) and applicable laws, rules, and regulations.

Representatives of the FDA, EMA, or other regulatory agencies, including IRB/IEC representatives may also conduct an audit or inspection of the study. If informed of such an activity, the investigator should notify the sponsor immediately. The investigator will ensure that the auditors and inspectors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files and electronic records are available, if requested.

## 10.10 Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of the sponsor and signed by the sponsor's Medical & Scientific Director and Quality & Regulatory Affairs Director; thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report.

## 10.11 Publication and Disclosure Policy

All data generated from this study will be maintained by the sponsor and shared with the lead study group, as well as other participating cooperative groups according to the guidelines in the Steering Committee Charter and the rules for the respective cooperative groups. All data

generated from this study, and all information furnished by the sponsor, the lead study group, and other participating study groups shall be held in strict confidence. Independent analysis and/or publication of these data by the investigator(s) or any member of their staff are not permitted without the prior written consent of the sponsor, the lead study group, and participating cooperative groups. Written permission to the investigator will be contingent on the review of the statistical analysis and manuscripts/abstract by the sponsor and participating cooperative groups, and will provide for nondisclosure of the sponsor and cooperative groups confidential or proprietary information. In all cases, the parties agree to provide all manuscripts or abstracts to all other parties 60 days prior to submission or per specified timelines in the Steering Committee Charter. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

## 10.12 Investigator Oversight

The investigator has a responsibility for supervising all delegated staff. All staff delegated study responsibilities must be documented on an approved Delegation of Authority log for the study and this filed with the essential documents. In addition, the investigator must ensure that delegated staff are qualified by training, experience and licensure (as applicable). The investigator should implement procedures to ensure integrity of the study and data generated.

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# 12 APPENDICES

## Appendix 1 Response Evaluation Criteria in Solid Tumors Criteria

A summary of RECIST guidelines (Version 1.1) is provided below. For full details, please refer to RECIST guidelines (Version 1.1) described in Eisenhauer (2009)[83] and http://www.eortc.be/Recist/Default.htm..

**Measurable Disease**:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm)
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- A minimum size of 20 mm by chest X-ray

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

**Nonmeasurable Disease:**

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

**Bone Lesions**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

**Cystic Lesions**

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

**Lesions with Prior Local Treatment**

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

**Target Lesions**

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

**Nontarget Lesions**

RECIST Version 1.1 criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

**Guidelines for Evaluation of Measurable Disease**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

**Evaluation of Target Lesions**

| | |
|---|---|
| Complete Response | Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm. |
| Partial Response | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. |
| Stable Disease | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. |
| Progressive Disease | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression.) |

**Special Notes on the Assessment of Target Lesions**

**Lymph Nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

**Target lesions that become too small to measure:** While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

**Evaluation of Nontarget Lesions**

| | |
|---|---|
| Complete Response | Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis) |
| Stable Disease/Incomplete Response | Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits. |
| Progressive Disease | Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.) |

**Special Notes on the Assessment of Non-Target Lesions**

The concept of progression of non-target disease requires additional explanation as follows:

**When the patient also has measurable disease:** In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in RECIST1.1).[80] A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

**When the patient has only non-measurable disease:** This circumstance arises in some Phase 3 studies, such as this study, when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial. See further examples in Appendix II of the RECIST1.1 publication.[80]

**New Lesions**

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered that reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

**Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).

| Evaluation of Best Overall Response: Patients with Target (±Non-Target) Disease | | | |
|---|---|---|---|
| **Target Lesions** | **Nontarget Lesions** | **New Lesions** | **Overall Response** |
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not evaluated | No | PR |
| SD | Non-PD or not evaluated | No | SD |
| Not Evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

| Evaluation of Best Overall Response: Patients with Non-Target Disease Only | | |
|---|---|---|
| **Nontarget Lesions** | **New Lesions** | **Overall Response** |
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD[a] |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual

lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

**Duration of Response**

CT scans are required for this study at screening and every 12 calendar weeks (within 7 days before is permitted) after initiation of oral/IV combination therapy.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

# Appendix 2 Modified Gynecological Cancer Intergroup (GCIG) Guidelines for Response or Progression using CA-125

GCIG CA-125 definitions are available at https://gcigtrials.org/content/ca-125-response-definition

**RESPONSE**

**GCIG Guidelines for Response Using CA-125[74] (adapted for use in this trial).**

To be evaluable for response by CA-125 requires an elevated baseline value of at least 2 × ULN and at least 2 additional samples after the start of treatment.

A response to CA-125 has occurred if there is at least a 50% decrease as the result of the treatment. The pre- and post-treatment samples must satisfy the following criteria:

1. There must be at least 1 sample that is > 2 × ULN prior to initiation of treatment
2. The second sample (post-treatment) must be ≤ 50% of the pre-treatment sample;
3. The confirmatory third sample must be ≥ 21 days after the second sample and ≤ 110% of the second sample;
4. Any intervening samples between samples 2 and 3 must be ≤ 110% of the previous sample unless considered to be increasing because of tumor lysis.

**PROGRESSION**

GCIG Guidelines for Progression Using CA-125:

**For the purposes of evaluating a patient's eligibility only in the ATHENA study,** this guidance should be used to determine whether an increase observed in CA-125 levels during frontline treatment constitute progression by CA-125. Progressive disease should only be determined by RECIST v1.1 assessment for patients during the treatment phase of the study.

Per GCIG criteria, progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125, according to the following criteria:

A. Patients with elevated CA-125 pre-treatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on 2 occasions at least one week apart, or
B. Patients with elevated CA-125 pre-treatment, which never normalizes must show evidence of CA-125 greater than, or equal to, two times the nadir value on 2 occasions at least one week apart or
C. Patients with CA-125 in the normal range pre-treatment must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least 1 week apart.

Patients are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical or surgical interference with their peritoneum or pleura during the previous 28 days.

# Appendix 3 ECOG Performance Status Scale

**Eastern Cooperative Oncology Group (ECOG) Performance Status Scale**

| ECOG Performance Status | |
|---|---|
| 0 | Fully active, able to carry on all predisease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work or office work). |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

# Appendix 4 Examples of Sensitive Clinical Cytochrome P450 (CYP) Substrates

| Enzyme or Transporter | Sensitive Substrate Drugs[a] |
|---|---|
| CYP1A2 | Tizanidine, theophylline, alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon |
| CYP2C9 | celecoxib |
| CYP2C19 | S-mephenytoin, omeprazole |
| CYP3A | alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan |

Source: FDA Guidance on Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-mediated Drug Interactions, January 2020[84]

Abbreviations: AUC = area under the plasma concentration-time curve; CYP = cytochrome P450; DDI = drug-drug interaction; FDA = Food and Drug Administration.

[a] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.

# Appendix 5 FACT-O

Sample forms for the FACT-O is below and background for each questionnaire, respectively, is available at: http://www.facit.org/facitorg/questionnaires.

Patients will complete the IEC/IRB approved version of the assessment on an electronic device or other format (ie, paper form), as appropriate.

**FACT-O Sample Questionnaire**

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** |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

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

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

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

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

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

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

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| O1 | I have swelling in my stomach area | 0 | 1 | 2 | 3 | 4 |
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C3 | I have control of my bowels | 0 | 1 | 2 | 3 | 4 |
| O2 | I have been vomiting | 0 | 1 | 2 | 3 | 4 |
| B5 | I am bothered by hair loss | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| C7 | I like the appearance of my body | 0 | 1 | 2 | 3 | 4 |
| BM T5 | I am able to get around by myself | 0 | 1 | 2 | 3 | 4 |
| B9 | I am able to feel like a woman | 0 | 1 | 2 | 3 | 4 |
| O3 | I have cramps in my stomach area | 0 | 1 | 2 | 3 | 4 |
| BL4 | I am interested in sex | 0 | 1 | 2 | 3 | 4 |
| BM T7 | I have concerns about my ability to have children | 0 | 1 | 2 | 3 | 4 |

# Appendix 6 Euro-QoL5D-5L

A sample form for the EQ-5D-5L is below and background for the questionnaire is available at http://www.euroqol.org/home.html.

Patients will complete the IEC/IRB approved version of the assessment on an electronic device or other format (ie, paper form), as appropriate.

**Euro-QoL5D-5L (EQ-5D-5L) – English Version for the US**

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

**Mobility**

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

**Self-Care**

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

**Usual Activities** (*e.g. work, study, housework, family or leisure activities)*

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

**Pain/Discomfort**

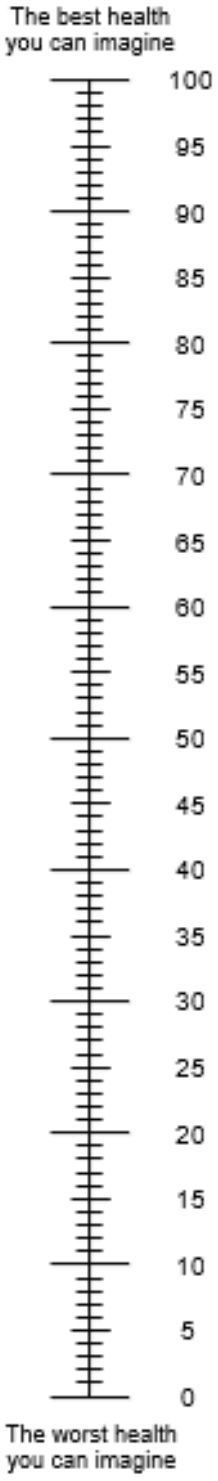
| | |
|---|---|
| I have no pain or discomfort | ❑ |
| I have slight pain or discomfort | ❑ |
| I have moderate pain or discomfort | ❑ |
| I have severe pain or discomfort | ❑ |
| I have extreme pain or discomfort | ❑ |

**Anxiety/Depression**

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

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

YOUR HEALTH TODAY = ☐



# Appendix 7 Management Algorithms for Immuno-Oncology Agents

These general guidelines (28 September 2020; CTCAE v5.0) constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnosis should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

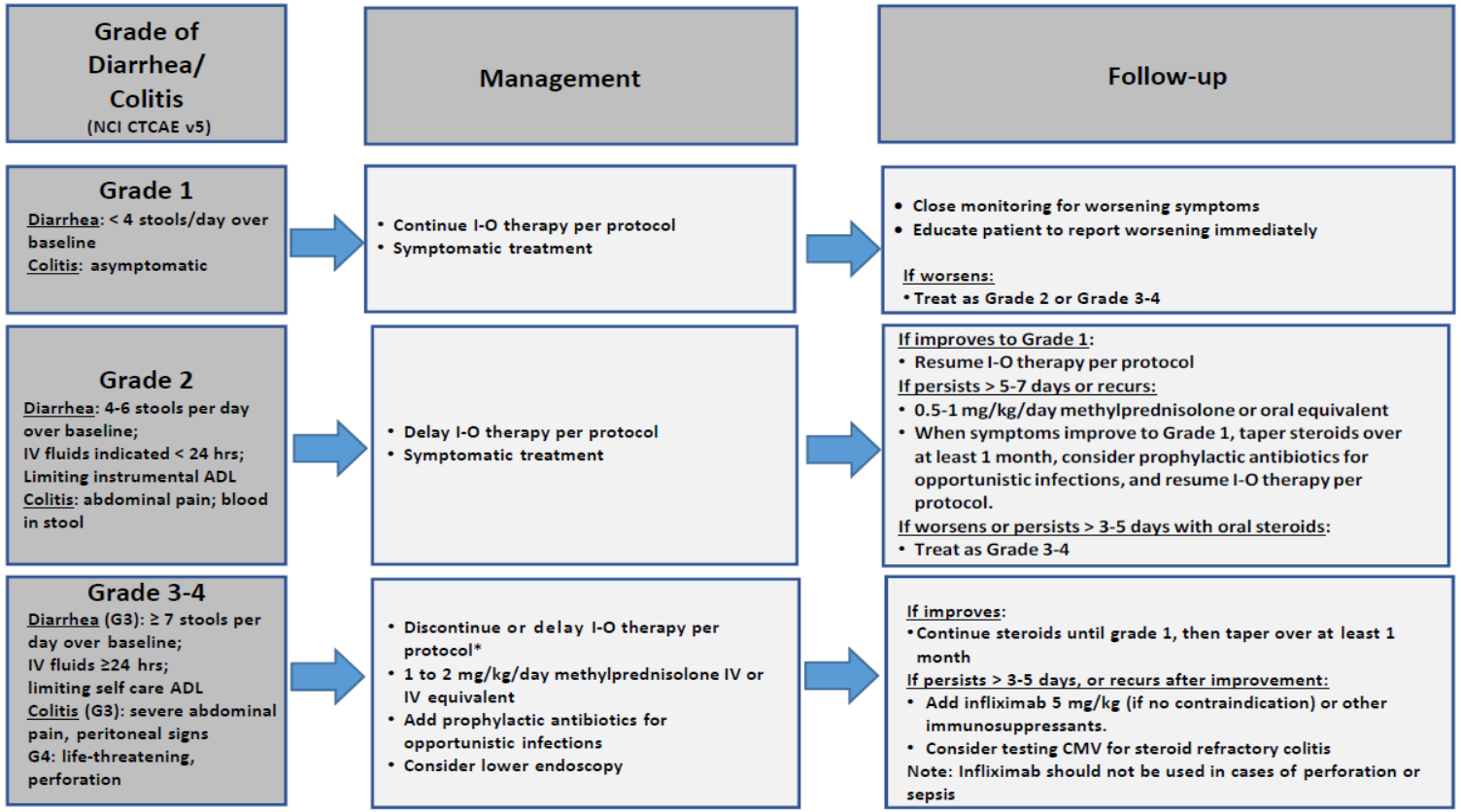
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

## GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

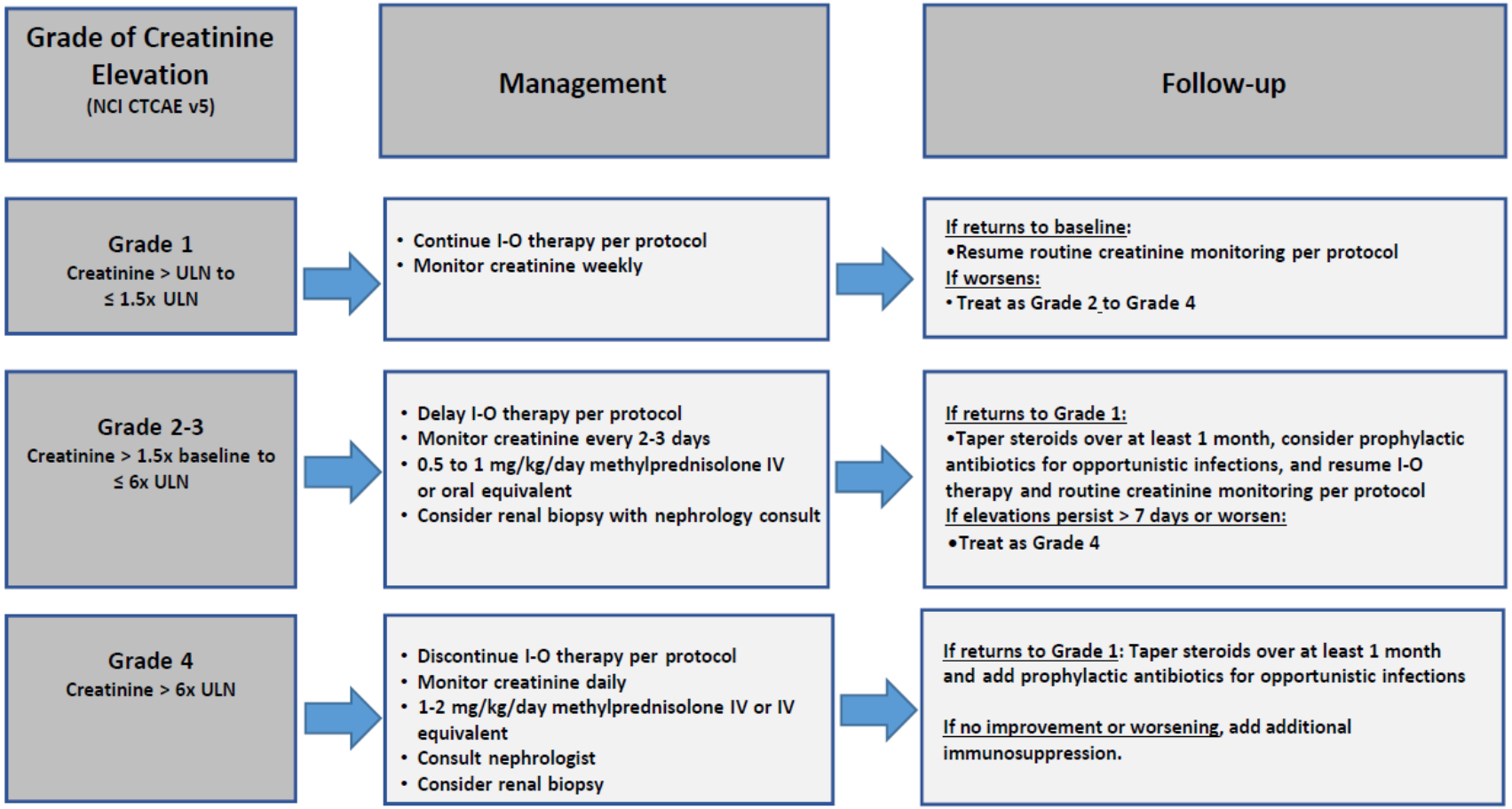



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, I-O therapy can be delayed. I-O therapy can be resumed when symptoms improve to Grade 1. Please refer to the protocol for dose delay and discontinue criteria for other combinations.

## Renal Adverse Event Management Algorithm – Rucaparib[a] and Nivolumab

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

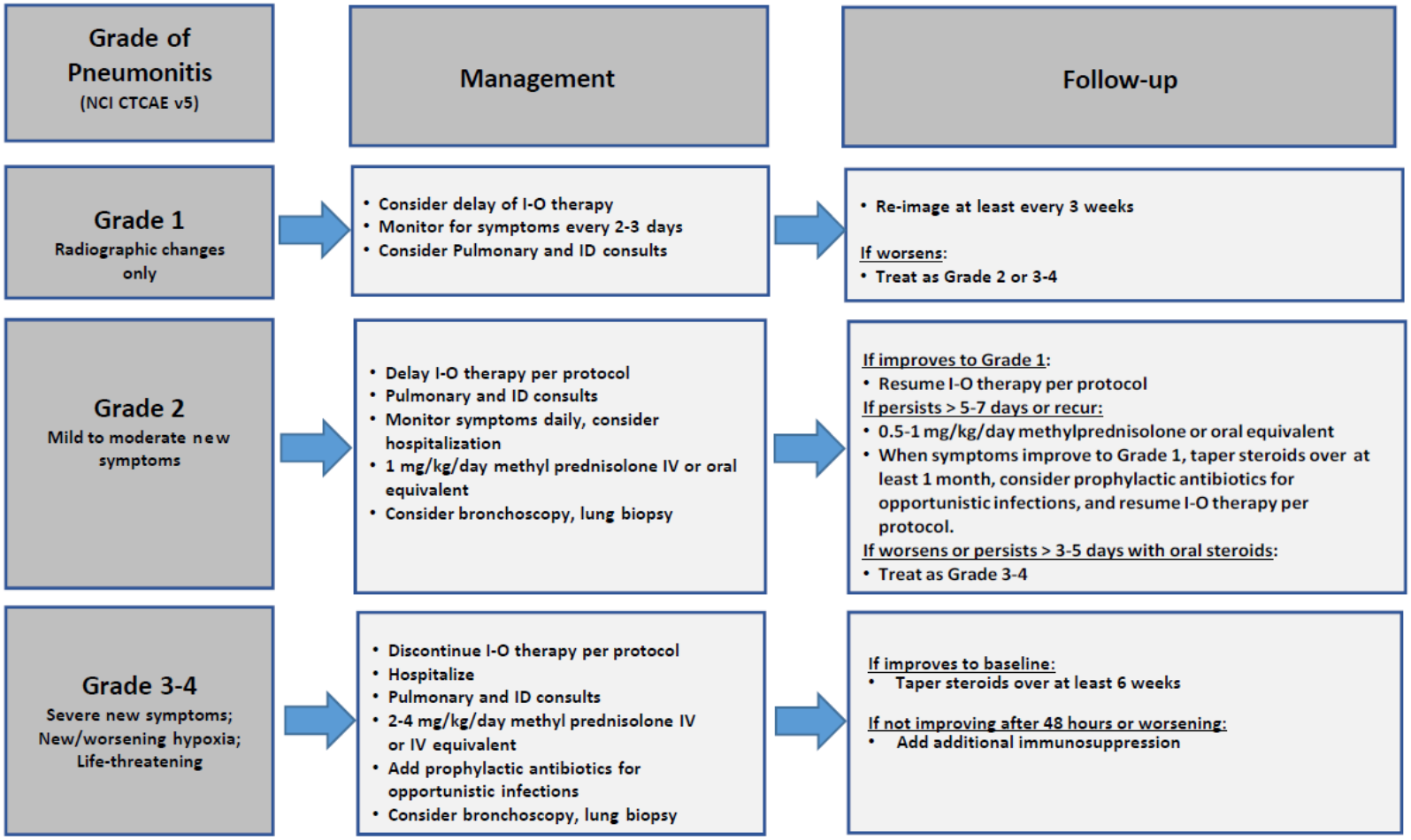



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[a] Baseline for creatinine will be considered pre-dose to the first IV infusion.

## Pulmonary Adverse Event Management Algorithm

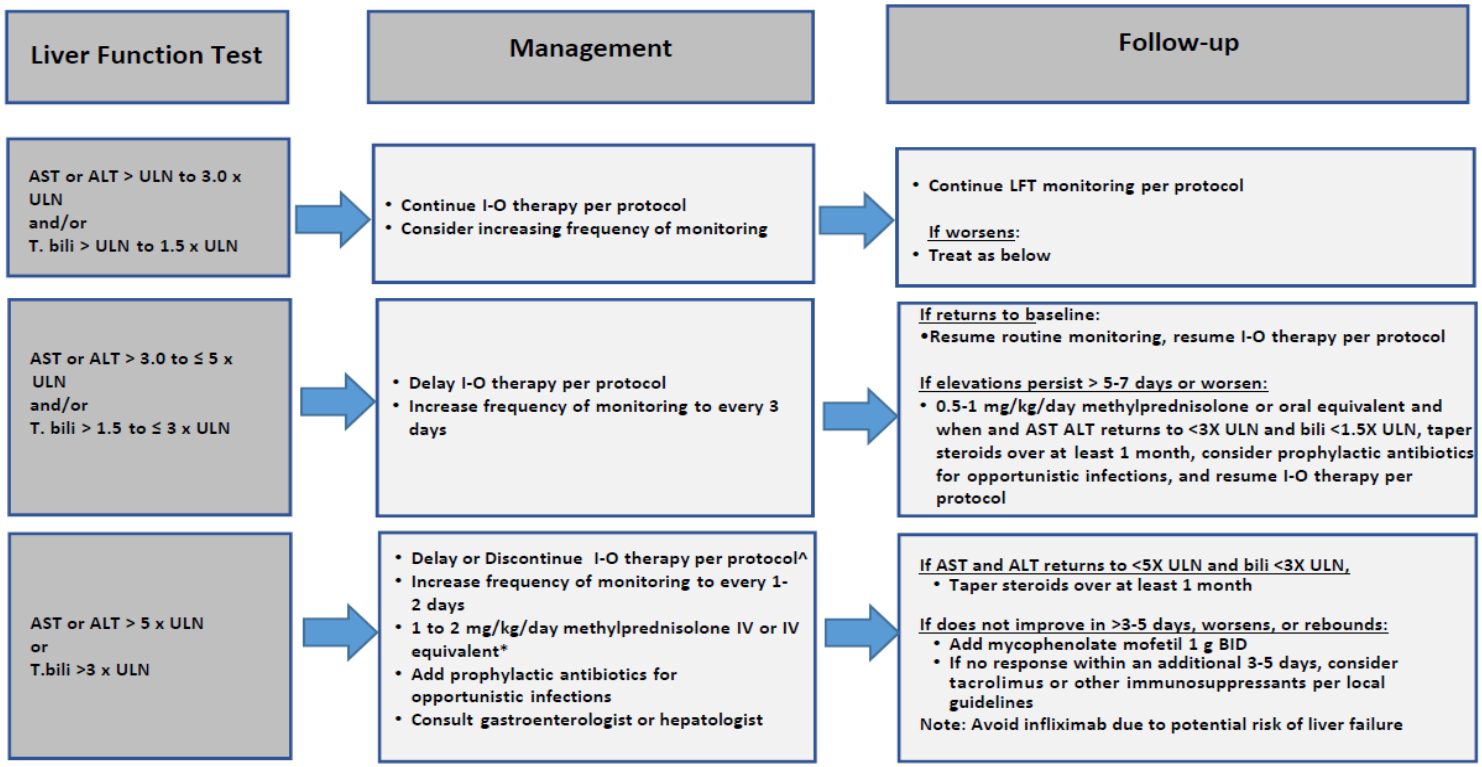
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Hepatic Adverse Event Management Algorithm-Rucaparib[a] and Nivolumab

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

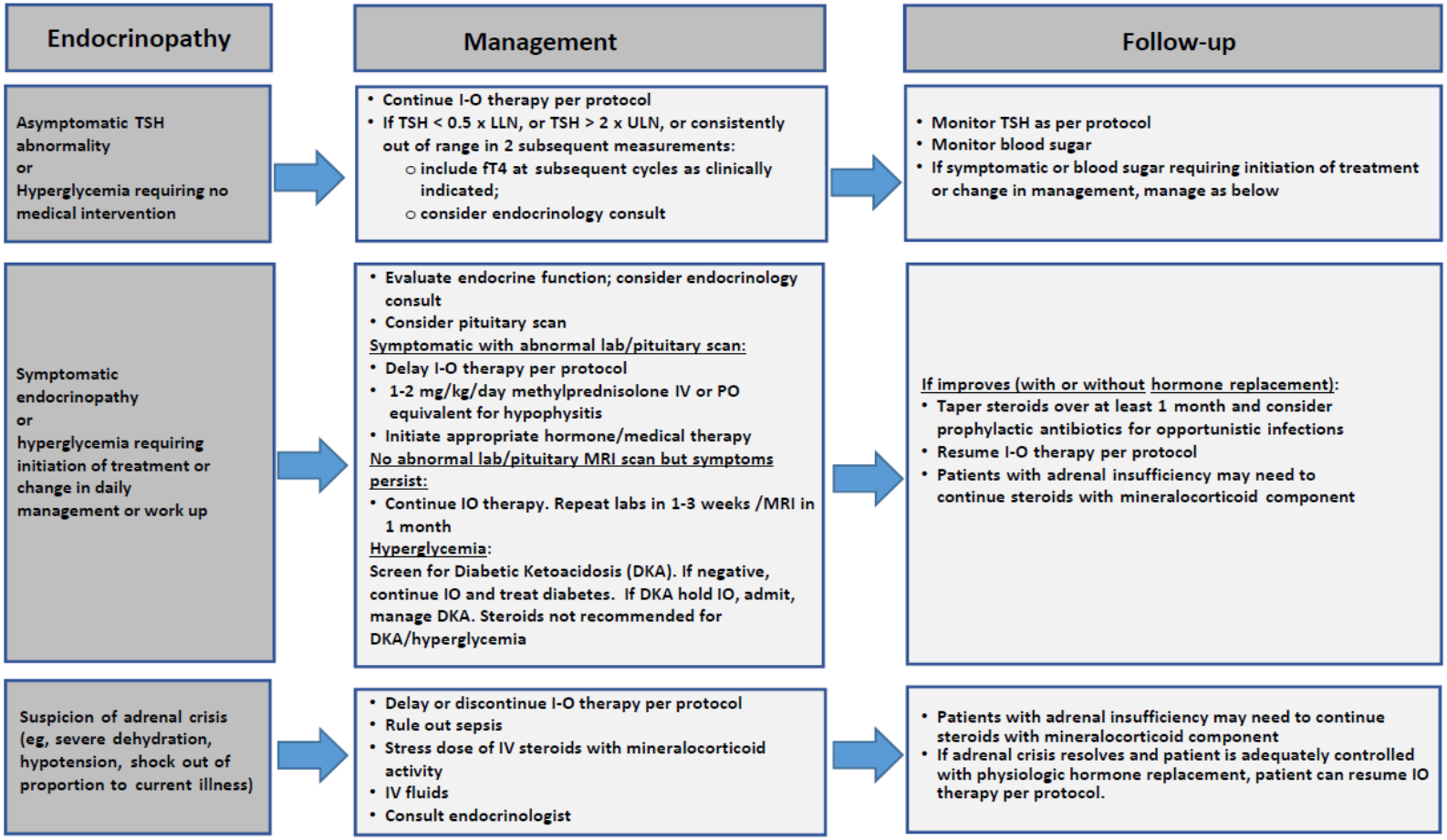
^ Please refer to the protocol dose delay and discontinue criteria for specific details.

* The recommended starting dose for AST or ALT > 20 × ULN or bilirubin > 10 × ULN is 2 mg/kg/day methylprednisolone IV.

[a] Rucaparib may cause transient AST and/or ALT elevations (without increased total bilirubin) in Cycle 1. Please see Section 5.6.1.2 and Section 5.6.4.2 for details about when a hold or discontinuation of IV drug is not required due to a background of AST and/or ALT elevations that are due to oral drug.

## Endocrinopathy Adverse Event Management Algorithm

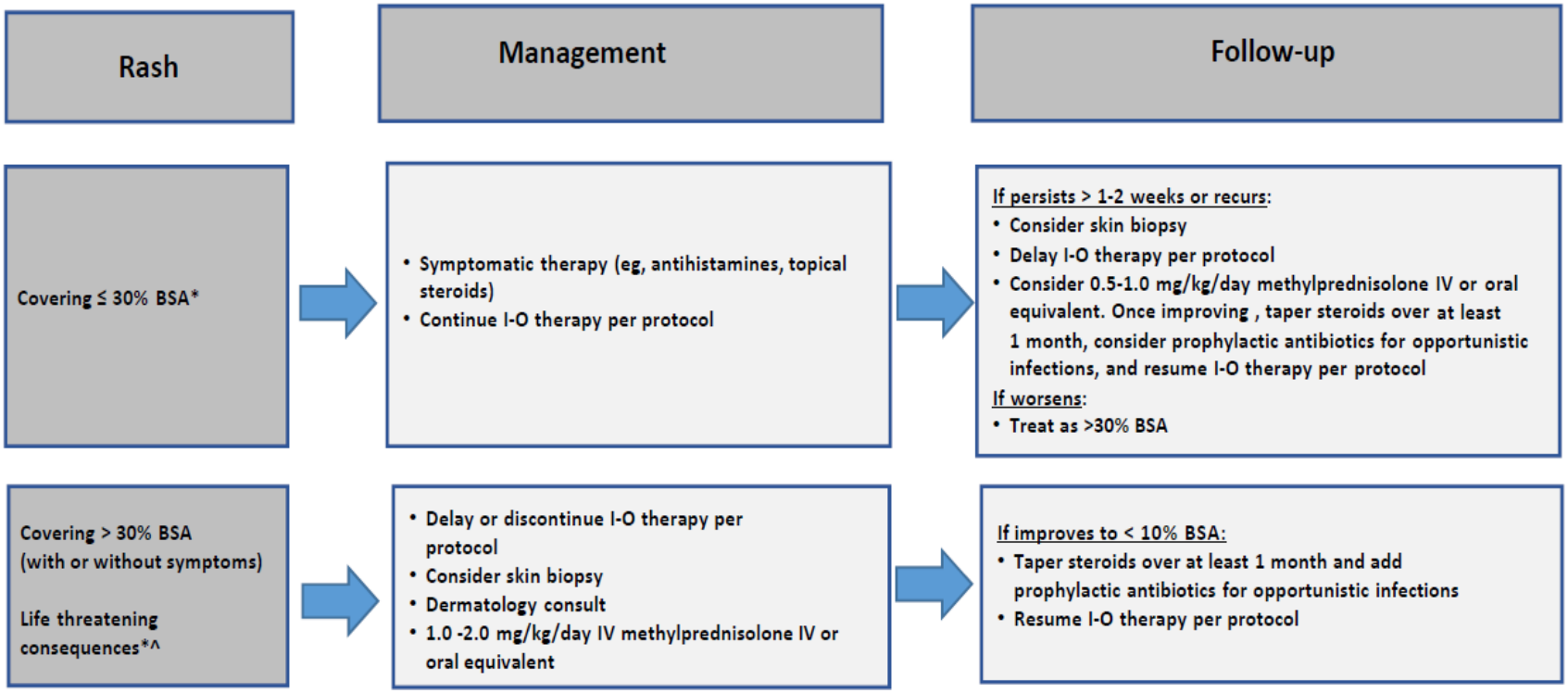
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



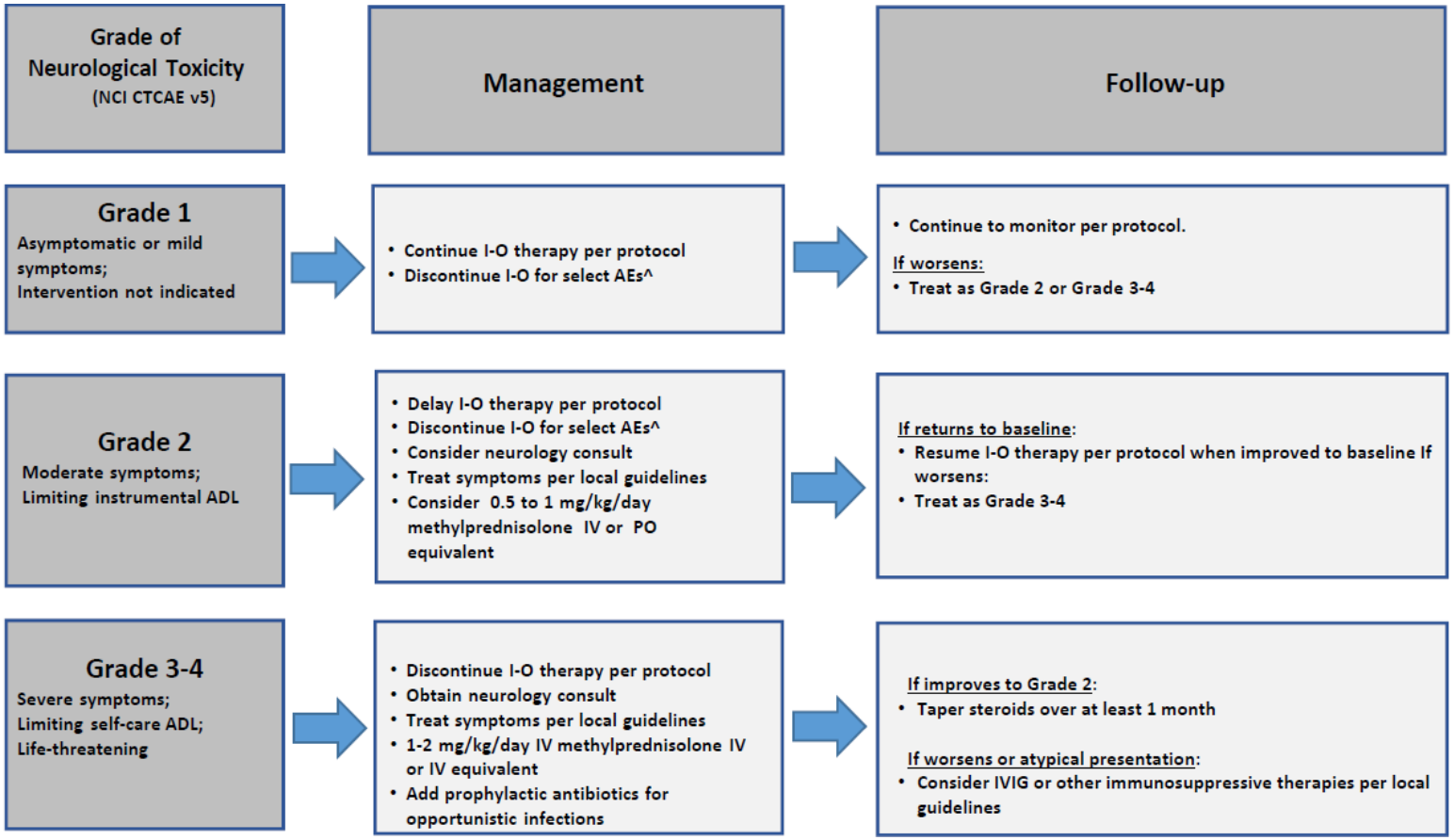

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Refer to NCI CTCAE v5 for term-specific grading criteria.

^ If Steven-Johnson Syndrome (SIS), toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SIS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

## Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

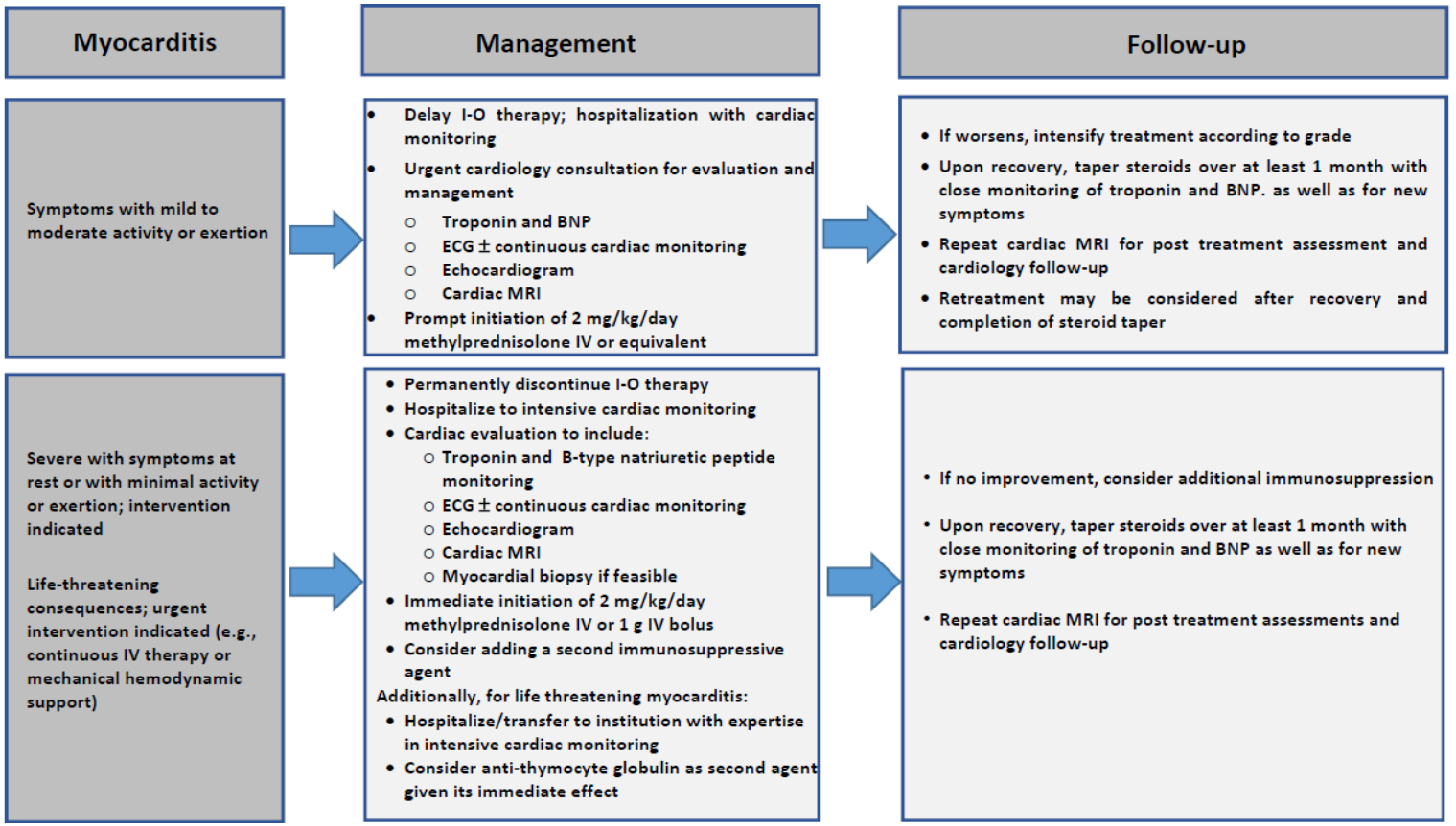



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^ Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

## Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting on ongoing immunosuppression.

# Appendix 8 Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab

| Drug-Related Adverse Event (AE) per CTCAE V5 | Severity | Action Taken | Clarifications, Exceptions, and Resume Criteria |
|---|---|---|---|
| Gastrointestinal | | | |
| Colitis or Diarrhea | Grade 2 | Delay dose | Dosing may resume when AE resolves to baseline |
| | Grade 3 | Nivolumab monotherapy: Delay dose | Dosing may resume when AE resolves to baseline |
| | Grade 4 | Permanently discontinue | |
| Renal | | | |
| Serum Creatinine Increased | Grade 2 or 3 | Delay dose | Dosing may resume when AE resolves to Grade ≤ 1 or baseline value |
| | Grade 4 | Permanently discontinue | |
| Pulmonary | | | |
| Pneumonitis | Grade 2 | Delay dose | Dosing may resume after pneumonitis has resolved to ≤ Grade 1. |
| | Grade 3 or 4 | Permanently discontinue | |
| Hepatic | | | |
| Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased | AST or ALT > 3x and ≤5x upper limit of normal (ULN) or T.Bili >1.5x and ≤3x ULN, regardless of baseline value | Delay dose | Dosing may resume when laboratory values return to baseline. |
| | AST or ALT > 5 x ULN or T. bili > 3 x ULN, regardless of baseline value | Permanently discontinue | |
| | Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value | Permanently discontinue | |

| | | | |
|---|---|---|---|
| **Endocrinopathy** | | | |
| Adrenal Insufficiency | Grade 2 adrenal insufficiency | Delay dose | Dosing may resume after adequately controlled with hormone replacement. |
| | Grade 3 or 4 adrenal insufficiency or adrenal crisis | Delay dose or permanently discontinue | Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug. |
| Hyperglycemia | Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3) | Delay dose | Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents. |
| | Grade 4 | Delay dose or permanently discontinue | Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug. |
| Hypophysitis/Hypopituitarism | Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan | Delay dose | Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement. |
| | Grade 4 | Delay dose or permanently discontinue | Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug. |
| Hyperthyroidism or Hypothyroidism | Grade 2 or 3 | Delay dose | Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management. |
| | Grade 4 | Delay dose or permanently discontinue | Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug. |

| | | | |
|---|---|---|---|
| **Skin** | | | |
| Rash | Grade 2 rash covering >30% body surface area or Grade 3 rash | Delay dose | Dosing may resume when rash reduces to ≤10% body surface area |
| | Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS) | Delay dose | Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤10% body surface area |
| | Grade 4 rash or confirmed SJS,TEN, or DRESS | Permanently discontinue | |
| Neurological | | | |
| Guillain-Barre Syndrome (GBS) | Any Grade | Permanently discontinue | |
| Myasthenia Gravis (MG) | Any Grade | Permanently discontinue | |
| Encephalitis | Any Grade encephalitis | Delay dose | After workup for differential diagnosis, (i.e. infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves |
| | Any Grade drug-related encephalitis | Permanently discontinue | |
| Myelitis | Any Grade myelitis | Delay dose | After workup for differential diagnosis, (i.e. infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves |
| | Any Grade drug-related myelitis | Permanently discontinue | |
| Neurological (other than GBS, MG, encephalitis, or myelitis) | Grade 2 | Delay dose | Dosing may resume when AE resolves to baseline |
| | Grade 3 or 4 | Permanently discontinue | |
| **Myocarditis** | | | |
| Myocarditis | Symptoms induced from mild to moderate activity or exertion | Delay dose | Dosing may resume after myocarditis has resolved |

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| | Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated. | Permanently discontinue | |
| **Other Clinical AE** | | | |
| Pancreatitis:<br><br>Amylase or Lipase increased | Grade 3 with symptoms | Delay dose | Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay.<br>Dosing may resume when patient becomes asymptomatic. |
| | Grade 4 | Permanently discontinue | |
| Uveitis | Grade 2 uveitis | Delay dose | Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If patient requires oral steroids for uveitis, then permanently discontinue study drug. |
| | Grade 3 or 4 uveitis | Permanently discontinue | |
| Other Drug-Related AE **(not listed above)** | Grade 2 non-skin AE, except fatigue | Delay dose | Dosing may resume when AE resolves to Grade ≤ 1 or baseline value. |
| | Grade 3 AE - First occurrence lasting ≤ 7 days | Delay dose | Dosing may resume when AE resolves to Grade ≤ 1 or baseline value. |
| | Grade 3 AE- First occurrence lasting > 7 days | Permanently discontinue | |
| | Recurrence of Grade 3 AE of any duration | Permanently discontinue | |
| | Grade 4 or Life-threatening adverse reaction | Permanently discontinue | |
| **Other Lab abnormalities** | | | |
| Other Drug-Related lab abnormality **(not listed above)** | Grade 3 | Delay dose | Exceptions:<br><u>No delay required for</u>: Grade 3 lymphopenia<br><br><u>Permanent Discontinuation for</u>: Grade 3 thrombocytopenia > 7 days or associated with bleeding. |

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| | Grade 4 | Permanently discontinue | Exceptions: The following events do not require discontinuation of study drug:<br>• Grade 4 neutropenia ≤ 7 days<br>• Grade 4 lymphopenia or leukopenia<br>• Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset |
| **Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)** | | | |
| Hypersensitivity reaction or infusion reaction | Grade 3 or 4 | Permanently discontinue | Refer to Section 7.4.4 on Treatment of Related Infusion Reactions |