CLINICAL STUDY PROTOCOL: CO-338-097

Study Title:	A Phase 2, open-label study to evaluate rucaparib in combination with nivolumab in patients with selected solid tumors (ARIES)
Study Number:	CO-338-097
Study Phase:	Phase 2
Product Name:	Rucaparib (CO-338); Nivolumab (BMS-936558-01)
IND Number:	[redacted]
EUDRA CT Number	[redacted]
Indication:	Selected solid tumors
Investigators:	Multicenter
Sponsor Name:	Clovis Oncology, Inc.
Sponsor Address:	[redacted]
Responsible Medical Officer:	[redacted]

Protocol Version	Date
[redacted]	[redacted]
Amendment 1	30 July 2019

PROTOCOL APPROVAL SIGNATURE PAGE

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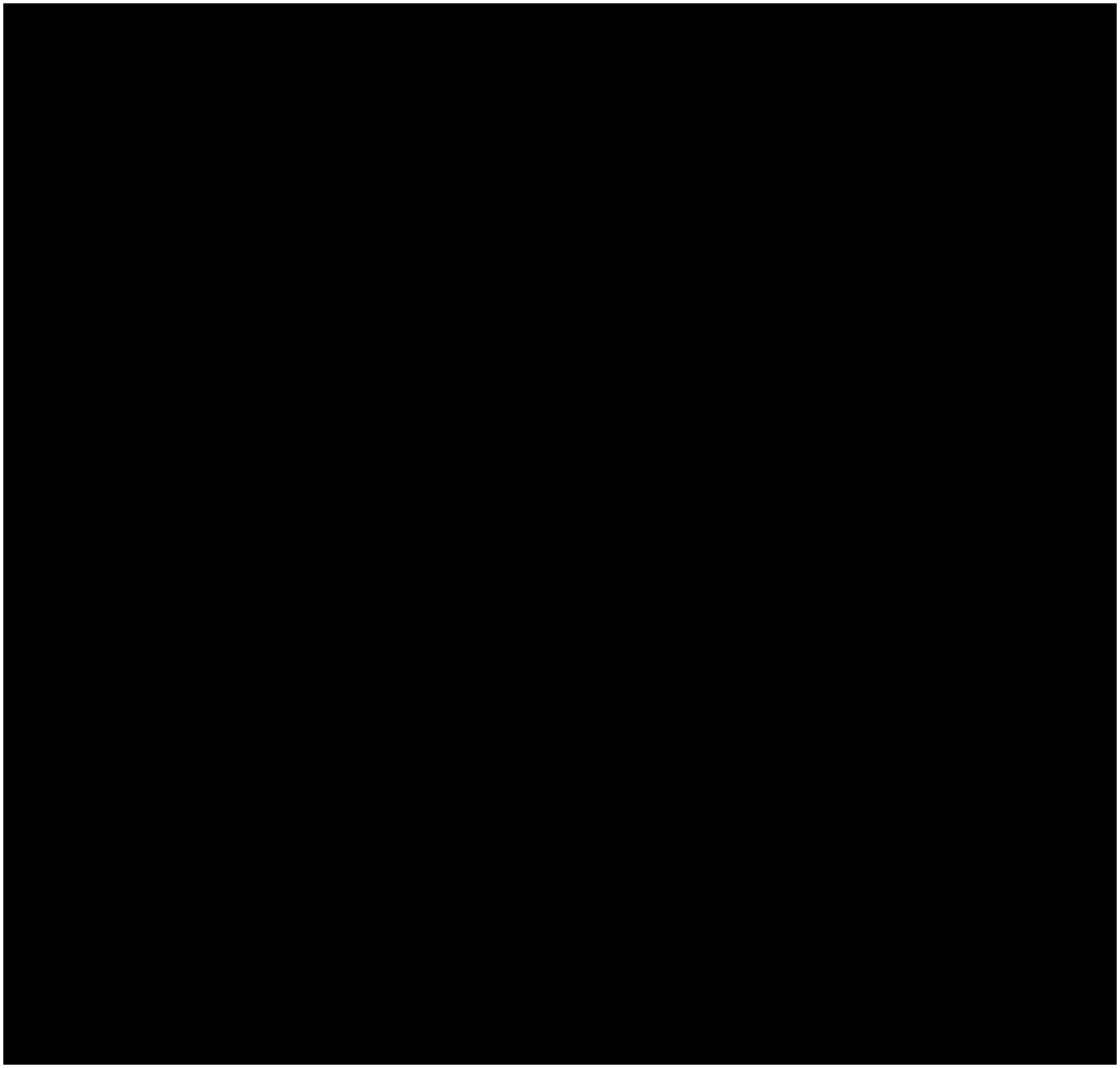
Date: 30 July 2019

Version: Amendment 1



PROTOCOL ACCEPTANCE FORM

Protocol: CO-338-097

Title: A Phase 2, open-label study to evaluate rucaparib in combination with nivolumab in patients with selected solid tumors (ARIES)

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I have carefully read this protocol and agree that it contains all the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH E6(R2) Guidelines for GCP, and all applicable regulatory requirements.

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

Name (printed)

SPONSOR'S MEDICAL EXPERT FOR THE STUDY

Medical Expert:

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 Clovis Oncology, Inc.
Name of Finished Product Rucaparib tablets; Nivolumab injection
Name of Active Ingredient Rucaparib camsylate (CO-338); Nivolumab (BMS-936558-01)
Study Title A Phase 2, open-label study to evaluate rucaparib in combination with nivolumab in patients with selected solid tumors (ARIES)
Study Number CO-338-097 (ARIES)
Study Phase Phase 2
Background and Study Rationale Study CO-338-097 will evaluate the combination of rucaparib and nivolumab as treatment for patients with either high-grade serous or endometrioid epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer, referred to collectively as ovarian cancer. Rucaparib is an inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes, which play a critical role in base excision repair (BER) of deoxyribonucleic acid (DNA).[1] When PARP function and effective BER are impaired, double-stranded 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 and other cancers. 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] Rucaparib monotherapy has demonstrated preclinical and clinical activity in cancers associated with a deleterious mutation in BRCA1/2 or other HRR gene, and different levels of genomic LOH (LOH High, Low, or Unknown). Rucaparib (Rubraca®) has been approved in the United States (US) and in the European Union (EU) as monotherapy treatment and maintenance treatment for ovarian cancer.[4,5] Nivolumab 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 receptor interaction with programmed-death ligand 1 (PD-L1) and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response. Nivolumab monotherapy has shown anti-tumor activity preclinical models[6] and in patients with ovarian cancer.[7-9] Nivolumab (OPDIVO®) monotherapy is approved in multiple regions, including the US[8] and EU,[9] and for multiple indications, including unresectable or metastatic melanoma, previously treated advanced renal cell carcinoma (RCC), and previously treated advanced or metastatic urothelial carcinoma.

The rationale for combining rucaparib with nivolumab as treatment for patients with ovarian cancer 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.[10-13] BRCA1 and BRCA2 mutations have been reported to increase the number of tumor infiltrating lymphocytes (TILs), and BRCA mutations are associated with improved overall survival (OS).[13-15] It is estimated that approximately 50% of patients with high-grade serous ovarian cancer (HGSOC)[10] have HRD (Clovis Oncology, Inc. [Clovis], data on file). In addition, internal data (Clovis) indicate a significant association between percentage of genomic LOH and level of tumor mutational burden (TMB). A high TMB (TMB^{high}) 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.

Cohorts A1 and A2 will investigate the efficacy and safety of rucaparib in combination with nivolumab, with the hypothesis that this drug combination may benefit patients with either (Cohort A1) germline BRCA wild-type ($gBRCA^{wt}$) ovarian cancer or (Cohort A2) germline BRCA-mutant ($gBRCA^{mut}$) ovarian cancer, who have previously received 1 or 2 prior regimens of standard treatment. The $gBRCA^{wt}$ population in Cohort A1 will be comprised of predominantly BRCA wild-type ($BRCA^{wt}$) patients, as well as patients with a deleterious somatic BRCA mutation ($sBRCA^{mut}$). Rucaparib in combination with nivolumab represents a potential new therapy for the treatment of ovarian cancer patients with relapsed disease. In addition, the combination will be evaluated in the $gBRCA^{mut}$ ovarian cancer population[16] included in the exploratory Cohort A2, for translational research to examine the impact of rucaparib on immune response in the tumor.

Study Objectives

All objectives (unless otherwise specified) will be assessed for Cohorts A1 and A2. Assessments will be conducted separately per Cohort A1 and A2.

Primary Objective:

- To evaluate the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as assessed by the investigator *(Cohort A1 only)*
- To study the effect of rucaparib on the immune microenvironment *(Cohort A2 only)*

Secondary Objectives:

- To evaluate the ORR by RECIST v1.1 and Gynecological Cancer InterGroup (GCIG) cancer antigen 125 (CA-125 criteria (*Cohort A1 only)*
- To evaluate the ORR by RECIST v1.1 as assessed by the investigator, according to molecularly-defined HRD subgroups: $BRCA^{wt}/LOH^{high}$; $BRCA^{wt}/LOH^{low}$; $BRCA^{wt}/LOH^{unknown}$; and sBRCA *(Cohort A1 only)*
- To estimate progression-free survival (PFS) *(Cohort A1 only)*
- To evaluate duration of response (DOR) (*Cohort A1 only)*
- To evaluate safety and tolerability of rucaparib in combination with nivolumab

Exploratory Objectives:

- To evaluate the ORR by RECIST v1.1 as assessed by the investigator *(Cohort A2 only)*
- To evaluate the ORR by RECIST v1.1 and GCIG CA-125 criteria *(Cohort A2 only)*
- To estimate PFS *(Cohort A2 only)*
- To evaluate DOR *(Cohort A2 only)*
- To assess mutations in BRCA1, BRCA2, and other HRR genes as molecular markers of efficacy
- To assess PD-L1 expression as a molecular marker of efficacy
- To assess LOH, TMB, and other genomic and transcriptional signatures 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 and nivolumab in combination
- To evaluate immunogenicity of nivolumab when administered in combination with rucaparib
- To explore exposure-response (ER) relationship between selected exposure measures of rucaparib and nivolumab, and safety and efficacy endpoints
- To study the effect of rucaparib on the immune microenvironment *(Cohort A1 only)*

Study Design

This is an open label, 2-stage, 2-cohort study to evaluate rucaparib in combination with nivolumab in patients with high-grade serous or endometrioid ovarian cancer:

Cohort A1: $gBRCA^{wt}$
Cohort A2: $gBRCA^{mut}$

For both Cohort A1 and A2, the study will enroll patients with either high-grade serous or endometrioid EOC, FTC, or PPC, measurable disease per RECIST v1.1, who received 1 or 2 prior regimens (including at least 1 prior platinum-containing regimen), who were sensitive to their last platinum regimen, and who had radiologic progression during or after the most recent regimen.

The study will use a Simon 2-stage design in Cohort A1. Patients who meet eligibility criteria will be entered into the applicable study cohort. Refer to detailed information on the Simon 2-stage calculation under the description of Statistical Methods below and Determination of Sample Size in Section 9.2. In Cohort A2, exploratory endpoints including efficacy will be evaluated.

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

Screening Phase

General (All patients)

All patients will undergo screening assessments within 28 days prior to enrollment (see exception for mandatory tumor tissue below). Patients must provide written informed consent prior to any screening procedures and must meet all inclusion and exclusion criteria as specified in the protocol prior to enrollment in the study. Patients undergoing repeated screening assessment(s) must also meet all inclusion and exclusion criteria prior to enrollment.

Screening assessments will include demographics and medical history, prior anticancer treatments, prior and current medications and procedures, 12-lead electrocardiogram (ECG), Eastern Cooperative Oncology Group (ECOG) performance status, local laboratory hematology and clinical chemistry measurements, serum pregnancy test (for women of childbearing potential only), urinalysis, physical examination, height, weight, and vital signs measurements, new adverse events (AEs) during screening, and tumor assessment by computed tomography (CT) scan. Other complementary assessments (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. Blood sampling for ctDNA in plasma will also be collected for central laboratory analysis.

Submission of tumor tissue at screening is mandatory as described below for each cohort. Tumor tissue will be analyzed by the central laboratory for tumor mutation classification as described below for each cohort. In addition, the tumor tissue will be analyzed by the central laboratory for baseline assessment of molecular markers associated with efficacy and the immune microenvironment.

Collection of adequate tumor tissue at screening is mandatory. Tissue must be sent to and analyzed by the central laboratory for all patients enrolled.

Tumor tissue samples should be from primary or metastatic tissue and must be collected within 42 days of the first dose of rucaparib. Alternatively, tumor tissue collected > 42 days prior to the first dose of rucaparib may be submitted, provided there have been no intervening anticancer treatments during this period and the tissue is of adequate quality. Patients may be enrolled prior to tumor tissue being analyzed by the central laboratory, provided there is confirmation that tumor tissue has been received by the central laboratory.

Sequencing of BRCA1/2 and analysis of genomic LOH in the tumor sample will be performed by the central laboratory (Foundation Medicine, Inc. [FMI]). A prior test result for $gBRCA^{mut}$ is required to determine eligibility for patients enrolled into Cohort A1 and A2.

Treatment Phase

Dosing Procedures:

Patients will commence treatment with oral rucaparib, beginning on Cycle 1 Day 1. Oral study drug will be taken twice a day (BID) continuously thereafter.

Dosing with intravenous (IV) nivolumab will commence on Cycle 2 Day 1; IV nivolumab will be administered every 4 weeks (Q4W).

Study Visits and Procedures:

General (All patients)

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 treatment will continue in 28-day cycles until 24 months from the start of the oral/IV combination treatment (ie, 25 months for Cohorts A1 and A2), 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.

Tumor assessments by CT scan will be performed every 8 calendar weeks (±7 days) from the start of the oral/IV combination treatment on Cycle 2 Day 1 for Cohorts A1 and A2, up to 18 months and then every 12 calendar weeks (±7 days) thereafter and at the End of Treatment Visit, if applicable, until confirmed objective radiological disease progression, as assessed by the investigator. Tumor assessments are to be performed prior to the next scheduled IV nivolumab treatment.

Patients experiencing confirmed disease progression by RECIST v1.1 will be discontinued from treatment and enter follow-up. If the patient has met criteria for confirmed radiologic progression by RECIST, but the patient is still receiving benefit from the study drug(s) according to the investigator (eg, patient has mixed radiologic response or is continuing to have symptomatic benefit), then continuation of treatment will be considered for a maximum cumulative duration of 24 months following initiation of combination 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 at their next routine study visit. Patients will continue to have all protocol-required assessments specified in the Schedule of Assessments (Table 6) and Pharmacokinetic and Immunogenicity Sample Collections (Table 7).

Safety and efficacy data will be periodically reviewed by the study Data Monitoring Committee (DMC).

Within 5 days and prior to commencement of IV nivolumab treatment on Cycle 2 Day 1, collection of a primary or metastatic tumor sample is mandatory for patients in Cohorts A1 and A2, unless tumor biopsy procedure is contraindicated (eg, unacceptable risk in the opinion of the investigator). The tumor sample will be analyzed by the central laboratory

to assess molecular markers of efficacy or resistance, as well as the effect of rucaparib on the immune microenvironment.

Post-Treatment Follow-up Phase for Both Cohorts

All patients will be followed for at least 100 days (+7 days) after the last dose of IV nivolumab treatment. There will be 2 follow-up visits: the 28-day Follow-up Visit (FU-28) should occur 28 days (±3 days) after last dose of the oral and/or IV study drug (whichever occurs later), and the 100-day Follow-up Visit (FU-100) should occur at least 100 days (+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, FU-100 can be performed at a cycle visit, provided it has been at least 100 days (+7 days) 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 from Cycle 2 Day 1 for the first 18 months after initiation of oral/IV combination study drug treatment and then every 24 weeks thereafter until objective radiological disease progression by RECIST v1.1, as assessed by the investigator, is documented. An optional tumor biopsy will be collected from patients who experience disease progression and provide appropriate consent.

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

Number of Patients

Approximately 28 to 53 patients will be enrolled. A maximum of 43 patients (Cohort A1), and 10 patients (Cohort A2) will be enrolled.

Number of Sites

Patients will be enrolled at approximately 15 sites in the US.

Inclusion Criteria

Eligible patients must meet the following applicable inclusion criteria:

General Inclusion Criteria (All patients)

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) prior to any study-specific evaluation.
2. ≥ 18 years of age at the time the ICF is signed.
3. Have adequate organ function confirmed by the following laboratory values obtained at screening (within 14 days prior to the first dose of study drug):
   a. Bone Marrow Function
      - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
      - Platelets ≥ 100×10^9/L
      - Hemoglobin ≥ 9 g/dL

b. Hepatic Function
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 × upper limit of normal (ULN)
   - Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome
   - Serum albumin ≥ 30 g/L (3.0 g/dL)

c. Renal Function
   - Serum creatinine ≤ 1.5 × ULN unless estimated glomerular filtration rate (GFR) ≥ 30 mL/min using the Cockcroft Gault formula

4. Have life expectancy ≥ 16 weeks, in the opinion of the investigator.
5. Women of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to administration of the first dose of study drug.
6. Have a histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer. If mixed histology, > 50% of the primary tumor must be confirmed to be high-grade serous or endometrioid upon re-review by local pathology.
7. Have measurable disease as defined by RECIST v1.1 (Cohort A1 only).
8. A mandatory biopsy or resection of tumor tissue must be collected ≤ 42 days prior to first dose of rucaparib. Alternatively, tumor tissue collected > 42 days prior to the first dose of rucaparib may be submitted, provided there have been no intervening anticancer treatments during this period and the tissue is of adequate quality. See Section 7.5.6.1. Patients may be enrolled prior to tumor tissue being analyzed by the central laboratory, provided there is confirmation that the tumor tissue has been received by the central laboratory.
9. (Cohort A1) Have gBRCA^{wt} ovarian cancer (ie, patients with a deleterious germline mutation in BRCA1 or BRCA2, as determined by a local laboratory that has received an international or country-specific quality standards certification, are excluded).

   OR

   (Cohort A2) Have gBRCA^{mut} ovarian cancer (ie, deleterious germline BRCA1/2 mutation, as determined by a local laboratory that has received an international or country-specific quality standards certification).
10. Be willing to have a mandatory biopsy of tumor tissue collected at Cycle 1 Day 28 of treatment.
11. Have relapsed/progressive disease as confirmed by radiologic assessment.
12. Received 1 or 2 prior regimens, including ≥ 1 prior platinum-based therapy and have platinum-sensitive disease:
    a. Received ≥ 1 prior platinum-based treatment regimen; AND

b. Received a platinum-based regimen as their last treatment; continuous or switch maintenance treatment as part of this regimen is permitted (hormonal treatment may be permitted following the last platinum regimen); AND

c. Was sensitive to the last platinum regimen. Platinum-sensitive disease is defined as documented radiologic progression > 6 months after the last dose of platinum administered in the treatment setting.

13. Have an ECOG performance status of 0 to 1 < 14 days prior to first dose of rucaparib.

Exclusion Criteria

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

General Exclusion Criteria (All patients)

1. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment.
   - 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, or non-melanoma skin cancers are allowed to enroll.
2. Known central nervous system brain metastases.
3. Has evidence of interstitial lung disease, active pneumonitis, myocarditis, or history of myocarditis.
4. 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.
5. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
6. 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.
7. 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.
8. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, hepatitis B surface antigen (HBsAg, Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
9. For female patients of childbearing potential, the following are exclusion criteria, as applicable:

a. Refusal to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib study treatment
b. Pregnant or breast feeding.
c. Women of childbearing potential must not be considering getting pregnant during the study and for 6 months following the last dose of rucaparib and/or nivolumab.

10. 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.
11. 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.
12. Hospitalization for bowel obstruction within 12 weeks prior to enrollment.
13. Prior treatment with a PARP inhibitor (PARPi) or immune checkpoint inhibitor (Exception: patient is eligible if they received a prior PARPi as frontline maintenance therapy and patient did not have disease progression whilst on the PARPi, providing inclusion criterion 11 is also met at time of screening).
14. Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > NCI CTCAE v5.0 Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug.
15. Non-epithelial tumors (pure sarcomas) or ovarian tumors with low malignant potential (ie, borderline tumors) or mucinous tumors. Mixed Mullerian tumors/carcinosarcomas are allowed.

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

Enrollment and Study Treatment

Eligible patients meeting all applicable inclusion/exclusion criteria will be enrolled in the applicable open-label treatment cohort by the investigator:

- Cohorts A1 and A2: rucaparib + nivolumab

No randomization or blinding will be performed in the study.

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

Nivolumab is administered as 480 mg via a 30-minute IV infusion on Day 1 of every 4-week cycle, starting Cycle 2 Day 1 (Cohorts A1 and A2).Patients will receive both study drugs for a maximum of 24 months after initiation of oral/IV combination treatment, or until disease progression by RECIST v1.1 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.

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 the patient is still receiving benefit from the study drug(s) according to the investigator, the investigator has consulted with the sponsor's medical officer or designee, and the patient has provided additional consent at her next study visit;
- 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;
- Noncompliance by the patient with protocol mandated procedures;
- A positive pregnancy test at any time during the study; and/or
- Study-specific treatment withdrawal rules for rucaparib and nivolumab (defined in Section 5.5.1.2).

Efficacy Assessments

Tumor assessment measurements will be performed at screening, at the end of every 8 weeks of treatment (±7 days) relative to Cycle 1 Day 1 for the first 18 months after initiation of oral/ IV study treatment, and then every 12 weeks thereafter until objective radiological disease progression, or discontinuation of treatment, and as clinically indicated.

Disease assessment will comprise clinical examination and appropriate imaging techniques per RECIST v1.1 (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1). Other complementary assessments (MRI, 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. 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 in imaging manual should be followed for the collection of images and the radiological assessment of disease.

Tumor response will be interpreted using RECIST v1.1, as assessed by the investigator. Disease progression will primarily be determined by RECIST v1.1.

Blood samples to assess CA-125 will be collected at screening and throughout the study (Table 6) and assessed by a local laboratory. Cohort A1 and A2 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.

Patients who discontinued study treatment for a reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals (±7 days) for the first 18 months after initiation of oral/IV combination study treatment 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.

Safety Assessments

Safety and tolerability will be assessed based on the following:

- Incidence, type, seriousness, and severity of adverse events (AEs) reported (CTCAE v5.0);
- Clinical laboratory investigations (hematology, clinical chemistry, urinalysis);
- Vital signs (blood pressure, heart rate, and body temperature);
- 12-lead electrocardiograms (ECGs);
- Physical examinations; and
- ECOG performance status.

Statistical Methods

Sample Size

Approximately 28 to 53 patients will be enrolled in this open-label, 2-stage, 2-cohort study.

A maximum of 43 patients (Cohort A1) and 10 patients (Cohort A2) will be enrolled.

Study Design

A Simon 2-stage design to evaluate ORR by RECIST v1.1 criteria per investigator will be used for Cohort A1. Enrollment in the study will continue while the interim analysis (Stage 1 criteria) occurs for Cohort A1. The DMC will review data for the interim analysis and provide recommendation if Stage 1 criteria are not met for Cohort A1. If Stage 1 criteria are not met, the DMC will evaluate the overall benefit:risk for study treatment, and make a recommendation whether further enrollment should be discontinued. If Stage 1 criteria in the Simon 2-stage design are met, the enrollment will continue with additional patients in Stage 2. Further details on the Simon 2-stage design is outlined below:

Cohort A1 (gBRCA^{wt})

With an optimal design, a minimum of 18 patients and a maximum of 43 patients will be enrolled in this cohort.

Stage 1 evaluation will be performed after the first 18 patients have either:

a) completed 16 weeks of treatment, or b) discontinued treatment prior to completing. If ≥ 3/18 patients have a confirmed objective response, then enrollment will continue with additional patients in Stage 2. With 43 total patients, characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug (ie, ORR of 10%)
- 80% probability of accepting an effective drug (ie, ORR of 25%)

Cohort A2 (gBRCA^{mut})

Cohort A2 is an exploratory cohort that will enroll approximately 10 ovarian cancer patients classified as gBRCA^{mut}. Due to the exploratory nature of this cohort, a sample size of 10 patients is considered sufficient in order to study the effect of rucaparib on the immune microenvironment in this cohort for comparison to the immune microenvironment in the cohort of patients harboring gBRCA^{wt} tumors (Cohort A1). No stopping rule in enrollment will be used for Cohort A2.

Data Monitoring Committee

A study DMC will be established and comprise the coordinating investigator and sponsor representatives. The DMC composition, responsibilities, and procedures for this study will be documented in the DMC Charter, which will be endorsed by the DMC members and signed by the DMC chair prior to the first data review meeting.

The DMC will review on an ongoing basis the study progress and clinical data to ensure the study remains beneficial to patients. The DMC will review the overall safety and efficacy data of rucaparib in combination with nivolumab, and by study cohort, to determine whether the study benefit: risk remains positive during the study.

The DMC will meet after the first 10 patients (Cohort A1) have either **a)** received at least 1 cycle of study treatment with rucaparib and nivolumab, **b)** discontinued study treatment or **c)** died of any cause. The DMC will perform continuous safety review at least every 6 months. The DMC chairperson or sponsor may convene an unscheduled DMC meeting if there are any emergent significant safety concerns.

Following data review, the DMC will recommend continuation, revision, or termination of the study and/or continuing or suspending enrollment into the study or a particular study cohort.

Date of Amendment 1 Approval

30 July 2019

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	
2QW	twice weekly
ADA	anti-drug antibody
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALCOA-C	attributable, legible, contemporaneous, original, accurate, complete
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
Bcl-xL	B-cell lymphoma-extra large
BCRP	breast cancer resistance protein
BER	base excision repair
BID	twice a day
BMS	Bristol-Myers Squibb
BRCA	breast cancer gene
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
$BRCA^{wt}$	wild-type breast cancer gene
$BRCA^{wt}/LOH^{high}$	wild-type breast cancer gene and high loss of heterozygosity (LOH ≥ 16%)
$BRCA^{wt}/LOH^{low}$	wild-type breast cancer gene and low loss of heterozygosity (LOH < 16%)
$BRCA^{wt}/LOH^{unknown}$	wild-type breast cancer gene and unknown loss of heterozygosity (LOH unknown due to missing results and/or failed test result(s))
BTLA	B and T lymphocyte attenuator
BUN	blood urea nitrogen
$C_{av,ss}$	average nivolumab steady-state exposures
CA-125	cancer antigen 125
CD	cluster of differentiation
C_{eoi}	concentration at the end of infusion
CFR	Code of Federal Regulations
CI	confidence interval

CL	clearance
CLcr	creatinine clearance
CL_{ss}	steady-state clearance
C_{max}	maximum concentration
$C_{max,ss}$	steady-state maximal concentrations
C_{min1}	trough concentration after first dose
$C_{min,ss}$	steady-state trough concentrations
CMV	cytomegalovirus
CO_2/HCO_3^-	Bicarbonate
CR	complete response
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
DNAseq	deoxyribonucleic acid sequencing
DOR	duration of response
DMC	Data Monitoring Committee
EC	European Commission
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ENGOT	European Network for Gynecological Oncological Trial groups
EOC	epithelial ovarian cancer
ER	exposure-response
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded

FMI	Foundation Medicine, Inc.
FSH	follicle-stimulating hormone
fT3	free thyroxine
fT4	free triiodothyronine
FU-28	28-day Follow-up Visit after last dose of study drug (oral or IV, whichever is later)
FU-100	100-day Follow-up Visit after last dose of IV study drug
FTC	fallopian tube cancer
gBRCA	germline BRCA
$gBRCA^{mut}$	germline BRCA mutation
$gBRCA^{wt}$	germline BRCA wild-type
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GOG	Gynecologic Oncology Group
H&E	hematoxylin and eosin
HDPE	high-density polyethylene
HGSOC	high-grade serous ovarian cancer
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HRD	homologous recombination deficiency
HRR	homologous recombination repair
HuMAb	human monoclonal antibody
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICJME	International Committee of Medical Journal Editors
ICOS	inducible T-cell co-stimulator
IEC	Independent Ethics Committee
IFN	interferon
IgG4	immunoglobulin G4
IL	interleukin
IMAE	immunotherapy-related adverse event
INN	International Nonproprietary Name
INR	international normalized ratio
I-O	immuno-oncology

IRB	Institutional Review Board
IRR	independent radiology review
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
LD	longest diameter
LDH	lactate dehydrogenase
LOH	loss of heterozygosity
LOH^{high}	high loss of heterozygosity
$LOH^{unknown}$	unknown loss of heterozygosity, due to missing results and/or failed test result(s)
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 Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
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	PARP inhibitor
PD	progressive disease
PD-1	programmed death-1or programmed death receptor 1
PD-L1/PD-L2	programmed-death ligand 1/2
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PMDA	Japanese Pharmaceuticals and Medical Devices Agency

PO	oral
PPC	primary peritoneal cancer
PPI	proton pump inhibitors
PPK	population pharmacokinetics
PR	partial response
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	stable disease
StD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TAI	telomeric allelic imbalance
$tBRCA^{mut}$	tumor tissue BRCA1 or BRCA2 mutation, includes gBRCA and sBRCA mutations
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse event
TILs	tumor infiltrating lymphocytes
TMB	tumor mutational burden
TSH	thyroid stimulating hormone
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
V_{ss}	volume of distribution at steady-state
WBC	white blood cell

1 INTRODUCTION

Study CO-338-097 is a Phase 2, open-label study to evaluate rucaparib in combination with nivolumab in patients with either high-grade serous or endometrioid epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer, referred to collectively as ovarian cancer.

The ovarian cancer cohorts will include patients who have either:

- Cohort A1: germline breast cancer gene wild-type (gBRCA^{wt}) , or
- Cohort A2: a germline breast cancer gene mutation (gBRCA^{mut}).

Patients in Cohorts A1 and A2 are to have received 1 or 2 prior regimens (including at least 1 prior platinum-containing regimen), be sensitive to their last platinum regimen, and (for Cohort A1) have radiologic progression during or after the most recent regimen.

The ovarian cancer cohorts planned for this study represent populations of patients who may be responsive to the combined therapy given the molecular characteristics of their tumors and mechanisms of action of rucaparib and nivolumab.

1.1 Background

1.1.1 Ovarian Cancer

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.[17] The median age at presentation of 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 (Stage III/IV), and these women have particularly poor outcomes.[18] 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.[19] The site of origin of EOC remains unclear. Some studies suggest that serous EOC and PPC arise from the fallopian tube epithelium; however, other studies suggest an origin within stem cells of the ovarian surface epithelium.[19-22] EOC, PPC, and 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 intrastrand-cross links with deoxyribonucleic acid (DNA).[19,23] Despite a 70% to 80% initial response rate,[18,24,25] most women with advanced ovarian cancer will experience disease relapse, usually within 15 months of initial diagnosis.

The choice of treatment for relapsed disease is based on the treatment-free interval relative to last therapy administered and chemotherapy agents used. Platinum-based regimens dominate ovarian cancer therapy and define treatment groups.[26] In general, patients whose disease progresses during treatment with a platinum-based regimen are considered to have platinum-refractory disease; patients whose disease relapses within 6 months after the last platinum agent was administered are considered to have platinum-resistant disease; and patients whose disease relapses more than 6 months after last platinum-based therapy was administered are considered to have platinum-sensitive disease. Patients with a ≥ 6 to 12-month interval are considered to have partially platinum-sensitive disease, while those with a ≥ 12-month interval are considered to have fully platinum-sensitive disease. However, all of these classifications are somewhat arbitrary as resistance to platinum-based therapy is a time continuum, not a categorical variable, and a status of 'platinum-resistant' is not absolute as it can be partially overcome. In addition, 'platinum-sensitivity' was defined when there was no alternative to platinum-based treatment and in clinical practice typically only refers to second-line treatment. These definitions also do not take into account the molecular characteristics of a patient's tumor (such as the presence of a BRCA mutation). For the patients enrolled in clinical studies of rucaparib, patients were considered sensitive if they had progressive disease (PD) ≥ 6 months after the last dose of platinum, resistant if they had PD 0 to < 6 months after the last dose of platinum and with a best of response to treatment other than PD, or refractory if they had a best response of PD during platinum treatment or PD ≤ 2 months after the last dose of platinum.

Treatment decisions for relapsed ovarian cancer are driven in part by type of response achieved and the duration between completion of treatment and disease relapse. Patients with platinum-sensitive disease are typically retreated with platinum-based therapy until they no longer respond to or can no longer tolerate such treatment.[18,24,25] Patients with platinum-resistant disease have more limited treatment options such as bevacizumab in combination with chemotherapy (paclitaxel, pegylated liposomal doxorubicin [PLD], or topotecan)[27,28] or single-agent treatment with PLD, topotecan, gemcitabine, or weekly paclitaxel. However, these agents have limited utility due to poor efficacy (objective response rates [ORR] ranging 20% to 30% with median progression-free survival [PFS]/time to tumor progression < 6 months) and are accompanied by significant toxicities that further reduces the ultimate therapeutic benefit. In later lines of therapy, treatment choice is often restricted according to the individual patient situation (eg, performance status, organ function, residual toxicities from prior treatment, other comorbidities, and patient choice).

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 treatments for patients with recurrent ovarian cancer.[29,30]

1.1.2 Rucaparib

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

In the United States (US), rucaparib received accelerated approval in December 2016 as monotherapy treatment for ovarian cancer, followed by a regular approval in April 2018, as both monotherapy treatment (Section 1.1.2.3.2.1) and maintenance treatment (Section 1.1.2.3.2.2) for ovarian cancer.[5] In the European Union (EU), rucaparib was authorized in May 2018 as monotherapy treatment (Section 1.1.2.3.2.1), and in January 2019 as maintenance treatment (Section 1.1.2.3.2.2) for ovarian cancer.[4] The mechanism of action and summary of data from nonclinical and clinical studies are provided below, and described in more detail in the rucaparib Investigator's Brochure (IB). A summary of the benefit:risk is also provided in the rucaparib IB.

1.1.2.1 Mechanism of Action

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 homologous recombination deficiency (HRD).[10] Similarly, based on an analysis of TCGA bladder cancer data set (http://cancergenome.nih.gov), approximately 60% of bladder cancer tumors may have HRD (Clovis Oncology, Inc. [Clovis], data on file).

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 and other cancers. Over the past decade, it has been determined that patterns of genomic LOH can predict HRD.[3] Comprehensive genomic profiling based on next generation sequencing (NGS) can be utilized to identify non-BRCA-mutant (ie, $BRCA^{wt}$) patients with HRD. The main advantage of detecting tumor genomic LOH is that it can identify HRD tumors regardless of the underlying mechanisms.[3,31] 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 ($BRCA^{wt}$) subgroup provided the optimum discrimination of rucaparib treatment benefit; this group is referred to as LOH high or the $BRCA^{wt}/LOH^{high}$ subgroup.[16,32] In addition, data also support that BRCA wild-type ($BRCA^{wt}$) patients with unknown LOH ($BRCA^{wt}/LOH^{unknown}$) or low LOH ($BRCA^{wt}/LOH^{low}$), also benefit from treatment.[16,32]

Given the overlap in various DNA repair pathways, inhibition of a single pathway is unlikely to have a significant effect on cancer cell death. Inhibition of DNA damage repair in cancer cells represents an attractive opportunity for the development of new therapies. In normal cells, single-strand breaks (SSBs) in DNA are repaired through BER via PARP enzymes. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn primarily repaired by HRR of DNA, a complex process involving multiple proteins. Homologous recombination pathway defects, either as an initiating event or a

late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers.

Inhibition of multiple DNA repair pathways may lead to cell death, a concept known as synthetic lethality. For example, normal cells treated with a PARP inhibitor still have other intact DNA repair pathways and are able to survive, whereas cancer cells, with pre-existing HRD, treated with a PARP inhibitor accumulate DNA damage and enter apoptosis. This concept of synthetic lethality has been demonstrated in key in vitro and in vivo studies, as well as in several clinical studies that evaluated a single-agent PARP inhibitor.[33-35]

1.1.2.2 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 uridine diphosphate 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.[36-38]

1.1.2.3 Clinical Experience

Rucaparib monotherapy is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer with and without evidence of HRD. Clinical studies evaluating rucaparib as monotherapy treatment or maintenance treatment in patients with relapsed, high-grade EOC, FTC, or PPC are ongoing. In addition, Phase 2 and Phase 3 studies of rucaparib monotherapy treatment for patients with metastatic castration-resistant prostate cancer (mCRPC) are ongoing.

Clinical pharmacology studies in patients with advanced solid tumors continue to more fully characterize rucaparib drug-drug interactions (DDI), 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, including immune checkpoint inhibitors, are ongoing in ovarian and prostate cancer, as well as other tumor types.

1.1.2.3.1 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 daily (BID) dosing, rapid absorption with maximum concentration (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 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.

Results from the mass balance and metabolite profiling Study CO-338-045 showed rucaparib excretion primarily in feces, followed by urine. The PK profile obtained for the female patients enrolled in this study were similar to those reported previously for male patients. M324 derived from oxidation of rucaparib was the major metabolite identified. Other metabolic pathways included N-demethylation, N-methylation, glucuronidation, and N-formulation.

1.1.2.3.2 OVERVIEW OF EFFICACY

1.1.2.3.2.1 Rucaparib as Monotherapy Treatment for Ovarian Cancer

Rucaparib (Rubraca®) received accelerated approval in December 2016, followed by regular approval in April 2018, by the US Food and Drug Administration (FDA) for treatment of patients with deleterious BRCA mutation (germline and/or somatic)-associated EOC, FTC, or PPC who have been treated with 2 or more chemotherapies.[5] In May 2018 , the European Commission (EC) authorized rucaparib (Rubraca) as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade EOC, FTC, or PPC, who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.[4] 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, of whom 79 were platinum-sensitive, 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.[5]

The primary outcome measure on which approval was based is investigator-assessed 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.[39] Responses were durable, indicated by a duration of response (DOR) by investigator assessment of approximately 9.2 months.

In Part 1 of Study CO-338-017, which supported approval of rucaparib as treatment for BRCA-mutant ovarian cancer, patients with platinum-sensitive, relapsed ovarian cancer who received ≥ 1 prior platinum regimen and the following HRD signatures were enrolled.

- tBRCA: Patients whose tumor had a BRCA1/2 mutation, irrespective of genomic LOH measurement

- Non-tBRCA LOH+[1]: Patients whose tumor did not have a BRCA1/2 mutation and had a tumor genomic LOH ≥ 14%
- Non-tBRCA LOH-: Patients whose tumor did not have a BRCA1/2 mutation and had a tumor genomic LOH < 14%.
- Non-tBRCA LOH Unknown: Patients without a BRCA mutation and indeterminate for genomic LOH.

Response data (from investigator-assessed responses) indicate that rucaparib has activity in patients classified into the different HRD subgroups (Table 1). The greatest activity was observed in patients with a tBRCA mutation, with a confirmed ORR of 80.0% and median DOR of 12.9 months. Confirmed response by RECIST or GCIG CA-125 criteria was 85.0%. Similar activity was demonstrated in gBRCA and sBRCA mutations, with confirmed ORRs of 85.0% (17/20) and 75.0% (15/20), respectively.[16]

The majority (97.5% [39/40]) of $tBRCA^{mut}$ patients had some level of target lesion measurement reduction. Rucaparib was also effective in non-tBRCA LOH+ patients, with a confirmed ORR of 28.0% and median DOR of 11.3 months.

[1] Non-BRCA LOH+ is the nomenclature used in Study CO-338-017. This term is consistent with $BRCA^{wt}/LOH^{high}$ used in the current protocol, although different cut-offs for LOH^{high} were applied.

Table 1. Investigator-assessed Tumor Response by HRD Classification in Study CO-338-017 Part 1

Parameter	HRD Subgroup				Total (N = 204)
	tBRCA (N = 40)	non-tBRCA LOH+ (N = 82)	non-tBRCA LOH- (N = 70)	Non-tBRCA LOH Unknown (N = 12)	
Confirmed ORR (CR + PR) (n [%])	32 (80.0)	23 (28.0)	7 (10.0)	4 (33.3)	66 (32.4)
Best Overall Confirmed Response (n [%])					
CR	6 (15.0)	2 (2.4)	1 (1.4)	1 (8.3)	10 (4.9)
PR	26 (5.0)	21 (25.6)	6 (8.6)	3 (25.0)	56 (27.5)
SD	7 (7.5)	38 (46.3)	43 (61.4)	6 (50.0)	94 (46.1)
PD[a]	1 (2.5)	17 (20.7)	17 (24.3)	2 (16.7)	37 (18.1)
NE	0	4 (4.9)	3 (4.3)	0	7 (3.4)
Confirmed Response by RECIST or GCIG CA-125 (n [%])	34 (85.0)	36 (43.9)	14 (20.0)	4 (33.3)	91 (44.6)
DOR (median, 95% CI [months])[b]	12.9 (7.7-18.2)	11.3 (7.4-16.6)	5.8 (4.6-8.5)	ND	ND

Abbreviations: CA-125 = cancer antigen 125; CR = complete response; DCR = disease control rate; DOR = duration of response; GCIG = Gynecologic Cancer InterGroup; ND = not determined; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Progressive Disease by RECIST or if no assessments were done, by reason for discontinuing study.

[b] The Kaplan-Meier methodology was used to summarize DOR, based on confirmed responses per RECIST.

1.1.2.3.2.2 Rucaparib as Monotherapy Maintenance Treatment for Ovarian Cancer

In both the US (April 2018) and EU (January 2019), rucaparib (Rubraca) is approved for maintenance treatment for adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.[4,5] Efficacy and safety data were from the Study CO-338-014 (ARIEL3), the pivotal study in support of the approval for the maintenance treatment indication.

Efficacy of rucaparib monotherapy for patients with advanced ovarian cancer in the maintenance setting was demonstrated from Study CO-338-014 results showing significant benefit of rucaparib compared to placebo across primary, secondary, and exploratory endpoints.[40] In this study, investigator-assessed PFS (invPFS) was the primary efficacy endpoint, with PFS by blinded central independent radiology review (IRR) 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. The median invPFS for rucaparib vs. placebo was 16.6 months vs. 5.4 months, 13.6 months vs. 5.4 months, and 10.8 months vs. 5.4 months, with

hazard ratios of 0.231 ($p < 0.0001$), 0.317 ($p < 0.0001$), and 0.365 ($p < 0.0001$), for the tBRCA, HRD, and ITT populations, respectively. The invPFS results were confirmed by the secondary endpoint analysis of PFS by independent review (irrPFS), with median irrPFS for rucaparib vs. placebo of 26.8 months vs. 5.4 months, 22.9 months vs. 5.5 months, and 13.7 months vs. 5.4 months, with hazard ratios of 0.201 ($p < 0.0001$), 0.336 ($p < 0.0001$), and 0.354 ($p < 0.0001$), for the tBRCA, HRD, and ITT populations, respectively.

Overall, rucaparib as maintenance treatment reduced the risk of progression by 63.5% (hazard ratio 0.365 [95% CI, 0.295 0.451]; $p < 0.0001$) in the intent-to-treat (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 (deleterious tumor mutation in BRCA) subpopulations. Nearly half (44.6%) of the patients in the rucaparib group showed benefit at 1 year compared to 8.8% in the placebo group.[40] 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.[40] These investigator-assessed results were confirmed by results of central IRR assessment.[40]

1.1.2.3.3 Overview of Safety

Results of an integrated safety analysis in over 1,000 patients with ovarian cancer who received 600 mg BID rucaparib in the treatment or maintenance setting showed that the most common treatment-emergent adverse events (TEAEs) reported were primarily mild to moderate (Grade 1-2) in severity and include gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, decreased appetite, and dysgeusia. The most common TEAE ≥ 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),[41,42] and few patients discontinued rucaparib due to ALT/AST elevations.[32,39] 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 1.1.2.2).

An updated analyses of safety presented in the US prescribing information[5] and the EU Summary of Product Characteristics (SmPC)[4] for the recent approvals of rucaparib demonstrate that safety results in ovarian cancer patients treated with rucaparib have remained consistent with

those previously reported, and that the safety profile across both the treatment and maintenance indications is consistent.[5]

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.

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, as well as a deleterious BRCA mutation. Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib. More information on AESIs experienced by patients in rucaparib clinical studies is provided in the rucaparib IB.

1.1.3 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 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®) monotherapy is approved in multiple regions, including the US[43] and EU[9], for unresectable or metastatic melanoma, previously-treated advanced renal cell carcinoma (RCC), previously-treated relapsed or refractory classical Hodgkin lymphoma, previously-treated recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), previously-treated locally-advanced unresectable/metastatic non-small cell lung cancer (NSCLC), and previously-treated advanced or metastatic urothelial carcinoma. Nivolumab is also approved for the treatment of previously-treated metastatic colorectal cancer and previously-treated hepatocellular carcinoma in the US. In addition, nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma 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.

In the US the approved recommended dose of nivolumab as monotherapy is 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W) administered as an intravenous (IV) infusion over 30 minutes until disease progression or unacceptable toxicity, with the exception of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, where the recommended dose is 240 mg Q2W.

In the EU, the approved recommended dose as monotherapy is 240 mg Q2W over 30 minutes or 480 mg Q4W over 60 minutes in melanoma and renal cell carcinoma. In all other approved indications 240 mg Q2W over 30 minutes.

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)[9], US prescribing information (USPI),[43] or country-specific label) for more information.

1.1.3.1 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.[44-46] 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.[47] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the cluster of differentiation 28 (CD28) family of T-cell co-stimulatory receptors that also includes CD28, cytotoxic T lymphocyte-associated protein-4 (CTLA-4), inducible T-cell co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA).[48] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of interleukin 2 (IL-2), IL-10, IL-13, interferon-γ (IFN-γ), and B-cell lymphoma-extra large (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.[49] 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 (CMV) 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).[6]

1.1.3.2 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 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 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 weekly 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 weekly (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.[50] 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.

1.1.3.3 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.

1.1.3.3.1 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 CL_{ss} is not considered clinically relevant. The geometric mean volume of distribution at steady state (VSS) 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 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 (ER) analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg every 3 weeks (Q3W), and 480 mg 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.

1.1.3.3.2 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 studies, 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[7] 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.[51-53] However, the durability of the responses was an unexpected outcome, but a promising result 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.

1.1.3.3.3 Overview of Safety

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of adverse events (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, and pyrexia.

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.[7] 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.

1.1.3.3.4 IMMUNOGENICITY

Of 2,085 patients who were treated with OPDIVO as a single agent 3 mg/kg Q2W and evaluable for the presence of anti-nivolumab antibodies, 233 patients (11.2%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 15 patients (0.7%) had neutralizing antibodies against nivolumab. There was no evidence of altered PK profile or increased incidence of infusion reactions with anti-nivolumab antibody development. Overall, there was no evidence of increased incidence of infusion reactions or effects on efficacy with anti-nivolumab antibody development. 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.

1.1.4 PARP Inhibitors and Checkpoint Inhibitors

1.1.4.1 Nonclinical 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.[13] 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 intratumoral immune cells, and an elevated number of CD3-positive and CD8-positive tumor infiltrating lymphocytes (TILs).[13] 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.[16] Published data[54] and internal data (Clovis) 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.

1.1.4.2 Clinical Overview

The combination of immune checkpoint inhibitors and PARP inhibitors has been recently evaluated in 3 early-phase studies.[14,15,55] In a Phase 1 dose-escalation study of PD-L1 inhibitor, durvalumab, in combination with PARP inhibitor, olaparib, in 12 heavily pretreated patients (10 with ovarian cancer and 2 with triple-negative breast cancer), there were 4 patients with partial response (duration of response ≥ 15 months and ≥ 11 months) and 8 patients with stable disease ≥ 4 months (median, 8 months [4 to 14.5 months]), yielding an 83% disease control rate.[14] The most common TEAE with durvalumab plus olaparib was hematologic toxicity, with

no dose-limiting toxicity reported at the highest dose combination tested (olaparib 300 mg BID and durvalumab 1500 mg Q4W).

In a Phase 1/2 study of niraparib and pembrolizumab in patients with ovarian cancer (NCT02657889) who were platinum-resistant/refractory or unable to tolerate further platinum, an integrated efficacy analysis of 60 evaluable patients out of 62 patients was performed. The objective response rate (ORR) was 18% (11/60) overall. Notably, in platinum-resistant/refractory patients, efficacy was observed across the biomarker-selected populations, including BRCA wild-type (ORR 18%) and HRD negative patients (ORR 19%).[56] This may suggest that in this predominantly platinum-resistant ovarian cancer population, response to combination treatment was not determined by molecularly-defined HRD subgroups.

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 patients with advanced solid tumors.[55] Liver-related AEs were observed in 12 patients; all events were reversible with or without corticosteroid treatment. Complete or partial response was observed in 11 patients, 4 of whom had confirmed partial response (PR) or complete response (CR); responses were durable and observed in patients 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.[15]

A Clovis-sponsored Phase 3 study (Study CO-338-087 [ATHENA]) is being conducted in collaboration with Bristol-Myers-Squibb (BMS), the Gynecological Oncology Group (GOG), and the European Network for Gynecological Oncological Trial group (ENGOT) to evaluate rucaparib in combination with nivolumab as a front-line switch maintenance treatment in platinum-sensitive relapsed ovarian cancer. This Phase 3 study in ovarian cancer is implementing oral rucaparib dosing 1 cycle prior to initiating combination treatment with oral rucaparib/IV nivolumab, as planned for the current protocol to explore if immune priming of the tumor microenvironment with monotherapy rucaparib will enhance the activity in combination with nivolumab. In addition, a BMS-sponsored Phase 2 study (CA2099KD; CheckMate Study) is being conducted to evaluate rucaparib in combination with nivolumab as treatment for mCRPC.

As of 18 May 2018, data are available for 8 patients with Stage IV prostate cancer who have been treated with the combination of rucaparib and nivolumab in the Phase 2 CA2099KD study (Clovis, data on file). All patients received the full dose of nivolumab (480 mg IV q4 weekly) and rucaparib (600 mg BID continuous) in the first 28-day cycle. Overall, the commonly observed AEs were mild to moderate, and were consistent with the safety profile of rucaparib and nivolumab as single agents. Two of the 8 patients had Grade 1 rash, assessed as immune-mediated. The laboratory data were also consistent with what has been observed with rucaparib as a single agent. One patient had his rucaparib dose reduced from 600 mg BID to 500 mg BID at the beginning of Cycle 3, due to Grade 2 ALT elevations. There were no patients with Grade 3/4 AEs or serious adverse events (SAEs) assessed as related to study treatment.

Overall, the data from the 8 patients treated with nivolumab 480 mg IV Q4W and rucaparib 600 mg BID showed that the combination was well-tolerated, and there were no new safety signals identified.

1.1.5 Rationale for the Study and Benefit: Risk Assessment

The purpose of this Phase 2 study is to evaluate the safety and efficacy of rucaparib in combination of nivolumab in patients with selected solid tumors who may be responsive to the combined therapy. HRD-related biomarkers associated with efficacy of rucaparib will also be explored as a means to further identify patients who may be responsive to rucaparib and as an informative tool for clinicians to make treatment decisions.

1.1.5.1 Rationale for Ovarian Cancer

There is a clear and urgent clinical need for novel therapeutic approaches in advanced ovarian cancer. Despite the availability of newer and additional therapeutic options, 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.[17]

Homologous recombination pathway defects may be responsible for the genetic instability observed in many cancers, including ovarian cancer. It is estimated approximately 50% of high-grade serous ovarian cancer patients have alterations in HRR genes.[10] Clinical data with rucaparib have shown patients with and without a BRCA (germline or somatic) mutation benefit from rucaparib treatment in both the treatment and maintenance settings of ovarian cancer.[16,32] While patients with a BRCA mutation derived the most benefit, patients without evidence of a BRCA mutation also derived significant benefit, suggesting an incomplete understanding of biomarkers involved in sensitivity to PARP inhibition.[57]

1.1.5.2 Rationale for Rucaparib and Nivolumab Combination in Ovarian Cancer

The preclinical rationale for combining rucaparib with nivolumab for treatment of ovarian cancer 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.[10-13] BRCA1 and BRCA2 mutations have been reported to increase the number of TILs and are associated with improved OS.[13] In addition, internal data (Clovis) 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 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.

In Cohorts A1 (main cohort) and A2 (exploratory cohort), 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 immune priming of the tumor microenvironment will enhance activity of the combination for treatment of ovarian cancer associated with either a gBRCA^{wt} (Cohort A1) or a gBRCA mutation (Cohort A2). The gBRCA^{wt} population in Cohort A1 represents a broad population of ovarian cancer patients and is expected to consist of predominantly BRCA wild-type (BRCA^{wt}) patients, and rucaparib in

combination with nivolumab represents a potential new therapy for the treatment of ovarian cancer patients with relapsed disease. In addition, the combination will be evaluated in the gBRCA^{mut} ovarian cancer population[16] included in the exploratory Cohort A2, for translational research to examine the impact of rucaparib on immune response in the tumor. The rationale for including Cohort A2 is based on preclinical data that suggest the activity of PARP inhibition and PD-L1 blockade is predominantly observed in HRD tumors (eg, BRCA^{mut}) and that BRCA^{mut} high-grade ovarian cancer tumors have higher tumor mutation burden (TMB), PD-L1 expression, and tumor infiltrating lymphocytes (TILs) compared to gBRCA^{wt} tumors.[13] Therefore, Cohort A2 will serve as a comparator to Cohort A1.

Overall, the safety profiles of both rucaparib (oral study drug) and nivolumab (IV study drug) are manageable and generally consistent across completed and ongoing clinical studies (Section 1.1.4.2). Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. A pattern of immunotherapy-mediated adverse events (IMAEs) associated with nivolumab has been defined, for which management algorithms have been developed; these are provided in Appendix 6. 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.

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 benefit:risk assessment for patients enrolled into the present study, the following measures will be employed throughout the conduct of the study:

- A Data Monitoring Committee (DMC) will be established and meet to review safety, efficacy and study conduct, including review of data from the first 10 evaluable patients (Cohort A1), and subsequent periodic review of data thereafter.
- Rigorous safety monitoring by the sponsor to ensure patients' 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.

In conclusion, the overall benefit:risk of nivolumab in combination with rucaparib is deemed acceptable in ovarian cancer. 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.

1.2 Dose Rationale

1.2.1 Dose Rationale for Nivolumab

Intravenous flat doses of 240 mg Q2W nivolumab, 360 mg Q3W nivolumab, and 480 mg Q4W nivolumab have been incorporated in monotherapy and combination oncology studies, and the 240 mg Q2W and 480 mg Q4W nivolumab dose regimens are now approved in multiple indications.[8,9] Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing

regimens. Nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles compared to nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W.

Extensive ER analyses of multiple PK measures (maximum serum concentration at Day 1[C_{max1}], average serum concentration at Day 28 [C_{avg28}], and trough serum concentration at Day 28 [C_{min28}]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen (see nivolumab IB). In ER efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using C_{avg28} as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In ER safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade 3 or higher, and immune-mediated AEs (IMAEs) Grade 2 or higher are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

1.2.1.1 Rationale for Nivolumab 30-minute Infusion

Nivolumab is currently approved in the US at doses of 240 mg Q2W and 480 mg Q4W via a 30-minute IV infusion.[8]

1.2.2 Dose Rationale for Nivolumab and Rucaparib Combination

The recommended starting dose of rucaparib is 600 mg BID administered orally.[58] Dose modifications should be implemented as described in Section 5.5.

The starting dose for the combination of nivolumab plus rucaparib in this study will be the same as the monotherapy treatment. Rucaparib will be administered orally at 600 mg BID (as close as possible to 12 hours apart) on a 28-day cycle. Nivolumab will be administered at 480 mg via a 30-minute IV infusion on Day 1 of every 28-day cycle, starting with Cycle 2 for Cohorts A1 and A2. 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 Q4W, 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 1.1.4.2. A Phase 1 dose-escalation study of durvalumab in combination with olaparib in pretreated ovarian and triple-negative breast cancer patients was conducted.[14] The dose levels for this combination are also being evaluated in an ongoing Phase 2 study in patients with mCRPC and appear to be well-tolerated, with the most common Grade 3/4 AEs also being hematologic toxicity.[15] These studies have not identified any new safety signals when giving PARP inhibitor and an anti-PD-L1 antibody in combination. 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 (as described in Section 1.1.4.2).

The sponsor has initiated a Phase 3 study (Study CO-338-087 [ATHENA]) to evaluate the combination of rucaparib and nivolumab in newly diagnosed patients with advanced ovarian cancer as switch maintenance in women who have had a response to first-line platinum-based chemotherapy. Rucaparib and nivolumab are being administered at the same dose and regimen as proposed in the current protocol. Further, establishment of baseline laboratory values for each patient in Cohorts A1 and A2, 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, and the analysis is described in Section 9.10.

Please see Section 5.5 regarding appropriate dose modifications of the study drugs.

1.3 Rationale for Duration of Treatment

1.3.1 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.[59-63] A recent analysis in a melanoma study suggests the majority of patients 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 patients with metastatic melanoma, with a sustained plateau in survival starting at around year 3.[64] For these reasons, in the current study, treatment with nivolumab will be given for up to 24 months in the absence of disease progression, unacceptable toxicity, withdrawal of patient consent, or the end of the study, whichever occurs sooner.

1.3.2 Rucaparib

Rucaparib will be given for up to 25 months, 1 additional cycle over nivolumab) in the absence of disease progression, unacceptable toxicity, withdrawal of patient consent, or the end of the study, whichever occurs sooner. A total of 25 months was chosen to align with the duration of treatment for nivolumab.

2 STUDY OBJECTIVES

All objectives (unless otherwise specified) will be assessed for Cohorts A1 and A2. All endpoints will be summarized separately for each cohort.

2.1 Primary Objective

The primary objectives of this study are:

- To evaluate the ORR by RECIST v1.1 as assessed by the investigator *(Cohort A1 only)*
- To study the effect of rucaparib on the immune microenvironment *(Cohort A2 only)*

2.2 Secondary Objectives

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

- To evaluate the ORR by RECIST v1.1 and Gynecologic Cancer InterGroup (GCIG) cancer antigen 125 (CA-125) criteria *(Cohort A1only)*
- To evaluate the ORR by RECIST v1.1 as assessed by the investigator, according to molecularly-defined HRD subgroups: $BRCA^{wt}/LOH^{high}$; $BRCA^{wt}/LOH^{low}$; $BRCA^{wt}/LOH^{unknown}$; and sBRCA *(Cohort A1 only)*
- To estimate PFS *(Cohort A1only)*
- To evaluate DOR *(Cohort A1only)*
- To evaluate safety and tolerability of rucaparib in combination with nivolumab

2.3 Exploratory Objectives

Exploratory objectives in this study are:

- To evaluate the ORR by RECIST v1.1 as assessed by the investigator *(Cohort A2 only)*
- To evaluate the ORR by RECIST v1.1 and GCIG CA-125 criteria *(Cohort A2 only)*
- To estimate PFS *(Cohort A2 only)*
- To evaluate DOR *(Cohort A2 only)*
- To assess mutations in BRCA1, BRCA2, and other HRR genes as molecular markers of efficacy
- To assess PD-L1 expression as a molecular marker of efficacy
- To assess LOH, TMB, and other genomic and transcriptional signatures as molecular markers of efficacy
- To study variants in circulating tumor DNA (ctDNA) as markers of response and resistance

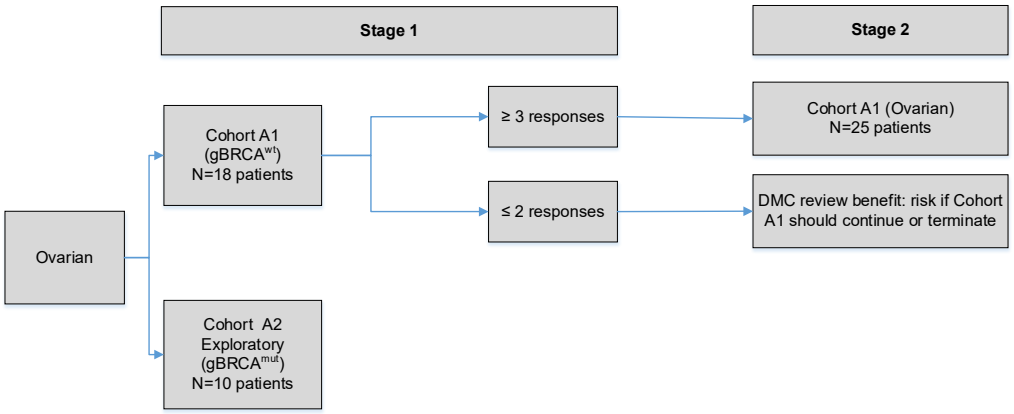
- To characterize PK of rucaparib and nivolumab in combination
- To evaluate immunogenicity of nivolumab when administered in combination with rucaparib
- To explore ER relationship between selected exposure measures of rucaparib and nivolumab, and safety and efficacy endpoints
- To study the effect of rucaparib on the immune microenvironment *(Cohort A1 only)*

3 STUDY DESIGN

3.1 Overall Study Design and Plan

The overall study design and plan is presented in Figure 1.

Figure 1. Study Design and Plan



Abbreviations: DMC = Data Monitoring Committee; gBRCA^{mut} = germline BRCA mutation; gBRCA^{wt} = germline breast cancer wild-type gene;

This is an open label, 2-stage, 2-cohort study to evaluate rucaparib in combination with nivolumab in patients with selected solid tumors:

Cohort A: high-grade serous or endometrioid ovarian cancer

Cohort A1: gBRCA^{wt}

Cohort A2: gBRCA^{mut} (exploratory)

The study will enroll patients with high-grade serous or endometrioid EOC, FTC, or PPC, with measurable disease per RECIST v 1.1 (in Cohort A1 only), who were sensitive to their last platinum regimen, and who received 1 or 2 prior regimens (including at least 1 prior platinum-containing regimen).

For Cohort A1, patients must be gBRCA^{wt} (ie, patients with a deleterious germline mutation in BRCA1 or BRCA2, as determined by a local laboratory that has received an international or country-specific quality standards certification, are excluded).

For Cohort A2, patients must be gBRCA^{mut} (as confirmed by local testing result).

The study will use a Simon 2-stage design for Cohort A1. Patients that meet all eligibility criteria will be entered into the applicable study cohort. Refer to detailed information on the Simon 2-stage calculations under the Determination of Sample Size (Section 9.2).

Unless contraindicated, a tumor sample will be collected from patients in Cohorts A1 and A2 after initiation of rucaparib treatment, but before initiation of nivolumab treatment, and analyzed by the central laboratory to assess molecular markers of efficacy or resistance, as well as the effect of rucaparib on the immune microenvironment (Section 7.5.6.1).

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

3.1.1 Screening Phase

A mandatory biopsy or resection of tumor tissue must be collected ≤ 42 days prior to first dose of rucaparib. Alternatively, tumor tissue collected > 42 days prior to the first dose of rucaparib may be submitted, provided there have been no intervening anticancer treatments during this period and the tissue is of adequate quality. Adequate tissue must be available for analysis by the central laboratory for all patients enrolled. Patients may be enrolled prior to tumor tissue being analyzed by the central laboratory, provided there is confirmation that tumor tissue has been received by the central laboratory. Detailed information is provided in Section 7.5.6.1.

All patients will undergo screening assessments within 28 days prior to enrollment.

The study will enroll patients with either high-grade serous or endometrioid ovarian cancer ($gBRCA^{wt}$ or $gBRCA^{mut}$).

Screening assessments will include demographics and medical history, prior treatments for serous or endometrioid EOC, FTC, or PPC (and other malignancies, if applicable) , prior and current medications and procedures, 12-lead ECG, Eastern Cooperative Oncology Group (ECOG) performance status, local laboratory hematology and clinical chemistry, and CA-125 measurement, urinalysis, physical examination, height, weight, and vital signs measurements, adverse events, radiologic assessment by computed tomography (CT) and/or other complementary assessments (MRI, X-ray, PET, and ultrasound) as required, and a blood sample for ctDNA analysis. 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.

Patients will be required to provide a mandatory screening biopsy for central laboratory analysis prior to enrollment. Patients may be enrolled prior to tumor tissue being analyzed by the central laboratory, provided there is confirmation that the tumor tissue has been received by the central laboratory. Genes of interest will be sequenced using Foundation Medicine, Inc. (FMI) 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 genomic LOH will also be assessed for each tumor.[3,31,54,65]

An analysis of mature data from previous rucaparib clinical studies in ovarian cancer that enrolled platinum-sensitive patients, showed that patients with a tBRCA mutation responded to rucaparib treatment, and also suggested that a cut-off of 16% or greater for the $BRCA^{wt}/LOH^{high}$ subgroup provided the optimum discrimination of rucaparib treatment benefit.[16,32] In addition, the data also support that BRCA wild-type ($BRCA^{wt}$) patients with LOH, which is either unknown ($BRCA^{wt}/LOH^{unknown}$) or low ($BRCA^{wt}/LOH^{low}$), also benefit from treatment.[16,32]

Patients participating in Cohort A1 of this study will be gBRCA^{wt} (ie, patients with a deleterious germline mutation in BRCA1 or BRCA2, as determined by a local laboratory that has received an international or country-specific quality standards certification, are excluded). For ovarian cancer patients in Cohort A1, patients will be analyzed by molecularly-defined HRD subgroups prospectively (as defined in Section 9).

The complete results of the NGS-based test will be provided to the physicians of all patients who opt to receive this information and provide appropriate consent. Tumor tissue results for the BRCA1/2 genes will be provided upon availability to patients who consent to receive this information. Note that per eligibility criteria for Cohorts A1 and A2, enrolled patients will be required to have adequate tumor tissue available prior to enrollment. Patients may be enrolled prior to tumor tissue being analyzed by the central laboratory, provided there is confirmation that the tumor tissue has been received by the central laboratory. 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 tested to determine whether any mutation identified is of germline or somatic origin. These data may be provided to the investigator.

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

- The details of prior anticancer therapies;
- Details of primary surgery and biopsies taken prior enrollment (if applicable); and
- Confirmation that sufficient tumor tissue was submitted.

3.1.2 Treatment Phase

The first dose of oral study treatment will be administered on Day 1 of Cycle 1 and continue BID throughout the cycle as monotherapy. Oral study drug administration will begin 28 days (1 cycle) prior to IV study drug administration to explore the hypothesis that immune priming of the tumor microenvironment with monotherapy rucaparib will enhance the activity in combination with nivolumab. Within 5 days and prior to commencement of IV nivolumab treatment on Cycle 2 Day 1 (= Cycle 1 Day 28 [window: −5 days), collection of a primary or metastatic tumor sample is mandatory, unless tumor biopsy procedure is contraindicated (eg, unacceptable risk in the opinion of the investigator). The tumor sample will be analyzed by the central laboratory to assess molecular markers of efficacy or resistance, as well as the effect of rucaparib on the immune microenvironment. Administration of IV study drug will begin on Day 1 of Cycle 2. Details on study drug administration are described in Section 5.4.

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 treatment will continue in 28-day cycles until 24 months from the start of the oral/IV combination treatment (ie, 25 months), 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.

Tumor assessments by CT scan will be performed every 8 calendar weeks (±7 days) from the start of the oral/IV combination treatment on Cycle 2 Day 1, up to 18 months and then every 12 calendar weeks (±7 days) thereafter and at the End of Treatment Visit, if applicable, until confirmed objective radiological disease progression, as assessed by the investigator. Tumor assessments are to be performed prior to the next scheduled IV nivolumab treatment.

Patients experiencing confirmed disease progression by RECIST v1.1 will be discontinued from treatment and enter follow-up. If the patient has met criteria for confirmed radiologic progression by RECIST, but the patient is still receiving benefit from the study drug(s) according to the investigator (eg, patient has mixed radiologic response or is continuing to have symptomatic benefit), then continuation of treatment will be considered for a maximum cumulative duration of 24 months following initiation of combination 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 at their next routine study visit. Patients will continue to have all protocol-required assessments specified in the Schedule of Assessments (Table 6) and Pharmacokinetic and Immunogenicity Sample Collections (Table 7).

Safety and efficacy data will be periodically reviewed by the study Data Monitoring Committee (DMC) (Section 8.12).

3.1.3 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, hematology, clinical chemistry, and CA-125 measurement , 12-lead ECG, ctDNA analysis, concomitant medications, therapies and procedures, ECOG performance status, disease status assessment, and study drug accountability.

An optional tumor biopsy will be collected from patients who experience disease progression and provide appropriate consent. This sample should be collected prior to any subsequent therapy.

3.1.4 Post-treatment Follow-up Phase

All patients will be followed for at least 100 days (+7 days) after the last IV dose of study treatment. The 28-day Follow-up Visit (FU-28) should occur 28 days (±3 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, local laboratory hematology, clinical

chemistry, and CA-125 measurement, ECG, ctDNA analysis, concomitant medications, therapies and procedures, and study drug accountability. Follow-up Visit for IV study drug (FU-100) should occur at least 100 days (+7 days) from the last IV dose of study drug. The same assessments performed at FU-28 will be performed at FU-100; however, clinical chemistry and hematology are only necessary if toxicities are present. If a patient remains on oral study drug after discontinuation of IV study drug, FU-100 can be performed at the next cycle visit, provided it has been at least 100 days (+7 days) since the last IV dose.

Patients who discontinue treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals from Cycle 2 Day 1 (flexibility with scheduling within 1 week prior to planned imaging date is permitted) until objective radiological disease progression by RECIST v1.1 is documented, as assessed by the investigator.

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

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:

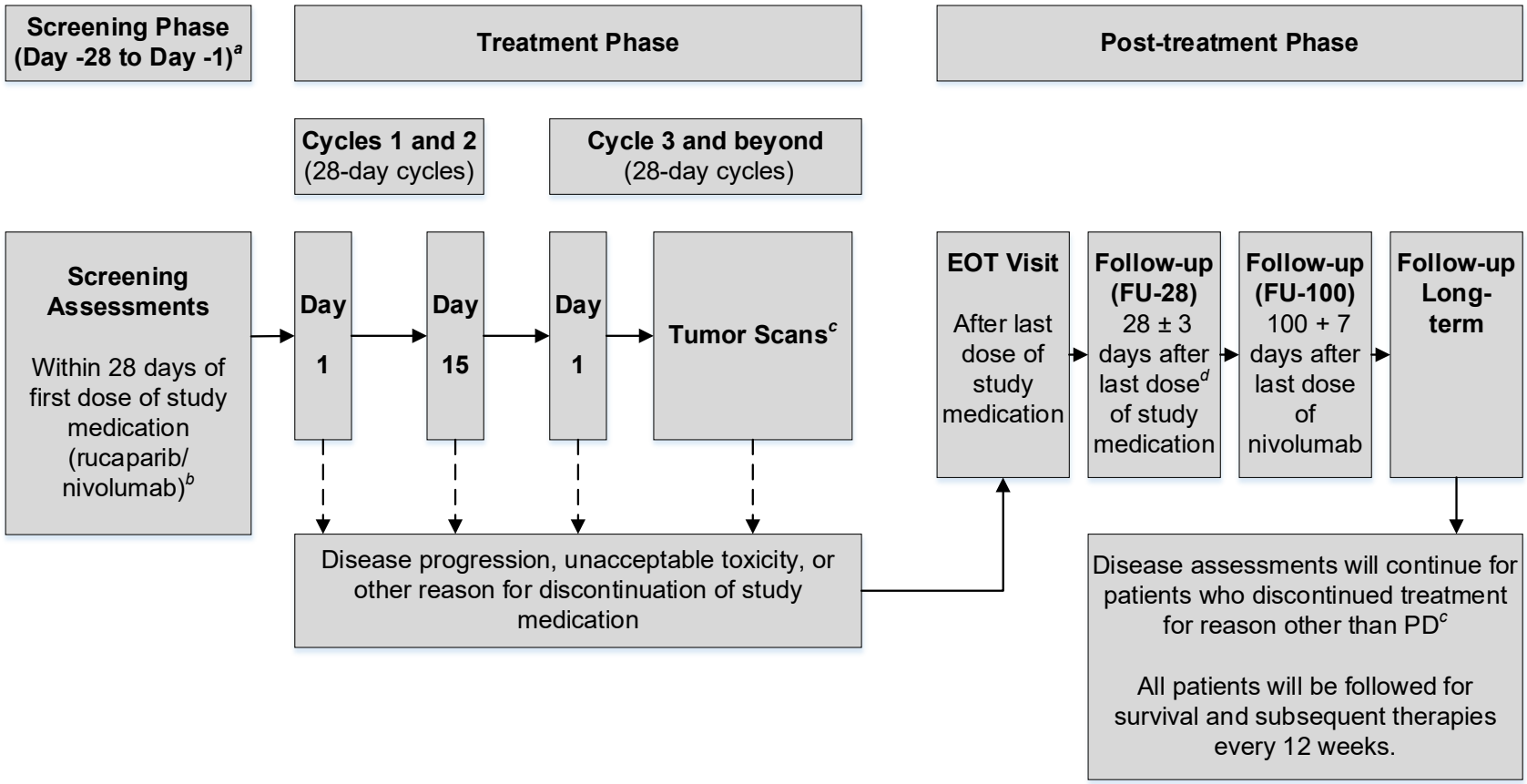
- Consent withdrawal at the patient's own request or at the request of their legally authorized representative.
- Progression of patient's underlying disease by RECIST v1.1 as assessed by the investigator, unless the patient is still receiving benefit from the study drug(s) according to the investigator, the investigator has consulted with the sponsor's medical officer or designee, and the patient has provided additional consent at the next study visit.
- 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.
- Noncompliance by the patient with protocol mandated procedures; and/or
- A positive pregnancy test at any time during the study.
- Study-specific treatment withdrawal rules for rucaparib and nivolumab (defined in Section 5.5.1.2).

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

3.3 Study Schema

The study schema is provided in Figure 2.

Figure 2. Study Schema



Abbreviations: EOT = End of Treatment; FU-100 = 100-day Follow-up Visit after last dose of IV study drug; FU-28 = 28-day Follow-up Visit after last dose of study drug (oral or IV, whichever is later); PD = progressive disease

[a] Mandatory tumor tissue collection for Cohorts A1 and A2 will be collected ≤ 42 days prior to the first dose of rucaparib (> 42d if no intervening therapy).

[b] For Cohort A1 and A2, within 28 days of first dose of oral rucaparib.

[c] Post-baseline tumor scans every 8 calendar weeks (±7 days) from the start of oral/IV combination treatment on Cycle 2 Day 1 for Cohorts A1 and A2, up to 18 months, then every 12 calendar weeks (±7 days) thereafter.

[d] Follow-up (FU-28) to occur 28 ±3 days after last dose of rucaparib and/or nivolumab, whichever occurs later.

3.4 End of Study

The study will close when all enrolled patients have discontinued treatment and completed the 100-day Follow-up Visit (Section 7.4.7.3), and the LTFU, as applicable (Section 7.4.8). If the study is closed for any other reason, individual patients who are continuing to benefit from treatment with study drugs at the time of study closure, and who do not meet any of the criteria for withdrawal, may have the option of entering an extension protocol in which they can continue to receive study drugs. The sponsor may discontinue the study early for any reason as noted in Section 10.6.

3.5 Discussion of Study Design

This is a multicenter, open-label, 2-stage, 2-cohort study to evaluate rucaparib in combination with nivolumab in patients with either high-grade serous or endometrioid ovarian cancer (Cohort A1 gBRCA^{wt}; Cohort A2 gBRCA^{mut}).

In Cohort A1, rucaparib 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 immune priming of the tumor microenvironment will enhance activity of the combination. This regimen will also be followed for the exploratory Cohort A2. Unless contraindicated, a tumor sample will be collected from patients in Cohorts A1 and A2 after initiation of rucaparib treatment, but before initiation of nivolumab treatment, and analyzed by the central laboratory to assess molecular markers of efficacy or resistance, as well as the effect of rucaparib on the immune microenvironment (Section 7.5.6.1).

4 STUDY POPULATION SELECTION

4.1 Number of Patients and Sites

A total of 28 to 53 patients are planned for enrollment at approximately 15 study sites in the US: 18 to 43 patients are planned for Cohort A1 (ovarian, $gBRCA^{wt}$), 10 patients are planned for Cohort A2 (ovarian, $gBRCA^{mut}$).

4.2 Inclusion Criteria

Eligible patients must meet the following applicable 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. ≥ 18 years of age at the time the ICF is signed
3. Have adequate organ function confirmed by the following laboratory values obtained at screening (within 14 days prior to the first dose of study drug):
   a. Bone Marrow Function
      - ANC ≥ 1.5×10^9/L
      - Platelets ≥ 100×10^9/L
      - Hemoglobin ≥ 9 g/dL
   b. Hepatic Function
      - AST and ALT ≤ 1.5 × upper limit of normal (ULN)
      - Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome
      - Serum albumin ≥ 30 g/L (3.0 g/dL)
   c. Renal Function
      - Serum creatinine ≤ 1.5 × ULN unless estimated glomerular filtration rate (GFR) ≥ 30 mL/min using the Cockcroft Gault formula
4. Have life expectancy ≥ 16 weeks, in the opinion of the investigator.
5. Women of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to administration of the first dose of study drug
6. Have a histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer. If mixed histology, > 50% of the primary tumor must be confirmed to be high-grade serous or endometrioid upon re-review by local pathology
7. Have measurable disease as defined by RECIST v1.1 (Cohort A1 only)
8. A mandatory biopsy or resection of tumor tissue must be collected ≤ 42 days prior to first dose of rucaparib. Alternatively, tumor tissue collected > 42 days prior to the first dose of

rucaparib may be submitted, provided there have been no intervening anticancer treatments during this period and the tissue is of adequate quality. See Section 7.5.6.1. Patients may be enrolled prior to tumor tissue being analyzed by the central laboratory, provided there is confirmation that the tumor tissue has been received by the central laboratory.

9. (Cohort A1) Have gBRCA^{wt} ovarian cancer (ie, patients with a deleterious germline mutation in BRCA1 or BRCA2, as determined by a local laboratory that has received an international or country-specific quality standards certification, are excluded).
   OR

   (Cohort A2) Have gBRCA^{mut} ovarian cancer (ie, deleterious germline BRCA1/2 mutation, as determined by a local laboratory that has received an international or country specific quality standards certification).
10. Be willing to have a mandatory biopsy of tumor tissue collected at Cycle 1 Day 28 of treatment.
11. Have relapsed/progressive disease as confirmed by radiologic assessment
12. Received 1 or 2 prior regimens, including ≥ 1 prior platinum based therapy and have platinum-sensitive disease:
    a. Received ≥ 1 prior platinum-based treatment regimen; AND
    b. Received a platinum-based regimen as their last treatment; continuous or switch maintenance treatment as part of this regimen is permitted (hormonal treatment may be permitted following the last platinum); AND
    c. Was sensitive to the last platinum regimen. Platinum-sensitive disease is defined as documented radiologic progression > 6 months after the last dose of platinum administered in the treatment setting.
13. Have an ECOG performance status of 0 to 1 ≤ 14 days prior to first dose of rucaparib.

4.3 Exclusion Criteria

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

1. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment.
   - 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 or non-melanoma skin cancers, are allowed to enroll.
2. Known central nervous system brain metastases.
3. Has evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis.

4. 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.
5. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
6. 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.
7. Known history of positive test for HIV or AIDS. **Note:** Testing for HIV must be performed at all sites where mandated locally.

8. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, hepatitis B surface antigen (HBsAg, Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
9. For female patients of childbearing potential, the following are exclusion criteria, as applicable:
    a. Refusal to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib study treatment.
    b. Pregnant or breast feeding.
    c. Women of childbearing potential must not be considering getting pregnant during the study and for 6 months following the last dose of rucaparib.
10. 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.
11. 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.
12. Hospitalization for bowel obstruction within 12 weeks prior to enrollment.
13. Prior treatment with a PARP inhibitor (PARPi) or immune checkpoint inhibitor. (Exception: patient is eligible if they received a prior PARPi as front-line maintenance therapy and patient did not have disease progression whilst on the PARPi, providing inclusion criterion 11 is also met at time of screening).
14. Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > NCI CTCAE v5.0 Grade 1, with the exception of Grade 2 non-hematologic

toxicity such as alopecia, peripheral neuropathy, and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug.

15. Non-epithelial tumors (pure sarcomas) or ovarian tumors with low malignant potential (ie, borderline tumors) or mucinous tumors. Mixed Mullerian tumors/carcinosarcomas are allowed.

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

4.4 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion. Women of childbearing potential must not be considering getting pregnant and must avoid pregnancy during the study and for at least 6 months after the last dose of study drug (oral or IV, whichever is later), or longer if requested by local authorities.

Female patients of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to administration of the first dose of rucaparib. In addition, a serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Treatment Phase and at the time of treatment discontinuation. Pregnancy testing will be conducted locally. Treatment should be discontinued immediately in any woman found to have a positive pregnancy test while taking rucaparib and/or nivolumab.

Female patients are considered to be of childbearing potential unless 1 of the following applies:

- Considered to be permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy; or
- Is postmenopausal, defined as no menses for at least 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.

Female patients of reproductive potential must practice highly effective methods (failure rate < 1% per year) of contraception with their partners, if of reproductive potential, during treatment and for 6 months following the last dose of rucaparib and/or nivolumab, or longer if requested by local authorities. Highly effective contraception includes:

- Ongoing use of progesterone only injectable or implantable contraceptives;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Bilateral tubal occlusion;
- Sexual abstinence as defined as complete or true abstinence, acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable; or

- Male sterilization, with appropriate post vasectomy documentation of absence of sperm in ejaculate.

Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with study drug.

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

Patients will receive open-label oral rucaparib + IV nivolumab combination treatment.

5.1.1 Investigational Drug Product – Rucaparib

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 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).

5.1.2 Investigational Drug Product – Nivolumab

Nivolumab, also referred to as BMS-936558-01 or 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 in Table 3 with details in the Pharmacy Manual.

Table 3. Description of Nivolumab for Injection

BMS Number:	BMS-936558-01
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:	As directed on the product label

5.2 Packaging and Labeling

5.2.1 Rucaparib Tablets

Rucaparib tablets are provided in 60-count high-density polyethylene (HDPE) bottles with child resistant caps and should be stored in the provided containers and as directed on the product label. Patients will be dispensed one or more strengths depending on their current dose of

rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28-days treatment per cycle, including a small overage.

Details with respect to packaging and labeling of rucaparib tablets are described in the pharmacy manual.

5.2.2 Nivolumab

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

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%).

Details with respect to packaging and labeling of nivolumab for injection are described in the pharmacy manual.

5.3 Method of Assigning Patients to Treatment Groups

All patients enrolled in the study will receive oral rucaparib at an initial dose of 600 mg BID continuously commencing C1D1, and IV nivolumab at an initial dose of 480 mg Q4W commencing C2D1.

5.4 Preparation and Administration of Protocol-specified Treatment

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

Rucaparib and nivolumab will be assigned by an interactive response technology (IRT) system.

5.4.1 Rucaparib

Rucaparib 600 mg is administered orally BID (as close as possible to 12 hours apart, preferably at the same times every day) with 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 mg, 250 mg, 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 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.

5.4.2 Nivolumab

Nivolumab is administered as 480 mg via a 30-minute IV infusion on Day 1 of every 28-day cycle, starting on **Cycle 2 Day 1**. 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.

5.5 Dose Modification Criteria

Doses of oral study drug (rucaparib), and/or IV study drug (nivolumab), 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 (see Section 5.5.1). The assessment for delay or discontinuation should be made separately for the oral study drug (rucaparib) and the IV study drug (nivolumab); 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. 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.

Dose modification and re-treatment of oral and/or IV study drug are to be based on the criteria presented in Table 4.

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment
Non-hematological Non-skin AEs					
Adverse event, except fatigue	2	None	N/A	Hold	Grade ≤ 1 or baseline[3]
Any adverse event (related events lasting > 7 days for nivolumab, exceptions below)	3 or 4	Hold	≤ Grade 2[4]	Discontinue	
Exceptions with rucaparib					
Alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines	3 or 4	None			
ALT/AST provided no signs of liver dysfunction (see laboratory section below)	3	None			
Exceptions with nivolumab					
Uveitis, pneumonitis, bronchospasm, neurological toxicity, myocarditis, hypersensitivity reason or infusion reaction of any duration	3			Discontinue	
Endocrinopathies, adequately controlled with only physiologic hormone replacement	3			Hold	Grade ≤ 1 or baseline[3]
Drug-related adrenal insufficiency or hypophysitis	2			Hold	Grade ≤ 1 or baseline[3]
Adrenal insufficiency regardless of control with hormone replacement	3			Discontinue	
Laboratory abnormalities except as specified below	3			Hold	Grade ≤ 1 or baseline[3]
Drug-related ALT, AST, or bilirubin	3			Discontinue[5]	
Adverse event or laboratory abnormality except for those below that do not require delay	4			Discontinue	
Asymptomatic amylase or lipase	4			Hold	Grade ≤ 1 or baseline[3]

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment
Isolated electrolyte imbalances/abnormalities not associated with clinical sequelae/corrected w/supplementation /appropriate management w/in 72 hours of onset	4			Hold	Grade ≤ 1 or baseline[3]
Endocrinopathy AEs[6]	3			Hold	Grade ≤ 1 or baseline[3]
Non-hematological Toxicity (Skin)					
Adverse event	3	Hold	Grade 2[4]	Hold	
Hematological Toxicity					
Hematological toxicity (related events lasting >7 days for nivolumab, exceptions below)	3-4	Hold[7]	Grade 2[4]	Discontinue	
Confirmed MDS or AML (all new secondary malignancies are Grade 4 per CTCAE 5.0)	4	Discontinue		Discontinue	
Exceptions with nivolumab					
Laboratory abnormalities except as specified below	3			Hold	Grade ≤ 1 or baseline[3]
Thrombocytopenia > 7 days or associated with bleeding	3			Discontinue	
Laboratory abnormality except for those below that do not require delay	4			Discontinue	
Neutropenia ≤ 7 days	4			Hold	Grade ≤ 1 or baseline[3]
Lymphopenia or leukopenia	4			Hold	Grade ≤ 1 or baseline[3]
Laboratory Abnormalities					
Laboratory abnormality	3	Hold	Grade 2[4]	Hold	
ALT, AST, and/or bilirubin abnormalities	2	None	N/A	Hold[8]	Grade ≤ 1 or baseline[3]
ALT/AST elevations	3	None, provided no	N/A	Discontinue[7]	

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment
		signs of liver dysfunction[9]			
ALT/AST elevations	4	Hold	≤Grade 2 Reduce dose[10]	Discontinue	
ALT or AST > 3 × ULN AND bilirubin > 2 × ULN (suspected DILI)		Hold[9] Follow guidelines in Section 8.10		Discontinue	
Creatinine elevations	2 (≥ 1.5 x baseline[11])	None	N/A	Hold	Grade ≤ 1 or baseline[3]
Creatinine elevations	3	Hold	Grade 2[4]	Hold	Grade ≤ 1 or baseline[3]
Exception with nivolumab					
Grade 3 lymphopenia or asymptomatic amylase or lipase	3			None	
Dosing-related					
Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the exception of dosing delays to allow for prolonged steroid tapers to manage AEs. • Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the study medical monitor/designee				Discontinue	
Toxicity despite dose reduction steps to 200 mg BID or interruption of oral drug for > 14 consecutive days except if allowed if approved by the study medical monitor/designee.		Discontinue			

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment
• Prior to re-initiating treatment in a patient with a dosing delay > 14 days, the study medical monitor/designee must be consulted.					

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; BID -= twice daily; CTCAE = Common Terminology Criteria for Adverse Events; DILI = drug-induced liver injury; IV = intravenous; MDS = myelodysplastic syndrome; N/A = not applicable; ULN = upper limit of normal

[1]Oral drug may be discontinued for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued oral study treatment dosing. 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.

[2]In addition to the criteria below, nivolumab should be held if there is any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication or discontinued if there is any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial risk to the patient with continued IV study drug dosing. Patients 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.

[3]Patients 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 which are allowed: Grade 2 fatigue, Grade 2 skin toxicity (if no Grade 3 drug related skin AE). For patients with Grade 2 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. Patients 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. Patients with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the study medical monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

[4]The patient may continue at same or reduced dose at the discretion of the investigator. 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; however, the investigator should consult with the sponsor's medical monitor before reducing to 300 mg BID.

[5]In most cases of Grade 3 ALT or AST elevation, IV study drug will be permanently discontinued. For patients with Grade 3 ALT or AST 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 ALT/AST 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

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment

Adverse Event Management Algorithm for a Grade 3 event will be followed (see Appendix 6). Treatment with IV drug may be resumed if levels return to Grade 2. If total bilirubin elevations > 2 × ULN accompany any of the ALT/AST elevations, IV drug should be discontinued.

[6]Such as, hyper- or hypothyroidism, or glucose intolerance, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the study medical monitor/designee. Grade 4 drug-related adrenal insufficiency or hypophysitis requires discontinuation regardless of control with hormone replacement.

[7]If any blood parameters remain clinically abnormal > 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.

[8]For patients with Grade 2 ALT or AST elevations with onset after dosing of oral study drug, IV study treatment hold is not required if ALT/AST elevations begin to resolve before the next scheduled infusion and toxicity is considered to be mainly related to oral study treatment. If a subsequent ALT/AST 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 6). In this case, IV study drug should be discontinued if Grade 2 elevations return post re-challenge. If total bilirubin elevations > 2 × ULN accompany any of the ALT/AST elevations, IV drug should be discontinued.

[9]Bilirubin must be within normal limits and alkaline phosphatase must be < 3 x ULN. Monitor liver function tests weekly. If the 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.

[10]Monitor liver function tests weekly for 3 weeks after oral study drug has been restarted.

[11]Grade 2 for nivolumab is described as ≥ 1.5 x baseline and baseline is the day the combination treatment starts (ie, Cycle 2 Day 1 in Cohort A1 and A2).

5.5.1 Dose Reduction

5.5.1.1 Rucaparib

The dose reduction steps for oral study drug are presented in Table 5.

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 5. 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

[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.

5.5.1.2 Nivolumab

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

5.6 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

The above algorithms are found in Appendix 6 of this protocol.

5.7 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.[66]

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 patient 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 patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor patient 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 patient closely. If symptoms recur, then no further study treatment will be administered at that visit.
- For future infusions, the following prophylactic pre-medications 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 patient 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. Patient 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 patient 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).

5.8 Treatment Compliance

5.8.1 Rucaparib 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.

5.8.2 Nivolumab Treatment Compliance

Each dose of IV study drug will be prepared by a pharmacist or authorized designee and transferred to an infusion set, in accordance with the protocol and applicable local safe handling procedures. The IV infusion will be monitored by the investigator or designee. 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.

5.9 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 system 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 and returned 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.

5.10 Treatment of Study Drug beyond Disease Progression

Patients will receive study drug until confirmed radiologic disease progression as assessed by investigator using RECIST v1.1 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 v1.1 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 sponsor's medical officer or designee should be informed. The patient must provide additional consent at their next scheduled study visit to continue 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 treatment will be considered for a maximum cumulative duration of 24 months after initiation of oral/IV combination study treatment, or until confirmation of further progression as assessed by the investigator, whichever is sooner.

6 PRIOR AND CONCOMITANT THERAPY

Drug-drug interactions between nivolumab and rucaparib are unlikely (see Section 1.1.3.2).

Cohorts A1 and A2 Ovarian:

Patients who have received prior treatment with a PARP inhibitor (PARPi), including IV or oral rucaparib or an immune checkpoint inhibitor for any previous malignancy are not eligible to participate in this study. Exception: patients who received a prior PARPi as front-line maintenance therapy and did not have disease progression on the PARPi, are eligible to participate in the study, providing inclusion criterion 11 is met at the time of screening.

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.

Any botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study, or provide supportive care are prohibited (except those prescribed as supportive care by a health care professional as per Section 6.1).

6.4 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo CYP interaction study (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 substrates of CYP1A2, CYP2C9, CYP2C19, and/or CYP3A with narrow therapeutic windows (Appendix 4). Selection of an alternative concomitant medication is recommended.

Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers (Appendix 5).

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 international normalized ratio (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. Patients 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.

Patients 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. Any botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study, or provide supportive care are prohibited (except those prescribed as supportive care by a health care professional). Any botanical preparations 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.

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 decrease metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of the BCRP

with IC_{50} value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (eg, rosuvastatin).

Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers.

6.8 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on patient attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each patient. 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. Patients 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, patients 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 patient population. In addition, patients are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual patient 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 6 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 7 summarize the timing of collection of PK and immunogenicity samples.

Table 8 and Table 9 summarize the timing of peripheral blood biomarker sample collection.

Applicable imaging guidelines should be followed for the collection of images and the radiological assessment of disease.

Tumor tissues (screening and optional sample at the time of disease progression), PK samples, and ctDNA, biomarker samples will need to be sent to central laboratories for processing. Clinical chemistry, hematology, urinalysis, pregnancy testing, serology testing, CA-125, and ECG will be conducted at a local laboratory. Please refer to study laboratory manuals for detailed collection, processing, and shipment requirement.

Table 6. Study CO-338-097 Schedule of Assessments

	Screening Phase	Treatment Phase[a] (±3 days of scheduled timepoint)						Post-treatment Phase			
		Cycle 1			Cycle 2		Cycle 3+				
Procedure	**D-28 to D-1[b]**	**D1[c,d]**	**D15[e]**	**D28**	**D1[d]**	**D15[d]**	**D1[d]**	**EOT**	**FU-28 28 ±3 d after last oral/IV dose**	**FU-100 100 +7 d after last IV dose**	**LTFU**
Informed Consent[e]	X										
Medical/Oncology History[f]	X										
Physical Examination[g], Height[g], Weight	X	X	X		X	X	X	X	X	X	
ECOG Performance Status	X[h]	X			X		X	X	X	X	
Vital Signs	X	X[i]	X[i]		X[i]	X[i]	X[i]	X	X	X	
Adverse Events[j]	X	X	X		X	X	X	X	X[i]	X[j]	X[j]
Prior/Concomitant Medications and Procedures	X	X	X		X	X	X	X	X	X	
12-lead ECG[k] (local lab)	X							X			
Hematology[l] (local lab)	X[h]	X	X		X	X	X	X	X	X[m]	
Clinical Chemistry[n] (local lab)	X[h]	X	X		X	X	X	X	X	X[m]	
Serum Pregnancy Test[o] (local lab)	X[h]	X			X		X	X			
Urinalysis[p] (local lab)	X[h]	X	X		X	X	X	X	X	X	

Table 6. Study CO-338-097 Schedule of Assessments

	Screening Phase	Treatment Phase[a] (±3 days of scheduled timepoint)						Post-treatment Phase			
		Cycle 1			Cycle 2		Cycle 3+				
Procedure	**D-28 to D-1[b]**	**D1[c,d]**	**D15[e]**	**D28**	**D1[d]**	**D15[d]**	**D1[d]**	**EOT**	**FU-28 28 ±3 d after last oral/IV dose**	**FU-100 100 +7 d after last IV dose**	**LTFU**
Disease Assessment/Tumor Scans[q,r]	X						X[r] (Start on C4D1)	(X)[s]	X[t]	X[t]	X[t]
Mandatory Tumor Tissue Biopsy/Resection/Sample	X[u]			X[v]				(X)[w]			
Peripheral Blood Samples for Biomarker Analyses[x] (central lab)	X	X			X		X	X	X	X	
Rucaparib Dispensation/ Administration		X			X		X				
Nivolumab IV Administration[y]					X		X				
Plasma PK Sample[z] (central lab)		X[aa]			X[aa]		X[aa]		X[aa]	X[aa]	
Survival and Subsequent Treatments											X[ab]
CA-125 Measurement (local lab)	X	X			X		X	X	X	X	X

Abbreviations: AE(s) = adverse event(s); AESI(s) = adverse event(s)of special interest; ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CLcr= creatinine clearance; CO_2 = carbon dioxide; CR = complete response, CT = computed tomography, ctDNA = circulating cell-free tumor DNA; D = day of cycle; ECG(s) = electrocardiogram(s), ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment Visit; FFPE = formalin-fixed, paraffin-embedded; FU-100 = 100-day Follow-up Visit after last dose of IV study drug; FU-28 = 28-day Follow-up Visit after last dose of study drug (oral or IV, whichever is later); fT3 = free triiodothyronine; fT4 = free thyroxine; FU = follow-up; HCO_3^- =

Table 6. Study CO-338-097 Schedule of Assessments

	Screening Phase	Treatment Phase[a] (±3 days of scheduled timepoint)						Post-treatment Phase			
		Cycle 1			Cycle 2		Cycle 3+				
Procedure	**D-28 to D-1[b]**	**D1[c,d]**	**D15[e]**	**D28**	**D1[d]**	**D15[d]**	**D1[d]**	**EOT**	**FU-28 28 ±3 d after last oral/IV dose**	**FU-100 100 +7 d after last IV dose**	**LTFU**

bicarbonate; HIV = human immunodeficiency virus; ICF = Informed Consent Form; LDH = lactate dehydrogenase, LTFU = long-term follow-up; MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetic, PR = partial response or PR interval, QRS = QRS complex/interval; QT = QT interval; QTcF = corrected QT interval Fridericia's formula; RBC = red blood cell, RECIST = Response Evaluation Criteria in Solid Tumors; SAE(s) = serious adverse event(s); T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cell.

[a] = Treatment cycles are 28 days. Unless otherwise specified, all assessments are to be completed within ±3 days of scheduled time point.

[b] = Exceptions to this screening window include the mandatory tumor tissue collection for Cohorts A1 and A2 as described under footnote 'u'.

[c] = Any procedures required on Cycle 1 Day 1 may be omitted if completed ≤ 3 days prior to first dose of study drug.

[d] = Patients are to refrain from taking their first dose of rucaparib at home on these days. Procedures are to be completed before any study drug is administered.

[e] = Consent may be completed outside the 28-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.

[f] = Patient's medical record must include prior treatments received, dates of administration, date of progression, and radiology report(s) to support assessment of disease progression. gBRCA test results, if known, will also be captured.

[g] = A complete physical exam should be performed at Screening and End of Treatment Visits; a limited physical exam may be performed at all other visits. Height at screening only.

[h] = To be performed ≤ 14 days prior to the first dose of rucaparib. Serum pregnancy test to be performed ≤ 3 days prior to the first dose of rucaparib, if applicable.

[i] = Vital signs (blood pressure, pulse, and temperature) to be taken on clinic visit days, after the patient has been resting for at least 5 minutes.

[j] = AEs (inclusive of SAEs and AESIs) occurring after first dose of rucaparib through 28 days after last dose of rucaparib will be recorded. In addition, SAEs occurring after signing of the ICF and that were related to a screening procedure will also be reported. Ongoing SAEs, AESIs, and treatment-related Grade 3/4 AEs will be followed to resolution or stabilization, death, or until lost to follow-up. Only related SAEs and AESIs (regardless of causality) will be reported after the 28-day Follow-up Visit.

Table 6. Study CO-338-097 Schedule of Assessments

	Screening Phase	Treatment Phase[a] (±3 days of scheduled timepoint)						Post-treatment Phase			
		Cycle 1			Cycle 2		Cycle 3+				
Procedure	**D-28 to D-1[b]**	**D1[c,d]**	**D15[e]**	**D28**	**D1[d]**	**D15[d]**	**D1[d]**	**EOT**	**FU-28 28 ±3 d after last oral/IV dose**	**FU-100 100 +7 d after last IV dose**	**LTFU**

[k] = Heart rate, PR, QRS, QT, QTcF and rhythm. Investigator to review results and assess as normal or abnormal (clinically significant or not clinically significant). ECGs to be repeated as clinically indicated.

[l] = Includes RBC count and parameters (hemoglobin, hematocrit, MCV, MCH, MCHC), reticulocyte count, WBC count, and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory and results must be reviewed by the investigator prior to dosing with rucaparib. Additional and more frequent tests may be performed at the investigator's discretion.

[m] = Only required if toxicities are present.

[n] = Includes total protein, albumin, measured or calculated CLcr (for CLcr calculation, the Cockcroft Gault formula or institutional standard formula can be used), BUN or urea, total bilirubin, ALP, ALT, AST, LDH, glucose, sodium, potassium, magnesium, chloride, CO_2/HCO_3^-, calcium, phosphorus, TSH, fT3, fT4, TSH, with reflexive fT3 and fT4 if TSH is abnormal on treatment, and total cholesterol. Total cholesterol testing does not require fasting. If pancreatitis is suspected clinically, serum lipase and amylase should be analyzed. Blood will be analyzed by a local laboratory and results must be reviewed by the investigator prior to dosing with rucaparib. 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. Additional and more frequent tests may be performed at the investigator's discretion.

[o] = Women of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to the first dose of rucaparib. A serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle from Cycle 2 and beyond during the Treatment Phase. A serum pregnancy test must be performed at the End of Treatment Visit.

[p] = Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings abnormal, perform microscopic evaluation. To be conducted at screening only, but may be conducted at other times as clinically indicated.

[q] = Disease assessment to include clinical examination and appropriate imaging techniques, including CT scans of the chest, abdomen, and pelvis, with appropriate slice thickness per RECIST; other assessments (MRI, 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. If a patient has known brain metastases, this disease should be evaluated at each required assessment. Copies of CT scans will be collected from all patients. Independent radiology review may be conducted on all or a subset of CT scans.

[r] = Tumor scans to be performed at the end of every 8 calendar weeks (±7 days) during the Treatment Phase, from the start of the oral/IV combination treatment on Cycle 2 Day 1.A confirmatory scan should be performed ≥ 4 weeks after an initial response of PR or CR is observed. Patients who have been on study at

Table 6. Study CO-338-097 Schedule of Assessments

	Screening Phase	Treatment Phase[a] (±3 days of scheduled timepoint)						Post-treatment Phase			
		Cycle 1			Cycle 2		Cycle 3+				
Procedure	**D-28 to D-1[b]**	**D1[c,d]**	**D15[e]**	**D28**	**D1[d]**	**D15[d]**	**D1[d]**	**EOT**	**FU-28 28 ±3 d after last oral/IV dose**	**FU-100 100 +7 d after last IV dose**	**LTFU**

least 18 months, may decrease the frequency of disease assessments to every 12 calendar weeks (±7 days). Tumor assessments should continue as per protocol even if dosing is delayed.

[s] = Disease assessments should also be done at the time of treatment discontinuation if it has been ≥ 8 weeks since the last assessment.

[t] = If treatment was discontinued for reasons other than radiologic disease progression or death, radiologic tumor assessment (using the same methodology as was used at initial study screening) will continue until confirmed radiographic disease progression, death, or initiation of subsequent treatment. Assessment at 12-week (±7days) intervals from Cycle 4 Day 1 for the first 18 months after initiation of study treatment, and every 24 weeks (±14 days) thereafter, until objective radiological disease progression by RECIST v1.1, as assessed by the investigator, is documented.

[u] = A mandatory biopsy or resection of tumor tissue must be collected ≤ 42 days prior to first dose of rucaparib. Alternatively, tumor tissue collected > 42 days prior to the first dose of rucaparib may be submitted, provided there have been no intervening anticancer treatments during this period and the tissue is of adequate quality. Tumor tissue samples should be from primary or metastatic tissue. Patients may be enrolled prior to tumor tissue being analyzed by the central laboratory, provided there is confirmation that the tumor tissue has been received by the central laboratory

Tumor tissue must be obtained from a soft tissue tumor lesion; ascites is not acceptable. Refer to the Laboratory Manual for detailed sample handling instructions.

[v] = An additional mandatory biopsy will be collected at Cycle 1 Day 28 (−5 days), unless tumor biopsy procedure is contraindicated (eg, unacceptable risk in the opinion of the investigator). This additional biopsy will be collected prior to commencement of nivolumab on Cycle 2 Day 1 (= Cycle 1 Day 28 [window:-5 days]). Tumor tissue must be obtained from a soft tissue tumor lesion; ascites is not acceptable. Refer to the Laboratory Manual for detailed sample handling instructions.

[w] = An optional post-treatment tumor biopsy sample may be collected from patients who progress on study treatment. If the progression is due to new lesions, the preference is to obtain the biopsy from the new lesion(s). Additional consent is required. Refer to the Laboratory Manual for detailed sample handling instructions.

[x] = Refer to Table 8 and Table 9, and the Laboratory Manual for detailed sample collection and processing instructions. Cycle 1 ctDNA must be collected even if within 3 days of screening ctDNA.

[y] = Nivolumab administration will commence on Cycle 2 Day 1.

Table 6. Study CO-338-097 Schedule of Assessments

	Screening Phase	Treatment Phase[a] (±3 days of scheduled timepoint)						Post-treatment Phase			
		Cycle 1			Cycle 2		Cycle 3+				
Procedure	**D-28 to D-1[b]**	**D1[c,d]**	**D15[e]**	**D28**	**D1[d]**	**D15[d]**	**D1[d]**	**EOT**	**FU-28 28 ±3 d after last oral/IV dose**	**FU-100 100 +7 d after last IV dose**	**LTFU**

[z] = A single sample should be collected as close as possible to 12 hours after the last dose has been taken and prior to the next dose. Refer to the Laboratory Manual for sample collection and processing instructions.

[aa] = Refer to PK sampling Table 7.

[ab] = All patients discontinued from treatment, regardless of reason, should be followed for survival and subsequent therapies every 12 weeks (±14 days) until death, loss to follow-up, withdrawal of consent from study, or study closure, whichever happens first. Follow-up can be performed via the telephone.

Table 7. 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, FU-28 and FU-100 (28 days and 100 days, respectively, from the treatment discontinuation during the Treatment Phase or at 24 months)	NA	NA	X	X	

Abbreviations: EOI = end of infusion; FU-100 = 100-day Follow-up Visit after last dose of IV study drug; FU-28 = 28-day Follow-up Visit after last dose of study drug (oral or IV, whichever is later); NA = not applicable; PK = pharmacokinetic.

[a] = If a patient discontinues study drug treatment during the sampling period (ie, prior to 24 months), all subsequent CXD1 samples will be inapplicable, but samples will be collected on FU-28 and FU-100 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.

Table 8. Peripheral Blood Biomarker Sample Collection

Study Day (Cycle, Day) (1 Cycle = 28 days)	Time	Genomic DNA from blood	Immunophenotyping (PBMC)	Neo-epitope DNAseq	Serum cytokine/ chemokine profiling
C1D1	Predose	X	X	X	X
C2D1	Predose		X	X	X
C5D1	Predose		X	X	X
C7D1	Predose			X	X
C9D1	Predose			X	X
Upon Disease Progression	N/A		X	X	X

Abbreviations: DNAseq = deoxyribonucleic acid sequencing; N/A = not applicable; PBMC = peripheral blood mononuclear cells.

Table 9. Blood Sample Collection for ctDNA

Blood for ctDNA Plasma	Screening	Predose				Upon Disease Progression	Safety Follow-up Visits, FU-28 and FU-100[b]
		C1D1	C2D1	C3D1	CXD1[a]		
Cohort A	X	X	X	X	X (starting with C4)	X	X

Abbreviations: ctDNA = circulating tumor DNA; FU-100 = 100-day Follow-up Visit after last dose of IV study drug; FU-28 = 28-day Follow-up Visit after last dose of study drug (oral or IV, whichever is later).

[a] = After cycle 3, collect blood for ctDNA at every other cycle from the start of the oral/IV combination treatment on Cycle 2 Day 1 for Cohorts A1/A2.

[b] = FU-28 and FU-100, 28 days and 100 days, respectively, from the treatment discontinuation during the Treatment Phase or at 24 months

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/IEC-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 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/ 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 enrollment 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 28-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 Up to 42 Days Prior to Start of Treatment

A mandatory biopsy or resection of tumor tissue must be collected ≤ 42 days prior to first dose of rucaparib. Alternatively, tumor tissue collected > 42 days prior to the first dose of rucaparib may be submitted, provided there have been no intervening anticancer treatments during this period and the tissue is of adequate quality. Tumor tissue samples should be from primary or metastatic tissue. Patients may be enrolled prior to tumor tissue being analyzed by the central laboratory, provided there is confirmation that tumor tissue is available to be sent to the central laboratory.

Tumor tissue must be obtained from a soft tissue tumor lesion; ascites is not acceptable. Refer to the Laboratory Manual for detailed sample handling instructions. See Section 7.5.6.1 for central laboratory analysis.

7.3.2 Up to 28 Days Prior to Start of Treatment

- Medical/oncology history, including demographic information
- Physical examination by body system, including height and weight
- Vital signs (blood pressure, pulse, and body temperature)
- SAE monitoring (only report if related to screening procedure)
- Prior and concomitant medications, any surgical/medical procedures
- 12-lead ECG (Local)
- Tumor assessment: assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1). Other assessments (MRI, 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.
- If a patient has known brain metastases, this disease should be evaluated at each required assessment time
- Collect ctDNA blood sample (Central)

7.3.3 Up to 14 Days Prior to Start of Treatment

- ECOG performance status (Appendix 3)
- SAE monitoring (only report if related to screening procedure)
- Hematology (Local)
- Clinical chemistry (Local). Note: fasting is not required
- Urinalysis (Local) (performed on freshly voided clean sample)
- Serum pregnancy test for women of childbearing potential (must be completed ≤ 3 days prior to the first dose of rucaparib)
- CA-125 Measurement (Local)

7.4 Treatment Phase

7.4.1 Cycle 1 Day 1

The following procedures will be completed before the first dose of rucaparib is administered, unless if completed ≤ 3 days prior to the first dose of rucaparib in which case they may be omitted, IV nivolumab will be administered after the first dose of rucaparib:

- Physical examination
- Weight
- ECOG performance status (Appendix 3)
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Hematology (Local)
- Clinical chemistry (Local) (fasting is not required)
- Serum pregnancy test for women of childbearing potential (Local)
- Urinalysis (Local)
- Collect ctDNA blood sample (this sample **must** be collected even if a sample was collected within 3 days prior to the first dose of rucaparib)
- CA-125 Measurement (Local)
- Blood sample for genomic analysis (Central) (If sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter)
- Blood sample for immunophenotyping (peripheral blood mononuclear cells [PBMC])
- Blood sample for neo-epitope DNA sequencing (DNAseq)
- Blood sample for cytokine/chemokine profiling
- AE monitoring
- Dispensation of rucaparib

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until the next rucaparib dispensation visit, with a small overage. Patients will ingest rucaparib twice daily at about the same times every day as close as possible to 12 hours apart. Rucaparib should be taken with water and with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. Nivolumab IV will be administered as described in the Pharmacy Manual. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Table 4.

Site personnel will account for all rucaparib that is administered or dispensed to the patient during the study visit and document appropriately.

7.4.2 Cycle 1 Day 15

Patients will be instructed to refrain from taking their first dose of rucaparib at home on the day of their visit. The following procedures will be completed prior to rucaparib dosing and ±3 days of this visit. IV nivolumab will be administered after rucaparib.

- Physical examination
- Weight
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Hematology (Local)
- Clinical chemistry (Local) (fasting is not required)
- Urinalysis (Local)
- AE monitoring

7.4.3 Cycle 1 Day 28

A mandatory tumor tissue biopsy will occur on C1D28 (window: −5 days) prior to commencement of IV study medication (See Section 7.5.6.1).

7.4.4 Cycle 2 Day 1

Patients will be instructed to refrain from taking their first dose of rucaparib at home on the day of their visit to collect plasma samples for PK and the ctDNA blood sample.

Plasma samples for PK analysis should be collected before the morning dose as close as possible to 12 hours after the previous dose. If the start of the next dose is delayed, the PK sample should still be collected during this visit instead of the delayed start of the next study visit.

The following procedures will be completed before the morning dose of rucaparib is administered and may be performed ±3 days of this visit. IV nivolumab will be administered after rucaparib.

- Physical examination
- Weight
- ECOG performance status (Appendix 3)
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Hematology (Local)
- Clinical chemistry (Local) (fasting is not required)
- Serum pregnancy test for women of childbearing potential (Local)
- Urinalysis (Local)
- Collect ctDNA blood sample (Central) – Reduced volume collected at this visit. Please see Laboratory Manual for details.

- CA-125 Measurement (Local)
- PK sample collection (Central) - according to Table 7
- Blood sample for immunophenotyping (PBMC)
- Blood sample for neo-epitope DNAseq
- Blood sample for cytokine/chemokine profiling
- AE monitoring
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for accountability
- Dispensation of rucaparib
- Administration of IV nivolumab (after the morning dose of rucaparib)

Patients will ingest rucaparib twice daily at about the same times every day as close as possible to 12 hours apart. Rucaparib should be taken with water and with or without food. Nivolumab IV will be administered as described in the Pharmacy Manual. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 5.5.

7.4.5 Cycle 2 Day 15

Patients will be instructed to refrain from taking their first dose of rucaparib at home on the day of their visit. The following procedures will be completed before the morning dose of rucaparib is administered and may be performed ±3 days of this visit. IV nivolumab will be administered after rucaparib.

- Physical examination
- Weight
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Hematology (Local)
- Clinical chemistry (Local) (fasting is **not** required)
- Urinalysis (Local)
- AE monitoring

7.4.6 Cycle 3 Day 1 and Every Cycle Thereafter

Patients will be instructed to refrain from taking their first dose of rucaparib at home on study visits when plasma samples for PK and/or ctDNA blood samples are collected.

Plasma samples for PK analysis should be collected before the morning dose on Cycle 3 Day 1, Cycle 4 Day 1, and Cycle 6 Day 1, as close as possible to 12 hours after the previous dose. If the start of the next dose is delayed, the PK sample should still be collected during this visit instead of the delayed start of the next study visit;

The following procedures will be completed before the morning dose of rucaparib is administered and may be performed ±3 days of these visits. IV nivolumab will be administered after rucaparib.

- Physical examination
- Weight
- ECOG performance status (Appendix 3)
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Tumor assessment scans at the end of every 8 calendar weeks (±7 days) from the first dose of nivolumab (ie, Cohorts A1/A2: commencing C4D1) for the first 18 months of treatment, and then every 12 calendar weeks (±7 days) thereafter
- Hematology (Local)
- Clinical chemistry (Local) (fasting is **not** required)
- Urinalysis (Local)
- Serum pregnancy test for women of childbearing potential (Local)
- Collect ctDNA blood sample (Central) (after Cycle 3, collect according schedule in Table 9)
- PK and immunogenicity sample collection (Central) - according to Table 7
- Blood sample for immunophenotyping (PBMC) (Table 9)
- Blood sample for neo-epitope DNAseq (Table 8)
- Blood sample for cytokine/chemokine profiling (Table 8)
- CA-125 Measurement (Local)
- AE monitoring
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for accountability
- Dispensation of rucaparib
- Administration of IV nivolumab (after the morning dose of rucaparib)

Patients will ingest rucaparib twice daily at about the same times every day as close as possible to 12 hours apart. Rucaparib should be taken with water and with or without food. Nivolumab IV will be administered as described in the Pharmacy Manual. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 5.5.

7.4.7 Post-treatment Follow-up Phase

7.4.7.1 End of Treatment

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

- Physical examination
- Weight
- Vital signs
- 12-lead ECG (Local)
- Concomitant medications and procedures
- Tumor scans (using the same methodology as was used at screening) if reason for treatment discontinuation was other than disease progression based on radiologic assessment
- ECOG performance status (Appendix 3)
- Hematology (Local)
- Clinical chemistry (Local) (fasting is **not** required)
- Urinalysis (Local)
- Serum pregnancy test for women of childbearing potential (Local)
- CA-125 measurement (Local)
- Blood sample for ctDNA analysis (Central)
- Blood sample for immunophenotyping (PBMC)
- Blood sample for neo-epitope DNAseq
- Blood sample for cytokine/chemokine profiling
- AE monitoring
- Optional tumor tissue biopsy collection at time of disease progression/treatment discontinuation (requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the Laboratory Manual for detailed sample handling instructions.
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for accountability

7.4.7.2 28-day Safety Follow-up (FU-28)

The procedures to be performed for all patients 28 (±3) days after the last dose of study drug (oral or IV, whichever is later) are listed below.

- Physical examination

- Weight
- Vital signs
- 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) for the first 3 years after initiation of oral/IV combination study treatment 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 (Local) should be performed at the same time as radiological imaging
- Hematology (Local)
- Clinical chemistry (Local) (fasting is not required)
- Urinalysis (Local)
- PK and immunogenicity sample collection (Central) - according to Table 7
- AE monitoring
- Concomitant medications and procedures

7.4.7.3 100-day Safety Follow-up (FU-100)

The procedures to be performed for all patients at least 100 days (+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 100-day Safety Follow-up Visit can be performed at a cycle visit, provided it has been at least 100 days since the last IV dose.

- Physical examination
- Weight
- Vital signs
- 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 (±7 days) intervals for the first 18 months years after initiation of study treatment 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 (Central)
- CA-125 measurement (Local) should be performed at the same time as radiological imaging.

- Hematology (Local) (only required if toxicities are present)
- Clinical chemistry (Local) (fasting is not required) (only required if toxicities are present)
- Urinalysis (Local)
- PK and immunogenicity sample collection (Central) - according to Table 7
- AE monitoring
- Concomitant medications and procedures

7.4.8 Long-term Follow-up

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 (±7 days) intervals for the first 18 months after initiation of study treatment, and every 24 weeks (±14 days) thereafter, until radiologic disease progression by RECIST v1.1, as assessed by the investigator, is documented.
- CA-125 measurement (Local) may be performed at the same time as radiological imaging, at the discretion of the investigator.
- Subsequent treatments, secondary malignancy monitoring, and overall survival 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. 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 8.10.
- SAEs related to study drug and all AESIs, irrespective of causality, are to be reported as specified in Section 8.10.

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 and as concomitant medications following receipt of the first dose of study drug through the completion of the 100-day Safety Follow-up Visit after IV treatment discontinuation. 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 (±7 days) or 24 weeks (±14 days), to coincide with the appropriate frequency of follow-up 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 100-day 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 8 weeks of treatment (±7 days is permitted) relative to Cycle 2 Day 1 until objective radiological disease progression. 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 ≥ 8 weeks since the last assessment. In addition, tumor assessments should be made as clinically indicated.

Disease assessment will comprise clinical examination and appropriate imaging techniques per RECIST v1.1 (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other complementary assessments (MRI, 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. 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. The sponsor may provide scans for IRR.

Tumor response will be interpreted using RECIST v1.1. Disease progression will only be determined by 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 (±7 days is permitted) 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) may be provided for IRR.

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 local laboratory.

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 study drug and 100 days after the last dose of IV study drug, whichever occurs later. After the 28-day (oral and/or IV, whichever occurs later) or 100-day (IV) window, only study drug-related SAEs and all AESIs, 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.

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

7.5.4.2 Clinical Laboratory Investigations

All clinical laboratory samples for safety will be collected and analyzed by the site's local laboratory. The panels of laboratory tests to be performed are shown below:

Hematology: Red blood cell (RBC) count and parameters (hemoglobin, hematocrit, MCV, MCH, and mean corpuscular hemoglobin concentration [MCHC]) and reticulocyte count, white blood cell (WBC) count and differential (with ANC), and platelet count will be assessed for all patients at screening, during treatment at each study visit, and at the End of Treatment Visit, 28-day Safety Follow-up Visit (FU-28), and at the 100-day Safety Follow-up Visit (FU-100), 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, measured clearance (CLcr), BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase (LDH), glucose, sodium, potassium, magnesium, chloride, bicarbonate (CO_2,/HCO_3^-), calcium, phosphorus, thyroid stimulating hormone (TSH), free triiodothyronine (T3; fT3), free thyroxine (T4, fT4),

TSH with reflexive fT3 and fT4 if TSH is abnormal on treatment, folic acid, and total cholesterol will be assessed for all patients at screening, during treatment at each study visit, and at the End of Treatment Visit, 28-day Safety Follow-up Visit (FU-28), and at the 100-day Safety Follow-up Visit (FU-100), if toxicities are present. Fasting is not required before blood sampling. If pancreatitis is suspected clinically, serum lipase and amylase should be analyzed. Clinical 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, during treatment at each study visit, at the End of Treatment Visit, at the 28-day Follow-up Visit, and at the 100-day Follow-up Visit for all patients, but may be conducted at other times as clinically indicated.

Local 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 8.6 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 End of Treatment 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) and at the end of treatment.

The following will be measured or calculated: heart rate, PR, QRS, QT, QTcF, 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 End of Treatment and Follow-up Visits.

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 the End of Treatment Visit. 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, End of Treatment Visit, and Follow-up Visits. 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 Pharmacokinetic and Immunogenicity Evaluations

Samples for nivolumab and rucaparib PK and immunogenicity assessments will be collected for all patients, as described in Table 7. 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).

7.5.5.1 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 laboratory manual for details on collection and processing of blood PK samples.

7.5.5.2 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 infusion site (ie, contralateral arm) on days of infusion. All samples collected predose should be collected just prior to the administration from the contralateral arm (ie, the arm not used for the infusion). If the nivolumab infusion was interrupted, the interruption details will also be documented on the eCRF. Further details of PK sample collection and processing will be provided to the site in the Laboratory Manual. Serum concentration analyses for nivolumab will be performed by validated bioanalytical method(s).

7.5.5.3 Nivolumab Immunogenicity Assessments

Samples for nivolumab immunogenicity assessment will be collected from all patients receiving nivolumab/rucaparib as described in Table 7.

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 patient'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 Laboratory Manual.

7.5.6 Biomarker Analysis

7.5.6.1 Biomarker Analysis – Mandatory Tumor Tissue Collection

A sufficient quantity of tumor tissue collected at screening must be provided during the screening process and submitted **to the central laboratory directly** for determination of HRD status. Patients may be enrolled prior to central tissue analysis, provided there is confirmation that the tumor tissue has been received by the central laboratory. Within 5 days and prior to commencement of IV nivolumab treatment on Cycle 2 Day 1 (= Cycle 1 Day 28 [window: −5 days]), collection of a primary or metastatic tumor sample is mandatory for patients, unless tumor biopsy procedure is contraindicated (eg, unacceptable risk in the opinion of the investigator).

All tumor specimens submitted need to contain enough tumor tissue for 1 × 4 µm section for hematoxylin and eosin (H&E) and approximately 5 × 10 µm sections [unstained], or equivalent, for determination of HRD status, and 4 × 4 µm sections and 2 × 10 µm sections, or equivalent for other planned analyses. 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. Check with sponsor if tumor tissue sample is inadequate for all testing.

Gene expression signatures associated with inflammation/immune activation will also be assessed.[67] Refer to the Laboratory Manual for details.

A tumor tissue biopsy sample at or following disease progression 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 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. 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 be associated with patient survival in HGSOC.[68] 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. Immunohistochemistry staining of immune lineage and immunogenic cell death markers on pre-rucaparib treatment tumor specimen (collected during screening) and post-rucaparib treatment tumor specimen (collected at Cycle 1 Day 28) will be performed to study the effect of rucaparib on the immune microenvironment. NGS results will be provided to the investigator.

7.5.6.2 Biomarker Analysis – ctDNA

Blood samples will be collected during screening, before dosing beginning on Day 1 of Cycles 1, 2, 3, and at specified subsequent cycles, at treatment discontinuation, and though the 100-day Follow-up Visit, as scheduled in Table 9. Sample collection details will be provided in the 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.

7.5.6.3 Biomarker Analysis - Genomic DNA from Blood

A blood sample for genomics analysis will be collected at Cycle 1 Day 1 (or next visit if not collected at Cycle 1 Day 1) from all patients for determination of germline status of mutations identified using NGS testing. Results of actionable alterations may be made available to the investigator, subject to patients consent. Sample collection details will be provided in the Laboratory Manual.

7.5.6.4 Other Peripheral Blood Biomarker Analyses

Peripheral blood samples will also be collected at selected time points on-treatment (C1D1, C2D1, C5D1, C7D1, C9D1), at the time of progression, and safety follow-ups for biomarker analyses that may predict sensitivity to nivolumab, including flow cytometry immunophenotyping, neo-epitope DNA sequencing, and serum cytokine/chemokine profiling.

A schedule of blood biomarker analysis is provided in Table 8. Sample collection and processing details will be provided in the Laboratory Manual.

7.5.6.5 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).

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 and 100 days after the last dose of IV study drug, whichever occurs later) must be treated as an SAE and reported as such. 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
- 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 study 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** (see Section 8.10 for reporting instructions).

8.4 Immune-mediated Adverse Events

Immune-mediated AEs (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the patient's eCRF.

Details on IMAEs can be found in the current nivolumab IB.

8.5 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 a serious adverse event.
- 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 screening procedures.

8.6 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
- at the discretion of the investigator should the abnormality be deemed clinically significant

8.7 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the course of the study, study drug(s) should be held immediately.

Pregnancy is not considered to be an AE or SAE; however, all pregnancies occurring during study participation or within 6 months of last dosing must be reported to the sponsor using the Pregnancy Report Form within the same timelines as for an SAE.

All pregnancies will be followed through to outcome. Once the outcome of a pregnancy is known, the Pregnancy Outcome Report Form will be completed and reported to the sponsor.

AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/ AESI processes using the appropriate AE or SAE/ AESI forms.

8.8 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, will be recorded on the Medical History eCRF. Any AE that occurs after first dose of study drug through 28 days after receiving the last dose of oral study drug or 100 days after receiving the last dose of IV study drug, whichever occurs later, will be recorded on the AE eCRF. After the 28-day or 100-day reporting window after discontinuation of treatment, only SAEs assessed as related to study drug and all AESIs, irrespective of causality, need to be reported. Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 8.9.

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 **causal relationship** to the investigational drug, severity, and, seriousness. 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 100 days 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.

8.8.1 Onset date of Adverse Events

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

8.8.2 Resolution date of Adverse Events

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

8.8.3 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, v5 or later grading scale.[66]

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
- Fatal events are events that lead to the patient's death

8.8.4 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 (Table 10).

Table 10. Causal Relationship of Adverse Events to 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.) • It does not follow a reasonable temporal sequence from administration of the study drug. • It does not follow a known pattern of response to study drug • It does not reappear or worsen when study drug is restarted. • An alternative explanation is likely, but not clearly identifiable.
Related to Study Drug	• An AE that is difficult to assign to alternative causes. • It follows a strong or reasonable temporal sequence from administration of study drug. • It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. • It follows a known response pattern to study drug • It is confirmed with a positive rechallenge or supporting laboratory data.

8.9 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 100 days 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- or 100-day window, treatment-related SAEs and all AESIs, irrespective of causality, need to be reported.

8.10 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,[41] must be reported as SAEs (see Section 8.11 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.

8.11 Regulatory Aspects of Serious Adverse Event and Adverse Events of Special Interest Reporting

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. For reporting SAEs/AESIs or pregnancies, use the applicable report forms. The contact information for reporting of SAEs and AESIs can be found on each of the forms.

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 US 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.

8.12 Data Monitoring Committee

A study DMC will be established and be comprised of the coordinating investigator and sponsor representatives. The DMC composition, responsibilities, and procedures for this study will be documented in the DMC Charter, which will be endorsed by the DMC members and signed by the DMC chair prior to the first data review meeting.

The DMC will review on an ongoing basis the study progress and clinical data to ensure the study remains beneficial to patients. The DMC will review the overall safety and efficacy data of rucaparib in combination with nivolumab, and by study cohort, to determine whether the study benefit/risk remains positive during the study.

The DMC will meet after the first 10 patients (Cohort A1) have either (a) received at least one Cycle of study treatment with Rucaparib and Nivolumab, (b) discontinued study treatment or (c) died of any cause. The DMC will perform continuous safety review at least every 6 months. The DMC chairperson or sponsor may convene an unscheduled DMC meeting if there are any emergent significant safety concerns. Following data review, the DMC will recommend

continuation, revision, or termination of the study and/or continuing or suspending enrollment into the study or a particular study cohort.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All safety analyses will be summarized for all patients who received at least 1 full or partial dose of protocol-specified treatment. Efficacy will be summarized for all treated patients according to the intent-to-treat principle. Cohorts A1 and A2 will be summarized separately for all safety and efficacy analyses.

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 (StD), 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, median (50th percentile) with the 95% confidence interval (CI) will be summarized. 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 9.3 or higher. Further details around the statistical analyses planned in this study will be outlined in the Statistical Analysis Plan (SAP).

9.2 Determination of Sample Size

Between 28 to 53 patients will be enrolled in this non-randomized 2-cohort study, which includes a 2-stage study design for Cohort A1.

- Cohorts A1 and A2 (Ovarian): Oral rucaparib + IV nivolumab
  - Cohort A1 (n = 18-43)
  - Cohort A2 (n = approximately 10)

9.2.1 Cohort A1

For Cohort A1, a Simon 2-stage design to evaluate ORR by RECIST v1.1 criteria per investigator will be used. With an optimal design, a minimum of 18 patients will be enrolled and a maximum of 43 patients. After the first 18 patients have either **a)** completed 16 weeks of treatment, or **b)** discontinued treatment prior to completing, an interim analysis will be performed (ie, Stage 1). If ≤ 2/18 patients in Stage 1 have a confirmed objective response (CR or

PR per investigator), a DMC will evaluate the overall benefit: risk for study treatment and make a recommendation whether further enrollment should be discontinued. If ≥ 3/18 patients have a confirmed objective response, then enrollment will continue with additional patients in Stage 2. With 43 total patients, characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug (ie, ORR of 10%)
- 80% probability of accepting an effective drug (ie, ORR of 25%)

9.2.2 Cohort A2

Cohort A2 is an exploratory cohort which will enroll approximately 10 patients classified as gBRCA^{mut}.

9.3 Analysis Populations

Safety Population: The Safety Population will consist of all patients who received at least 1 full or partial dose of any 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 from treatment 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 disease and baseline characteristics variables will also 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.

- Number of prior anticancer regimens; also split out by
  - Number of prior chemotherapy regimens
  - Number of prior platinum-based regimens
- Progression-free interval following the last platinum regimen received (months); 0-6, > 6-12, > 12-24, > 24;
- Partially Sensitive: PD ≥ 6 to < 12 months after last dose of platinum
- Sensitive: PD ≥ 12 months after last dose of platinum

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

9.6 Efficacy Analyses

All primary and secondary efficacy analyses will be summarized for the Safety Population for Cohort A1. Cohort A2 has an exploratory objective for evaluation of rucaparib on the immune microenvironment (see Section 9.6.3).

9.6.1 Primary Efficacy Analyses

The primary efficacy endpoint of ORR is defined as a best confirmed response of CR or PR by RECIST v1.1 as assessed by the investigator. The confirmed response rate by RECIST v1.1 is defined as the proportion of patients with a confirmed CR or PR on subsequent tumor assessment at least 28 days after first response documentation. The ORR will be summarized with frequencies and proportion together with 95% CI of the proportion using Clopper-Pearson methodology.

9.6.2 Secondary Efficacy Analysis

9.6.2.1 ORR Assessed by RECIST and GCIG CA-125 Criteria

The endpoint of ORR assessed by RECIST v1.1 or GCIG CA-125 criteria is defined as a best confirmed response of CR or PR using RECIST v 1.1 as assessed by the investigator or a confirmed response per GCIG CA-125 criteria. The endpoint of CA-125 response rate defined as at least a 50% reduction in CA-125 as assessed by GCIG criteria (Appendix 2). The response rate will be summarized with frequencies and percentages in addition to 95% CI of the proportion using Clopper-Pearson methodology. The combined ORR will be assessed as indicated in Table 11.

Table 11. RECIST and GCIG CA-125 Criteria

RECIST Response	GCIG CA-125 Response	RECIST + GCIG CA-125 Combined
CR (requires normalization of CA-125)	CA-125 within normal range	Response
PR	Response	Response
PR	No Response	Response
SD	Response	Response
SD	No Response	No Response
PD	Response	No Response
PD	No Response	No Response

Abbreviations: CA-125 = cancer antigen 125; CR = complete response; GCIG = Gynecologic Cancer InterGroup; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

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

9.6.2.2 ORR by RECIST v1.1 as Assessed by the Investigator and GCIG CA-125 Response According to Molecularly-defined HRD Subgroups

All patients in Cohort A1 will have a centralized tumor tissue test and the results from the NGS test will be utilized to divide the patients into the following molecularly-defined HRD subgroups:

- **Non-tBRCA LOH+**: Patients who are found to not have the a BRCA mutation in their tumor, but where the percent of LOH is ≥ 16% (ie, $BRCA^{wt}/LOH^{high}$);
- **Non-tBRCA LOH-**: Patients who are found to not have a BRCA mutation in their tumor, but where the percent of LOH is < 16% (ie, $BRCA^{wt}/LOH^{low}$);
- **Non-tBRCA Unknown**: Patients who are found to not have a BRCA mutation in their tumor, but where the percent of LOH is unknown due to missing results and/or failed test result(s) (ie, $BRCA^{wt}/LOH^{unknown}$); or
- sBRCA (somatic tBRCA): Patients who are found to have a BRCA mutation in their tumor but not in their blood sample.

The analyses of the response rates for each of these HRD subgroups will be performed as described in Section 9.6.2.1. In addition, different cut-off of LOH may be explored.

9.6.2.3 Progression-free Survival (PFS)

Progression-free survival as assessed by investigator by RECIST is defined as the time from first dose to disease progression, according to RECIST v1.1 criteria as assessed by investigator, or death due to any cause, whichever occurs first. PFS will be calculated as 1+ the number of days from the first dose of study treatment to first occurrence of disease progression (per RECIST v1.1) or death due to any cause, whichever occurs first. For patients who continue treatment post-progression, the first date of progression (per RECIST v1.1) will be used for the analysis. Patients without a documented event of progression will be censored on the date of their last adequate tumor assessment (ie, radiologic assessment) or date of first dose of study treatment if no post-baseline tumor assessments have been performed. Only tumor scans prior to start of any subsequent anticancer treatment are included.

The Kaplan-Meier methodology will be used to summarize PFS. If able to be estimated, the 50^{th} percentile (median) together with a 95% CI, will be presented based on log-log transformation. The number of patients with events and the number of censored patients will also be presented.

9.6.2.4 Duration of Confirmed Response (DOR)

Duration of response (DOR) for any confirmed RECIST CR or PR will be measured from the date of the first response until the first date that PD is documented. DOR will be summarized as a time to event variable. For patients who continue treatment post-progression, the first date of progression (per RECIST v1.1) will be used for the analysis. Any patients with an ongoing response will be

censored on the date of their last adequate tumor assessment (ie, radiologic assessment) or date of first dose of study treatment if no post-baseline tumor assessments have been performed. Only tumor scans prior to start of any subsequent anticancer treatment are included.

The Kaplan-Meier methodology will be used to summarize DOR. If able to be estimated, the 50th (median) together with a 95% CI, will be presented. The number of patients with events and the number of censored patients will also be presented

9.6.3 Exploratory Efficacy Analysis

The following exploratory analyses will be further described in the SAP:

- ORR by RECIST v1.1 as assessed by the investigator in exploratory Cohort A2
- ORR by RECIST v1.1 and GCIC CA-125 criteria in exploratory Cohort A2
- PFS in exploratory Cohort A2
- DOR in exploratory Cohort A2
- Explore mutations in BRCA1, BRCA2, other HRR genes as molecular markers of efficacy
- Explore PD-L1 expression as a molecular marker of efficacy
- Explore LOH, TMB, and other genomic and transcriptional signatures as molecular markers of efficacy

9.7 ctDNA and immunogenicity Analyses

Tumor tissue, plasma, and blood specimens will be used for exploratory biomarker analyses in an effort to understand the association of these markers with clinical activity or resistance to rucaparib and/or nivolumab, including efficacy and/or adverse events.

9.8 Safety Analyses

All safety analyses will be summarized by cohort.

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

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

9.8.1 Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v5 or later. Only 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 100 days 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 for the worst only once per patient. The number and percentage of patients with at least one TEAE will also be summarized.

Tables for TEAEs and treatment-related TEAEs will be presented as follows but are not limited to:

- All;
- By CTCAE grade;
- Grade 3 or greater;
- Serious;
- 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 1 TEAE of the given grade will be summarized.

The time to the first TEAE and first treatment-related TEAE that results in a dose reduction, delay, interruption or discontinuation of study drug is defined as 1+ the number of days from the first dose of study drug to the start of the first adverse event. The cumulative incidence is presented in a 1-KM graph for just the patients with an event and the median time to onset will be calculated together with the 95% CI.

Non-TEAEs (pre-treatment and post-treatment) will be presented in the by patient data listings for the safety population. MedDRA PTs were combined for the following similar terms

- Asthenia/Fatigue
- Alanine Aminotransferase (ALT)/ Aspartate Aminotransferase (AST) Increased

- Anaemia and/or Low/Decreased Haemoglobin
- Thrombocytopenia and/or Low/Decreased Platelets
- Neutropenia and/or Low/Decreased Absolute Neutrophil Count (ANC)

In addition, the analysis of combined terms for anemia is explored as a time to first event analysis as described above. Transfusions (blood or plasma) and concomitant medications/growth factor support received for cytopenias are provided in patient listings.

9.8.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, clinical chemistry, and urinalysis. The laboratory values will generally be presented in International System of Units (SI). The on-treatment period will be defined as the time from the first dose of study drug to 100 days after the last dose of study drug. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include 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 Grade 4 criteria according to CTCAE).

9.8.3 Vital Sign Measurements

The on-treatment period will be defined as the time from the first dose of study drug to 100 days after the last dose of study drug. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

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

9.9 Pharmacokinetic Analysis

9.9.1 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, StD, 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 ER analyses of selected efficacy and safety endpoints if the data permit. The PPK and the ER analyses may be presented separately from the main clinical study report.

9.9.2 Nivolumab Pharmacokinetic Analysis

In all patients with at least one PK sample collected, the serum nivolumab PK data, including C_{min} and concentration at the end of infusion (C_{eoi}) and summary statistics (N, mean, StD, 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 ER analyses of selected efficacy and safety endpoints if the data permit. The PPK and the ER analyses may be presented separately from the main clinical study report.

9.9.3 Anti-Nivolumab Antibodies

Anti-nivolumab antibodies in serum samples will be determined. Positive samples will be analyzed for neutralizing antibodies. The results will be reported.

9.10 Interim Analysis

An interim analysis of ORR by RECIST v1.1 criteria per investigator for Cohort A1 will be performed at Stage 1 of the Simon 2-stage design for the study. Enrollment in the study will continue while the interim analysis (Stage 1 criteria) occurs for Cohort A1. The DMC will review data for the interim analysis and provide recommendation if Stage 1 criteria are not met for Cohort A1. If Stage 1 criteria are not met, the DMC will evaluate the overall benefit: risk for study treatment, and make a recommendation whether further enrollment should be discontinued. If Stage 1 criteria in the Simon 2-stage design are met, the enrollment will continue with additional patients in Stage 2.

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 Council 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, Title 21, Part 50 and Part 56 (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.

The study will be registered on www.clinicaltrials.gov, European Clinical Trials Database (EudraCT), and other applicable trial registry systems as appropriate. Data generated from this study must be handled in accordance with any laws, rules, and regulations related to the privacy of personal data or medical information applicable in the jurisdiction where the data is processed, including without limitation, the United States Health Information Portability and Accountability Act of 1996 (HIPAA), and its implementing regulations, and the European Union General Data Protection Regulation 2016/679 (GDPR).

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 and approval.

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, applicable regulations, 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, in accordance with applicable data protection requirements. 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, as far as permitted by applicable local requirements. 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 by any employee or agent of the study center to any third party or otherwise into the public domain.

10.4 Study Monitoring

On behalf of the sponsor, a contract research organization (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. Sponsor representatives may also contact and visit the investigators and monitor data during the study.

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

The data will be collected using an electronic data capture (EDC) system by remote data entry on eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Data collection is the responsibility of the clinical study 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.

Prior to study start, the investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study center personnel and delegation list" must be kept current throughout the study.

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. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All laboratory data and investigator observations on the results and any other clinically significant test results must be documented on eCRFs.

Full information regarding electronic data capture and completing eCRFs is included in the investigator files. All questions or comments related to electronic capture should be directed to the assigned monitor.

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 or collaborator discontinues the development of study medication.

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.

If the study is terminated prematurely, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The investigators will promptly inform their IRB/IEC, providing the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

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 the Essential Documents for the Conduct of a Clinical Trial defined in ICH E6(R2) §8. The investigator should have control of all essential documents generated by the site. Source documents must be maintained, ALCOA-C (attributable, legible, contemporaneous/complete, original, accurate) used. Any changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (via an audit trail). The investigator must implement procedures to ensure the integrity of any data generated.

The sponsor and the investigator will maintain a record of the location(s) of their respective essential documents including source documents. The storage systems used during the study and for archiving (irrespective of media used) must provide for documentation identification, version history, search, and retrieval. 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 study-related records are no longer needed.

All clinical study information should be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification, irrespective of the media used.

The sponsor and the investigator will maintain a record of the location(s) of their respective essential documents including source documents. The storage systems used during the study and for archiving (irrespective of media used) must provide for documentation identification, version history, search, and retrieval.

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.

Aspects of the study that are essential to ensure human subject protection and reliability of study results should be the focus of these procedures.

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 authorized by the sponsor, and 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, European Medicines Agency (EMA), or other regulatory agencies, or 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 (CSR) will be prepared, regardless of whether the study is completed, under the responsibility and supervision of the sponsor and signed by the sponsor's Chief Medical Officer, Head of Biostatistics, and Head of Regulatory Affairs; thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report. The CSR will be provided to the regulatory agency(ies) as required by the applicable regulatory requirements.

10.11 Publication and Disclosure Policy

All data generated from this study will be maintained by the sponsor. All data generated from this study, and all information furnished by the sponsor, the investigators, 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. Any collaborative publications will be authored in accordance with the applicable guidelines (eg, International Committee of Medical Journal Editors [ICJME]).[69] 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 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. 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 any individual or party to whom they delegate study-related duties and functions conducted at the study site. This includes the services of any party or individual retained by the investigator for this purpose. 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-related duties, functions performed, and any 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)[70] 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).[71] 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.[71]

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 studies 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. Patients who have been on study at least 18 months, may decrease the frequency of disease/ tumor assessments to every 16 weeks.

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 Using CA-125

GCIG Guidelines for Response Using CA-125[72] (adapted for use in this study).

GCIG CA-125 definitions are available at http://gcig.igcs.org/CA-125.html.

To be evaluable for response by CA-125 requires an elevated baseline value of at least 2 x 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 x 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.

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 CYP Substrates with Narrow Therapeutic Range

CYP Enzyme	Substrates with Narrow Therapeutic Range[a]
CYP1A2	Tizanidine, theophylline
CYP2C9	Warfarin, phenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

[a] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

Source: Draft FDA Guidance on Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012[73]

Appendix 5 Example Strong CYP3A Inhibitors or Inducers

Enzyme and interaction	Example drugs
Strong CYP3A inhibitors	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir
Strong CYP3A inducers	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

This table is recommended by the Draft FDA Guidance: Clinical Drug Interaction Studies -Study Design, Data Analysis, and Clinical Implications, 2017.[74] The table is prepared and maintained by the FDA to provide examples of clinical strong CYP3A inhibitors or inducers but is not intended to provide an exhaustive list.

Appendix 6 Management Algorithms for Immuno-oncology Agents

These general guidelines 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.

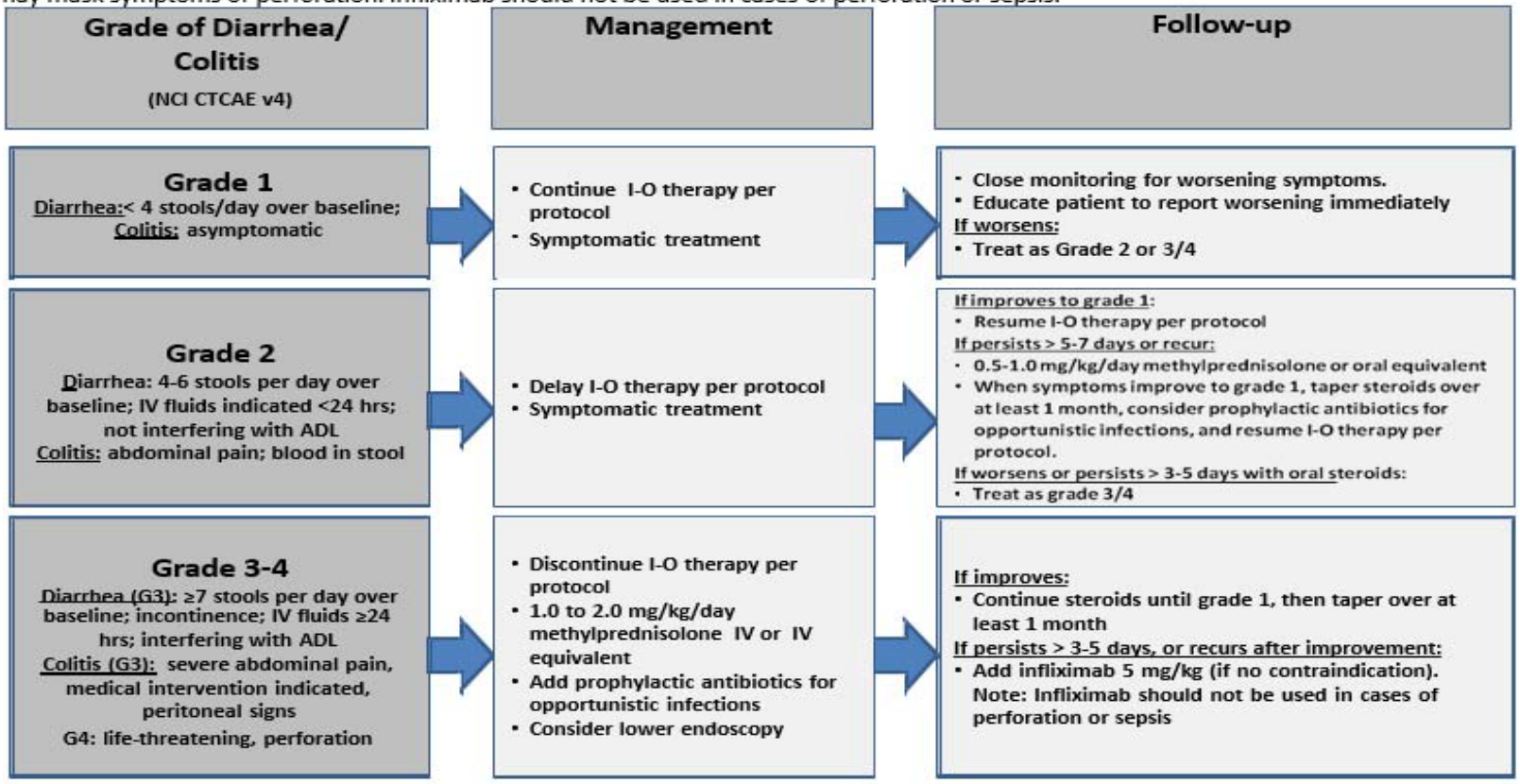
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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

Adverse events reported in this study, will be assessed according to NCI-CTCAE v5.0 or later. Please note, however, that the following AE management algorithms apply criteria from NCI-CTCAE v4 for the guidance and management decisions concerning the specified toxicities. While any difference between the 2 versions of the criteria are likely to be minimal, please ensure that there is documentation at the site explaining situations where an AE management decision may be based on a different grading to that entered in the database.

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 (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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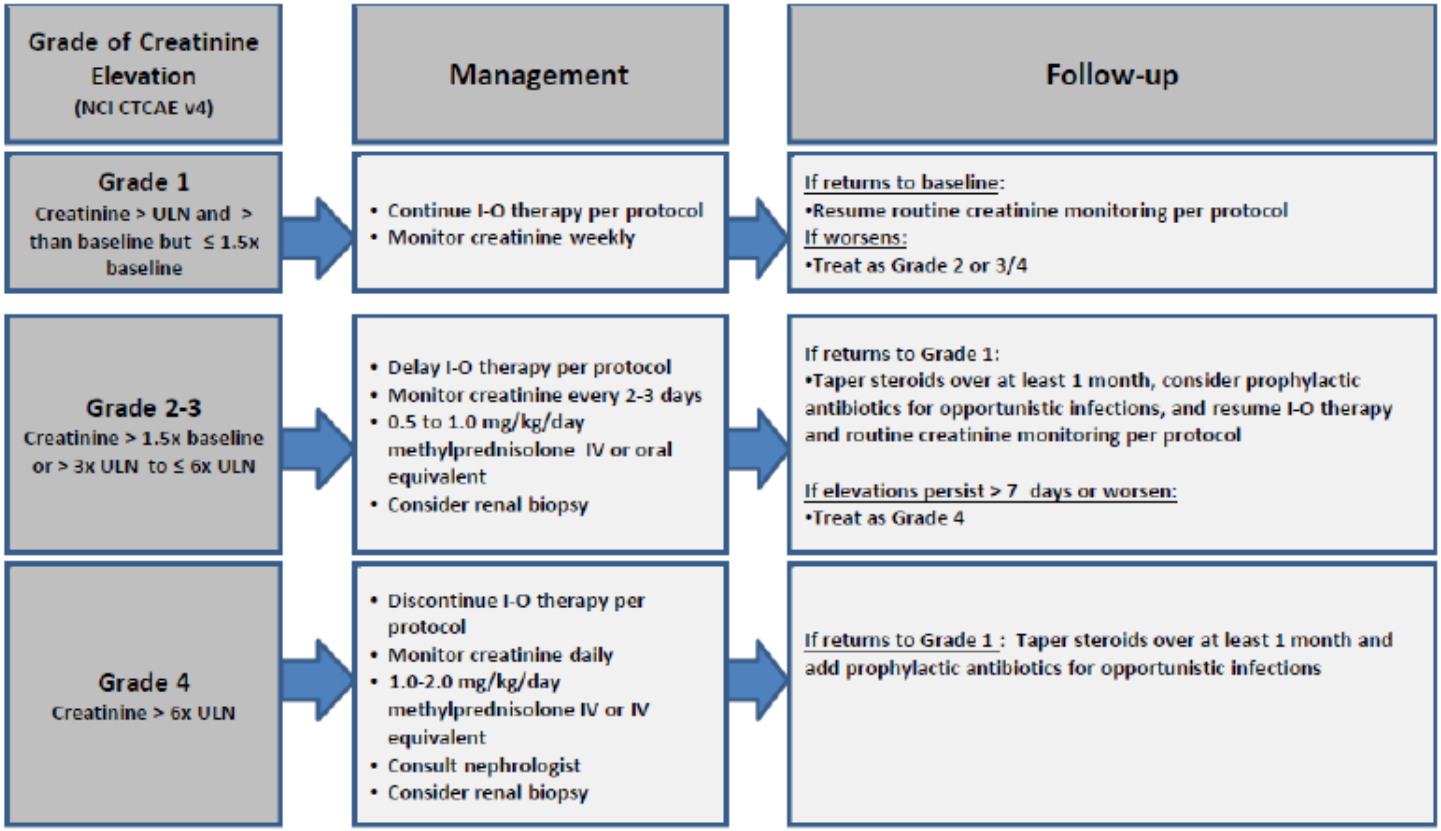
Renal Adverse Event Management Algorithm - Rucaparib*and Nivolumab

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 (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Baseline for creatinine will be considered pre-dose to the first 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.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: - When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: - Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections - Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: - Add additional immunosuppression

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

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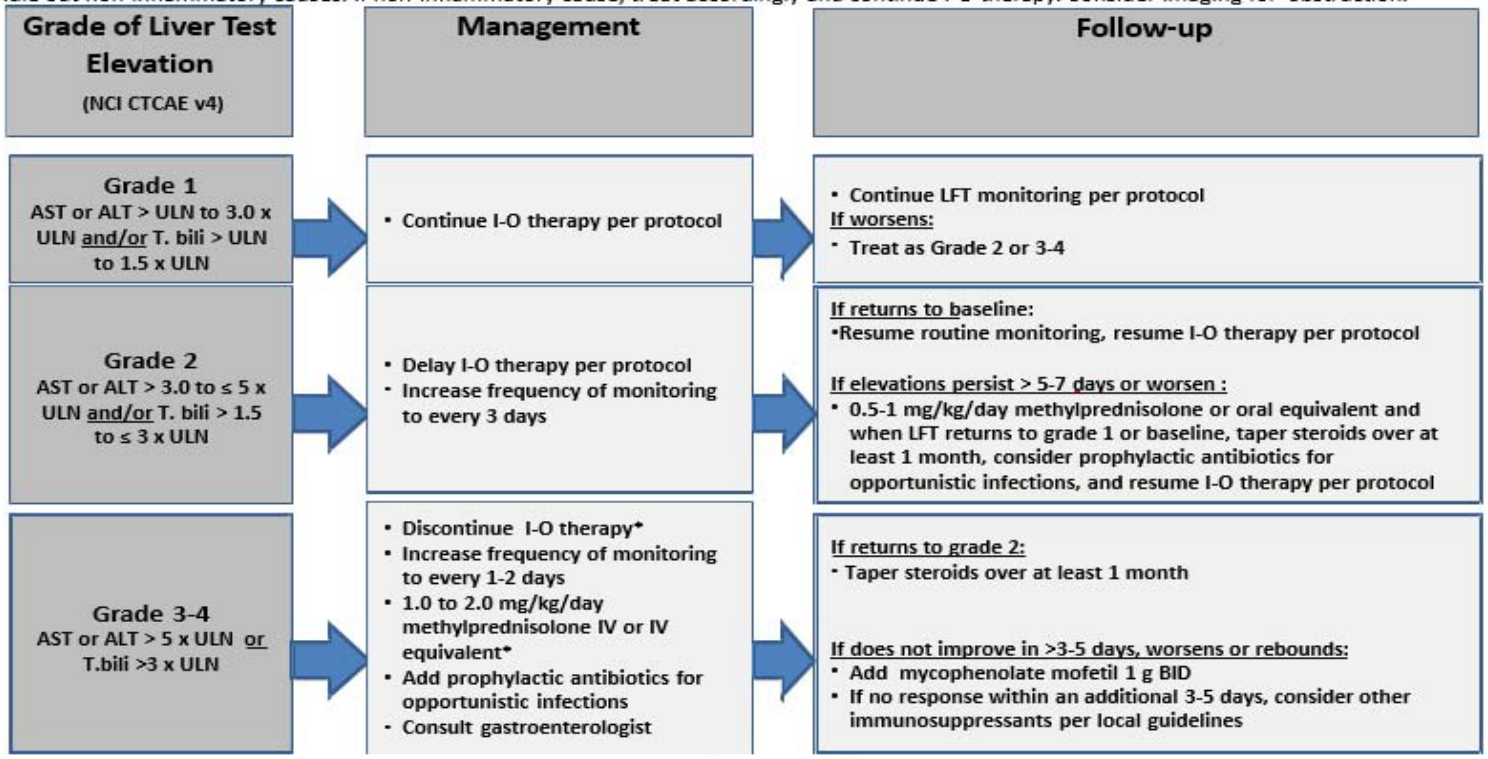
Hepatic Adverse Event Management Algorithm

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 (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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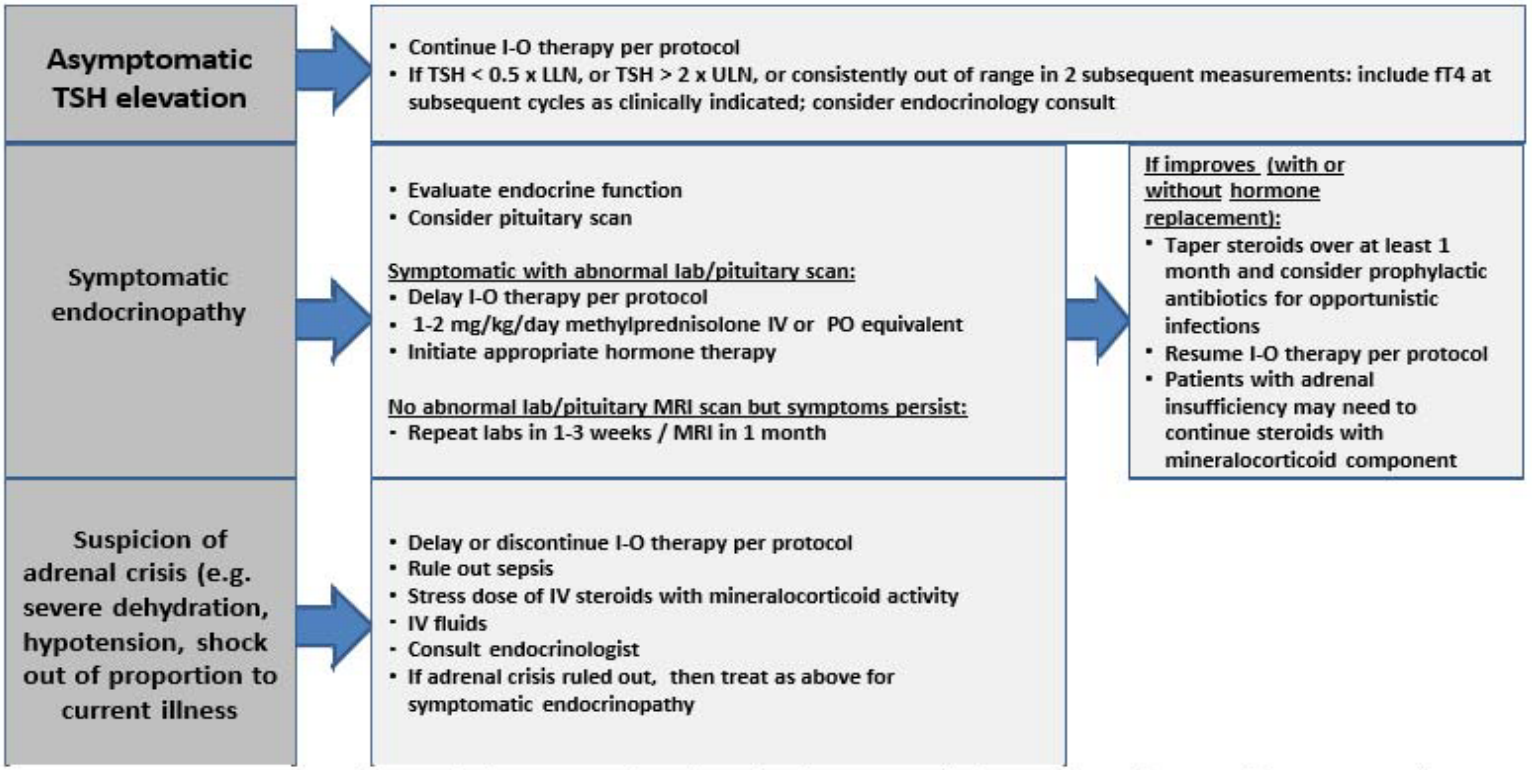
Endocrinopathy Adverse Event Management Algorithm

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 (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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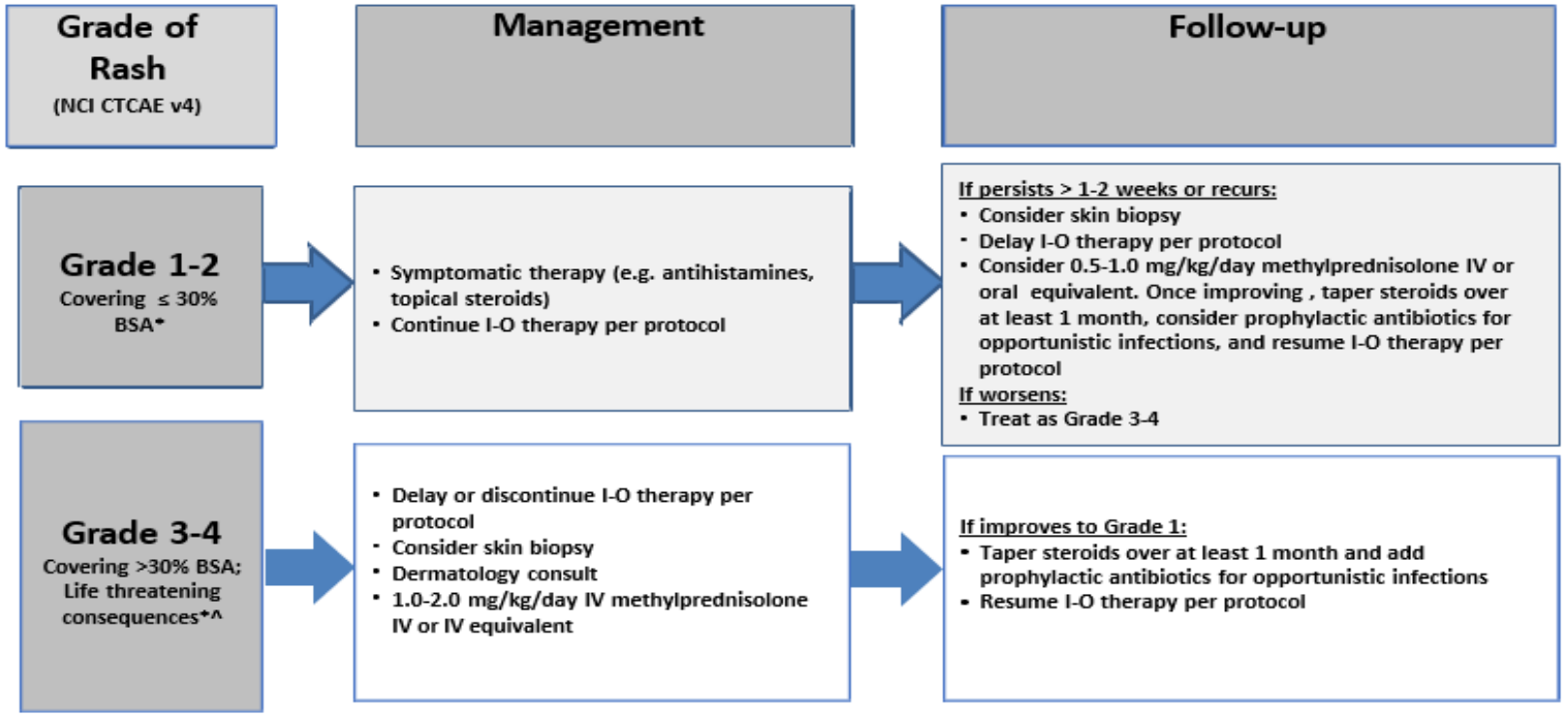
Skin Adverse Event Management Algorithm

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 (e.g. prednisone) at start of tapering or earlier, once 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 v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

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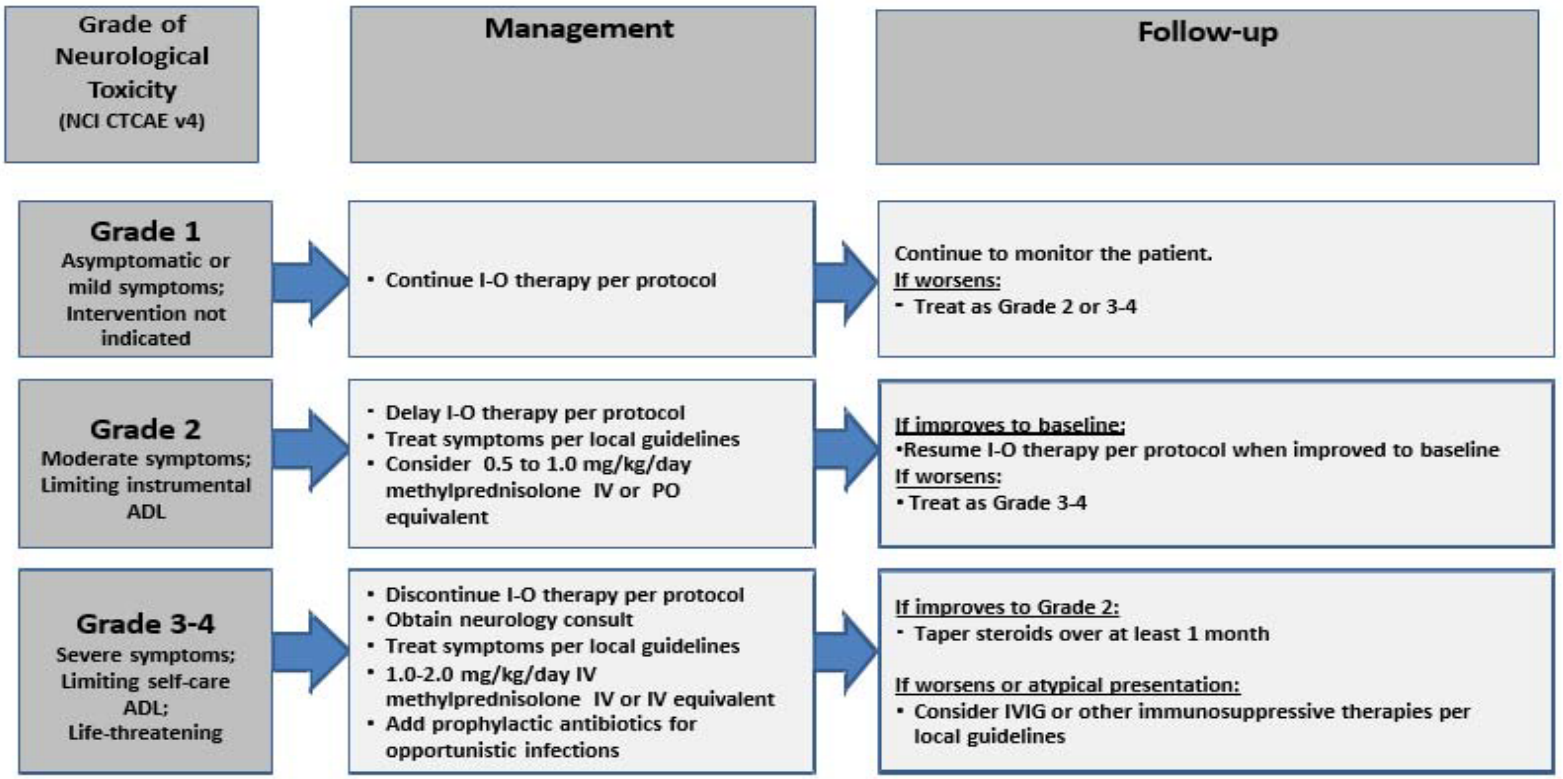
Neurological Adverse Event Management Algorithm

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 (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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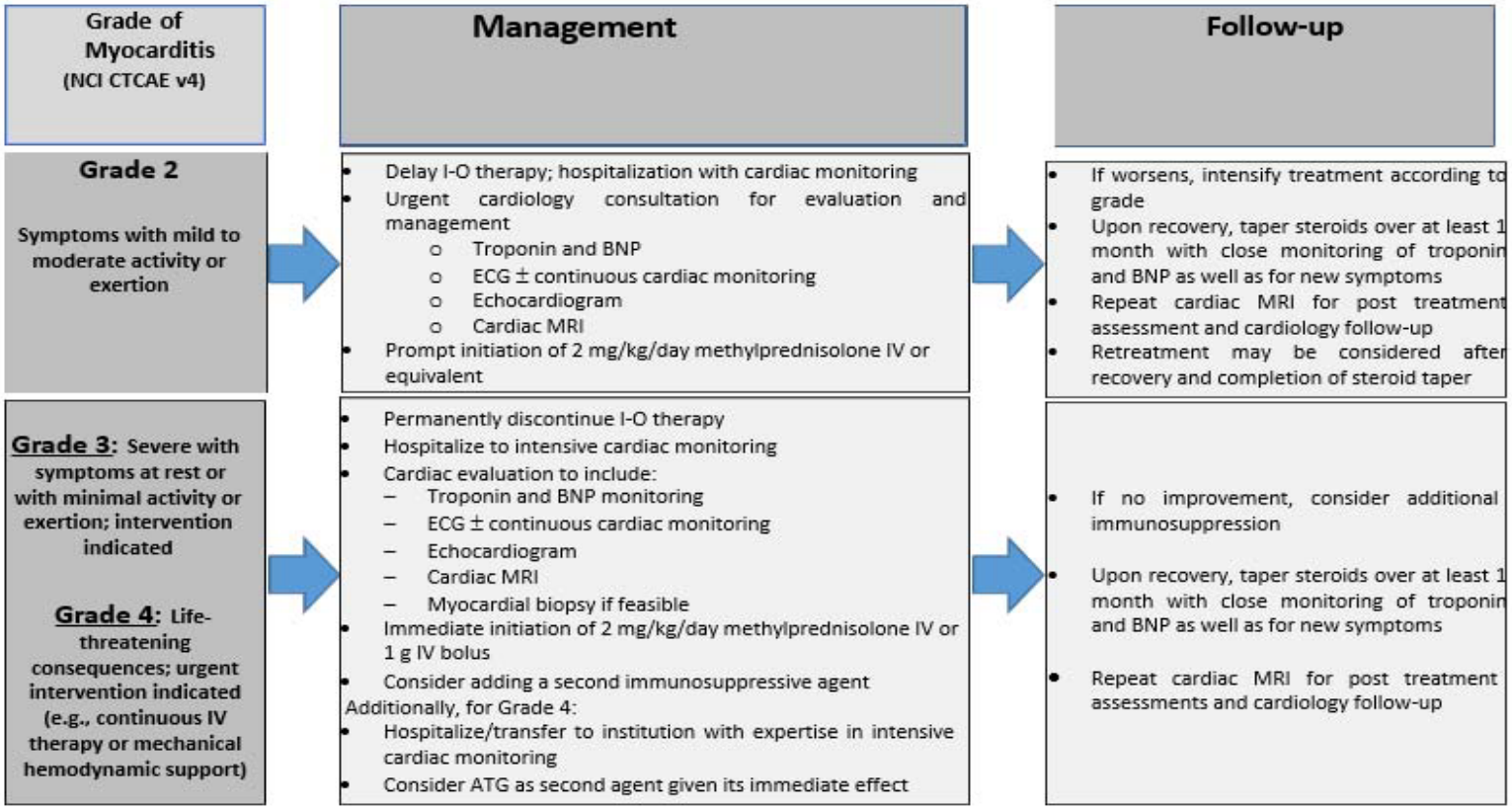
Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once 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 of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

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