Clinical Study Protocol: CO-338-043

Study Title:	ARIEL4 (**A**ssessment of **R**ucaparib **I**n Ovarian Canc**E**r Tria**L**): A Phase 3 Multicenter, Randomized Study of Rucaparib versus Chemotherapy in Patients with Relapsed, BRCA-Mutant, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Study Number:	CO-338-043
Study Phase:	Phase 3
Product Name:	Rucaparib (CO-338)
IND Number:	[redacted]
EUDRA CT Number	[redacted]
Indication:	Relapsed ovarian cancer
Investigators:	Multicenter
Sponsor Name:	Clovis Oncology, Inc.
Sponsor Address:	[redacted]
Responsible Medical Officer:	[redacted]

Protocol Version	Date
[redacted]	[redacted]
[redacted]	[redacted]
Amendment 2	23 October 2020

COORDINATING INVESTIGATORS FOR THE STUDY

Coordinating Investigator for North America:

[redacted]

Coordinating Investigator for Europe, Middle East, and all Other Regions:

[redacted]

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol:	CO-338-043
Title:	ARIEL4 (**A**ssessment of **R**ucaparib **I**n Ovarian Canc**E**r Tria**L**): A Phase 3 Multicenter, Randomized Study of Rucaparib versus Chemotherapy in Patients with Relapsed, BRCA-Mutant, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Amendment 2 Date:	23 October 2020

PROTOCOL ACCEPTANCE FORM

Protocol:	CO-338-043
Title:	ARIEL4 (**A**ssessment of **R**ucaparib **I**n Ovarian Canc**E**r Tria**L**): A Phase 3 Multicenter, Randomized Study of Rucaparib versus Chemotherapy in Patients with Relapsed, BRCA-Mutant, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Date:	23 October 2020
Version:	Amendment 2

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

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

1 SYNOPSIS

Sponsor Clovis Oncology, Inc.
Name of Finished Product Rucaparib tablets
Name of Active Ingredient Rucaparib camsylate (CO-338)
Study Title ARIEL4 (**A**ssessment of **R**ucaparib **I**n Ovarian Canc**E**r Tria**L**): A Phase 3 Multicenter, Randomized Study of Rucaparib versus Chemotherapy in Patients with Relapsed, BRCA-Mutant, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Study Number CO-338-043
Study Phase Phase 3
Study Duration Approximately 4 years
Rationale Globally, ovarian cancer is the eighth most common cancer and the seventh leading cause of cancer death among women, responsible for approximately 140,000 deaths each year.[1] Additionally, it is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer.[2, 3] The standard of care is cytoreductive surgery followed by carboplatin and paclitaxel chemotherapy. Despite a 70-80% initial response rate, most women have disease relapse.[3-5] The choice of treatment for relapsed disease is based on the treatment-free interval relative to last therapy administered, and also prior chemotherapy agents used. The treatment-free interval typically decreases with each course administered and almost all patients will develop acquired resistance, hypersensitivity, or intolerable toxicity upon repeated courses of treatment, and ultimately will succumb to their disease. Recently, inhibitors of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes, which play critical roles in DNA repair, have demonstrated clinical activity in patients with a breast cancer gene 1 or 2 (BRCA1/2) mutation or other evidence of homologous recombination deficiency (HRD) and have emerged as a new treatment option for relapsed ovarian cancer. Rucaparib is a potent, oral small molecule inhibitor of PARP enzymes (PARPi), including PARP-1, PARP-2, and PARP-3. Rucaparib has demonstrated in vitro and in vivo anti-tumor activity in BRCA1 and BRCA2 homozygous mutant cell lines. These findings provided rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary (germline) and acquired (somatic) deficiencies of BRCA1 and/or BRCA2.

The safety and efficacy profile of rucaparib have been evaluated in several Phase 1 and Phase 2 studies.

On 19 December 2016, the United States (US) Food and Drug Administration (FDA) granted accelerated approval for the marketing of rucaparib (Rubraca®) for monotherapy treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥ 2 chemotherapies. The recommended starting dose of rucaparib is 600 mg twice a day (BID). Refer to the Investigator's Brochure for updated approval status.

The basis for the approval of rucaparib as monotherapy for the treatment of ovarian cancer are the datasets and analyses for patients with Epithelial Ovarian Cancer (EOC), Fallopian Tube Cancer (FTC), or Primary Peritoneal Cancer (PPC) comprising the primary efficacy analysis population. The primary efficacy analysis population included 106 patients pooled from the open-label, single-arm Phase 2 studies, Study CO-338-010 (Study 10) Part 2A and Study CO-338-017 (ARIEL2) Parts 1 and 2, with BRCA-mutant ovarian cancer (EOC, FTC, or PPC), who had received ≥ 2 prior chemotherapy regimens, at least 2 of which were platinum-based, and who had received at least 1 dose of 600 mg rucaparib.[6]

The primary outcome measure on which approval was based is investigator-assessed ORR per RECIST v1.1, with ORR by central independent radiological review (IRR) conducted as a supportive analysis. ORR by investigator was 53.8%, while ORR by IRR was 41.5%, confirming the results of investigator assessment for this endpoint.[7] Responses were durable, indicated by a duration of response (DOR) by investigator assessment of approximately 9.2 months.

While PARP inhibitors have demonstrated consistent robust clinical activity in patients with relapsed ovarian cancer associated with HRD, prospective studies evaluating efficacy and safety of PARPi versus standard of care chemotherapy have been limited. The primary purpose of this Phase 3 study is to compare the efficacy and safety of rucaparib versus chemotherapy as treatment for relapsed ovarian cancer in patients with a deleterious BRCA1/2 mutation in their tumor.

Primary Objective

To determine investigator-assessed progression-free survival (invPFS) by RECIST Version 1.1 for rucaparib versus chemotherapy.

Secondary Objectives:

- To evaluate progression-free survival (PFS) by RECIST Version 1.1, as assessed by blinded independent central review (BICR; bicrPFS)
- To compare efficacy of rucaparib versus chemotherapy as measured by overall survival (OS)
- To compare efficacy of rucaparib versus chemotherapy as measured by ORR using RECIST Version 1.1 by investigator assessment
- To compare efficacy of rucaparib versus chemotherapy as measured by DOR by investigator assessment
- To compare efficacy of rucaparib versus chemotherapy as measured by ORR using RECIST Version 1.1 by investigator assessment and Gynecologic Cancer InterGroup (GCIG) CA-125 response criteria
- To evaluate patient-reported outcome (PRO) for rucaparib versus chemotherapy as assessed by the:
  - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30
  - EORTC ovarian cancer module QLQ-OV28
- To evaluate the safety and tolerability of rucaparib versus chemotherapy

Exploratory Objectives:

- To evaluate PFS of study treatment and the subsequent line of treatment received (PFS2), both by investigator assessment
- To evaluate disease control rate (RECIST Version 1.1 complete response [CR], partial response [PR], and prolonged stable disease [SD > 12 weeks], by investigator assessment)
- To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D)
- To assess molecular changes in tumor samples over time in matched pairs
- To assess circulating cell-free tumor DNA (ctDNA) as a molecular marker of efficacy
- To evaluate the impact of gene expression molecular subgroups on PFS and OS
- To assess efficacy in BRCA-mutation subgroups (ie, germline/somatic and BRCA1/BRCA2)
- To characterize steady-state trough concentrations of rucaparib
- To explore the relationship between rucaparib exposure and responses (safety and efficacy)

Study Design

This is a Phase 3 multicenter, randomized study evaluating rucaparib versus chemotherapy for treatment of patients with relapsed, high-grade epithelial serous or Grade 2 or 3 endometrioid ovarian, fallopian tube, or primary peritoneal ovarian cancer. The study will enroll patients with a deleterious BRCA1/2 mutation in their tumor. All patients will be required to have received at least 2 prior chemotherapy regimens. Patients with platinum-refractory disease (ie, disease progression during or within 4 weeks after last dose of the most recent platinum-based chemotherapy) and patients who have received

prior PARPi treatment will be excluded. Patients with platinum-resistant (ie, disease progression ≥ 1 to < 6 months after the last dose of most recent platinum-based chemotherapy) or partially platinum-sensitive disease (ie, disease progression ≥ 6 to < 12 months after last dose of most recent platinum-based chemotherapy) will be randomized 2:1 to receive either rucaparib or weekly paclitaxel. Patients with platinum-sensitive disease (ie, disease progression ≥ 12 months after last dose of most recent platinum-based chemotherapy) will be randomized 2:1 to receive either rucaparib or platinum-based chemotherapy consisting of the Investigator's selection of monotherapy platinum (cisplatin or carboplatin) or platinum-based doublet chemotherapy (carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine).

A 2:1 randomization to receive either rucaparib or chemotherapy will allow for statistical comparison of PFS, OS, and ORR between the treatment arms and provide access to rucaparib for a larger number of patients who would otherwise receive standard chemotherapy. Stratification by progression-free interval after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive) will occur upon study entry to maintain balance between treatment groups.

The chemotherapy agents that were selected as comparators for this study have demonstrated activity in advanced ovarian cancer. Weekly paclitaxel has robust clinical activity, a favorable safety profile, and is recommended by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines for the treatment of relapsed ovarian cancer.[8-10] Cisplatin and carboplatin are effective single-agent therapies as well as in combination (doublet therapy) with gemcitabine or paclitaxel for treatment of ovarian cancer in patients with platinum-sensitive disease as recommended by NCCN and ESMO guidelines.[8, 10, 11] Therefore, these chemotherapies are appropriate comparators to confirm rucaparib benefit for the planned patient population.

Screening:

All patients, with the exception of those known to harbor a deleterious BRCA1/2 mutation (germline or somatic), will be required to provide archival tumor tissue or a screening biopsy for central laboratory analysis prior to enrollment. Tumor analysis will be performed using the Foundation Medicine, Inc (FMI) next generation sequencing (NGS) test. Results of the FMI panel test will be provided to patients who consent to receive this information.

Patients with a known deleterious BRCA1/2 mutation (germline or somatic) must also submit archival tumor tissue for central laboratory testing; however, enrollment is not contingent upon central laboratory analysis of tissue before enrollment. A local BRCA1/2 mutation result from previous testing will be adequate for enrollment. Patients with a deleterious BRCA1/2 mutation who meet all other entry criteria will be eligible for the study. If archival tissue is not available, the patient may undergo a screening biopsy.

Additional screening assessments will include demographics and medical history, prior treatments for serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (and other malignancies, if applicable), prior and current medications and procedures, 12-lead ECG, ECOG performance status, local laboratory hematology, serum chemistry, and CA-125 measurement, serum pregnancy (for women of childbearing potential only), urinalysis, physical examination, height, weight, and vital signs

measurements, blood samples for ctDNA and genomic analyses, adverse events, and radiologic assessment by computed tomography (CT) or magnetic resonance imaging (MRI). Patient-reported outcomes (PRO) will be collected using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate.

Randomization:

Following classification (ie, deleterious BRCA1/2 mutation) detected by FMI (central laboratory) analysis or documented local results for deleterious germline or somatic BRCA1/2 mutation, with confirmation of adequate tumor tissue availability for known deleterious BRCA1/2 mutant patients, and confirmation of all other eligibility criteria in the screening phase, patients will be randomized 2:1 to receive rucaparib or chemotherapy.

Treatment and Follow-up:

Patients will receive treatment with either rucaparib or chemotherapy until disease progression by RECIST Version 1.1, as assessed by the investigator; unacceptable toxicity or inability to tolerate further treatment, as assessed by the investigator; pregnancy; death; loss to follow-up; withdrawal of consent; or another appropriate clinical reason. Patients will receive up to a maximum of 8 cycles of platinum monotherapy or doublet therapy and will be followed thereafter until disease progression or other reason for discontinuation. CT scans will be submitted to a central imaging vendor to allow for independent review of PFS.

Assessments and procedures during the study will include: AEs; physical examinations; 12-lead ECGs, vital signs and weight measurements; local laboratory hematology, serum chemistry, and CA-125 measurements; serum pregnancy for women of childbearing potential; blood samples for ctDNA and genomic analyses (before dosing in Cycles 1 to 6); plasma samples for pharmacokinetic (PK) analysis; concomitant medications, therapies, and procedures; disease/ tumor assessments; study drug administration and accountability; and PRO. Urinalysis will be performed as clinically indicated.

Patients randomized to chemotherapy have the option to cross over to receive rucaparib upon radiological progression per RECIST Version 1.1 following Sponsor (or designee) review and approval of the radiology report confirming disease progression. If clinical progression is diagnosed, confirmation of disease progression by radiologic assessment per RECIST Version 1.1 is required before cross over to rucaparib. If a patient randomized to rucaparib has radiologic progression, but continues to derive clinical benefit per the investigator, continuation of treatment beyond progression will be permitted. In such cases, the documented decision to continue will be made jointly between the investigator and the Sponsor (or designee), and the patient must provide consent within a reasonable timeframe of the documented decision to continue treatment with rucaparib. The patient will continue to have all protocol-required assessments.

Patients will be followed for safety and efficacy assessments for 28 days after the last dose of study drug. An optional tumor biopsy will be collected from patients who experience disease progression/discontinue treatment and provide appropriate consent. There will be long-term follow-up (LTFU) assessments every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent, or study closure. Information regarding subsequent treatments, secondary malignancies, and survival will be collected. For patients who have not had radiologic disease progression, LTFU will also include tumor scans every 8 calendar weeks until radiologic disease progression by RECIST Version 1.1, per

investigator, death, loss to follow-up, withdrawal, study closure, or initiation of subsequent treatment.

Study Population

The study will consist of patients with confirmed high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer and harbor a deleterious BRCA1/2 mutation. Patients with a histology other than serous or endometrioid known to harbor a deleterious BRCA1/2 mutation may also be eligible.

Number of Patients and Sites

Approximately 345 patients will be enrolled, with 230 patients randomized to rucaparib and 115 patients randomized to chemotherapy.
Study enrollment will be across approximately 100 study sites worldwide.

Inclusion Criteria

Eligible patients must meet the following inclusion criteria. Unless otherwise specified, the criteria below apply to all patients.

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form prior to any study-specific evaluation
2. Be ≥ 18 years of age at the time the informed consent form is signed
3. Have a histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer
    a. If mixed histology, > 50% of the primary tumor must be confirmed to be high-grade serous or endometrioid upon review by local pathology
    b. Patients with a histology of other than serous or endometrioid are also eligible if they are known to harbor a deleterious germline or somatic BRCA1/2 mutation
4. Received ≥ 2 prior chemotherapy regimens, with at least 1 regimen including a platinum, and have relapsed or progressive disease as confirmed by radiologic assessment
    a. Had documented treatment-free interval of ≥ 6 months following the first chemotherapy regimen received
    b. Hormonal agents (eg, tamoxifen, letrozole, etc.), anti-angiogenic agents (eg, bevacizumab, pazopanib, cediranib, etc.), and other non-chemotherapy agents will not be counted as a chemotherapy regimen for the purpose of determining patient eligibility
    c. Agents administered in the maintenance setting will not be counted as a separate regimen
5. Have a deleterious BRCA1/2 mutation as confirmed by the central laboratory. Note: patients known to harbor a deleterious germline or somatic BRCA1/2 mutation based on local assessment may be enrolled without central tissue analysis provided there is confirmation that tumor tissue is available to be provided to the central laboratory.

   a. Sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue must be available for planned analyses; cytospin blocks from ascites are not acceptable
      i. The most recently obtained tumor tissue that is of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content) should be submitted.
   b. In the event archival tumor tissue is not available, a screening biopsy sample may be collected and provided to the central laboratory
6. Have evaluable disease: ie, at least 1 target or non-target lesion that can be assessed per RECIST Version 1.1
7. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to randomization:
   a. Bone Marrow Function
      i. Absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/L
      ii. Platelets $> 100 \times 10^9$/L
      iii. Hemoglobin > 10 g/dL
   b. Hepatic Function
      i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ upper limit of normal (ULN); if liver metastases, then $\leq 5 \times$ ULN
      ii. Bilirubin $\leq 1.5 \times$ ULN; $< 2 \times$ ULN if hyperbilirubinemia is due to Gilbert's syndrome
      iii. Serum albumin $\geq$ 30 g/L (3.0 g/dL)
   c. Renal Function
      i. Serum creatinine $\leq$ 1.5 x ULN or estimated glomerular filtration rate (GFR) $\geq$ 45 mL/min using the Cockcroft-Gault formula
8. Women of childbearing potential must have a negative serum pregnancy test $\leq$ 3 days prior to administration of the first dose of study drug
9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Exclusion Criteria

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

1. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment
   a. Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/ or bone marrow transplant > 2 years prior to first dose of study drug. Ongoing hormonal treatment for previously treated breast cancer is permitted
2. Prior treatment with any PARP inhibitor, including rucaparib, regardless of duration

3. Prior treatment with single-agent paclitaxel or nab-paclitaxel
4. Prior known clinically significant hypersensitivity (per investigator judgement despite implementation of a desensitization protocol) to:
    a. paclitaxel treatment for patients with a progression-free interval of < 12 months after last platinum-based regimen, or
    b. platinum treatment for patients with a progression-free interval of ≥ 12 months after last platinum-based regimen
5. Platinum refractory disease: disease that progressed by radiologic assessment during or within 4 weeks after completing treatment with most recent platinum-based therapy
6. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously-treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks after completion of therapy
7. Pre-existing duodenal stent and/ or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib
8. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C, with exception of patients with sustained virologic response after completion of treatment for hepatitis C
9. Women who are pregnant or breast feeding
10. 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
11. Ongoing toxicity from prior cancer treatment ≥ Grade 2 by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (ongoing Grade 2 non-hematologic toxicity, with the exception of peripheral neuropathy, may be permitted with prior advanced approval from Sponsor)
12. Non study-related minor surgical procedure ≤ 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
13. Requires regular blood transfusions, granulocyte colony-stimulating factor, or platelet transfusions
14. Drainage of ascitic fluid 2 or more times in the 4 weeks prior to the first dose of study drug, uncontrolled pleural effusion, or permanent drain in place (eg, PleurX®) for ascites or pleural effusion
15. Hospitalization for bowel obstruction within 3 months prior to randomization
16. 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

To be eligible for participation in the crossover part of the study, patients must fulfill the following criteria and initiate treatment with rucaparib ≤ 8 weeks after radiologic disease progression:

1. Have documented radiological progression per RECIST Version 1.1 during or following completion of comparator arm chemotherapy
2. Receive Sponsor approval to cross over from chemotherapy to rucaparib treatment
3. Have adequate hematological and biological function, confirmed by the following local laboratory values ≤ 14 days prior to first dose of rucaparib:
    a. Bone Marrow Function
        i. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
        ii. Platelets > 100×10^9/L
        iii. Hemoglobin > 10 g/dL
    b. Hepatic Function
        i. AST and ALT ≤ 3 × ULN; if liver metastases, then ≤ 5 × ULN
        ii. Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome
        iii. Serum albumin ≥ 30 g/L (3.0 g/dL)
    c. Renal Function
        i. Serum creatinine ≤ 1.5 x ULN or estimated GFR ≥ 45 mL/min using the Cockcroft-Gault formula
4. Grade 3 and 4 hematologic and non-hematologic toxicities (except alopecia, nausea, vomiting, or adequately controlled diarrhea) have resolved to baseline or ≤ CTCAE Grade 1
5. Women of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to administration of the first dose of rucaparib in the crossover
6. Have an ECOG performance status of 0 or 1
7. Written consent on an IRB/IEC-approved ICF

In addition, any of the following will exclude patients from receiving rucaparib in the crossover part:

1. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment
    a. Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/ or bone marrow transplant > 2 years prior to first dose of study drug (non-melanoma skin cancer excepted)
2. Received treatment with chemotherapy, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs after discontinuation of study chemotherapy

3. Non study-related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of rucaparib in the crossover portion; in all cases, the patient must be sufficiently recovered and stable before treatment administration
4. Women who are pregnant or breastfeeding
5. Withdrawal of consent during treatment with the comparator arm chemotherapy
6. Presence of any other condition that may increase the risk associated with study participation and, in the opinion of the investigator, would make the patient inappropriate (including general noncompliance with study procedures during treatment with the comparator arm chemotherapy, per investigator judgement) for continuing in the study with crossover to rucaparib treatment

Randomization

Patients classified as having a deleterious BRCA1/2 mutation by central laboratory analysis or documented local results and confirmation of adequate tumor tissue availability for known BRCA1/2 mutant patients and confirmation of all other eligibility criteria in the screening phase, will be randomized 2:1 to receive rucaparib or chemotherapy. The following will be included as a randomization stratification factor at study entry to ensure treatment groups are balanced:

- Platinum resistant: patients who progressed ≥ 1 to < 6 months after the last dose of platinum-based chemotherapy;
- Partially platinum-sensitive: patients who progressed ≥ 6 to < 12 months after last dose of platinum-based chemotherapy; and
- Platinum sensitive: patients who progressed ≥ 12 months after last dose of platinum-based chemotherapy.

Patients with platinum-resistant or partially platinum-sensitive disease will be randomized 2:1 to receive rucaparib or weekly paclitaxel. Patients with platinum-sensitive disease will be randomized 2:1 to receive rucaparib or platinum-based chemotherapy. The investigator will select the appropriate platinum monotherapy (carboplatin or cisplatin) or platinum-based doublet chemotherapy (carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine). Prior to randomization, the Investigator must notify the Sponsor (or designee) which platinum chemotherapy a platinum-sensitive patient will receive if randomized to the chemotherapy arm.

Randomization will occur by a central randomization procedure using interactive response technology (IRT).

Study Treatment

The starting dose of rucaparib is 600 mg BID orally in 28-day cycles. Patients may take rucaparib with or without food. Each dose should be taken with at least 8 oz (240 mL) of water.

The starting dose of weekly paclitaxel is 60 to 80 mg/m^2 (dose per institutional standard of care) administered via IV infusion (ie, on Days 1, 8, and 15) in each 28-day cycle (with a week break from dosing on Day 22 in each cycle).

The dosage and administration of single-agent cisplatin or carboplatin or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine IV infusion will follow institutional guidelines for each agent.

Chemotherapy will be prepared and administered by study site personnel.

Treatment will continue until: a maximum of 8 cycles of platinum monotherapy or doublet therapy are administered to platinum-sensitive patients; disease progression by RECIST Version 1.1, per the investigator; unacceptable toxicity or inability to tolerate further treatment, as assessed by the investigator; pregnancy; death; loss to follow-up; withdrawal of consent; or other appropriate clinical reason. Eligible patients who were randomized to chemotherapy may cross over to rucaparib treatment following disease progression and Sponsor (or designee) approval.

Concomitant Medications

Premedication should be administered in accordance with standard of care associated with the comparator chemotherapy. Additional supportive care may be used at the investigator's discretion and in accordance with institutional procedures.

Withdrawal Criteria

A patient must be discontinued from protocol-prescribed therapy if <u>any</u> of the following apply:

- Consent withdrawal for any reason at the patient's own request or at the request of their legally authorized representative;
- Progression of patient's underlying cancer per RECIST Version 1.1 (unless, in the opinion of the investigator, the patient continues to derive clinical benefit; treatment beyond progression must be approved by the Sponsor);
- 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;
- Non-compliance by the patient with protocol-mandated procedures; or
- A positive pregnancy test at any time during the study.

Efficacy Assessments

Efficacy measures will include tumor assessments using computed tomography (CT) scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1, CA-125 measurement, and clinical examination; other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET], and ultrasound) may also be performed if required. Disease/ tumor assessments will be performed during screening, at the end of every 8 calendar weeks relative to Cycle 1 Day 1 (within 5 days before is permitted) until radiologically confirmed disease progression by RECIST Version 1.1, as assessed by the investigator, or death. Patients who cross over to treatment with rucaparib will have tumor assessments every 8 calendar weeks relative to Day 1 of initiating treatment with rucaparib. Tumor assessments should be performed at the time of treatment discontinuation if the reason was other than radiologically-confirmed disease progression and it has been $\geq$ 8 weeks since the last assessment. Patients who have

been on study at least 18 months will decrease the frequency of tumor assessments to every 16 weeks (within 5 days before is permitted). A CA-125 result < ULN will be required to designate a CR. Copies of CT scans (and other imaging, as appropriate) will be collected from all patients for BICR. BICR will review CT scans for a given patient in batches throughout the conduct of the study, but not necessarily in real-time. All treatment decisions will be made by the investigator based on local radiology results.

Safety Assessments

Safety and tolerability will be assessed based on the following:

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

Statistical Methods

Sample Size Justification

Approximately 345 patients will be randomized, with 230 patients randomized to rucaparib and 115 patients to chemotherapy.

The median PFS is assumed to be 12 months for rucaparib and 8 months for the comparator. Assuming an accrual over about 3 years; a dropout rate of 2%; with a hazard ratio of 0.65; and at least 275 events, a sample size of 345 patients (230 patients randomized to rucaparib and 115 patients randomized to chemotherapy) would yield at least 80% power at a two-sided 0.05 significance level.

Efficacy Analysis

The primary endpoint of invPFS will be analyzed using the stratified Cox proportional hazard methodology. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

All efficacy analyses will be performed for the Efficacy Population and the intent-to-treat (ITT) Population. The Efficacy Population consists of all randomized patients with a deleterious BRCA mutation, excluding those identified to have a BRCA reversion mutation, and the ITT Population consists of all randomized patients.

In order to preserve the overall Type 1 error rate, the primary endpoint will first be tested in the Efficacy Population. If the primary endpoint in the Efficacy Population is statistically significant, then the primary endpoint in the ITT Population will be tested. If the primary endpoint is significant for both populations, then the secondary efficacy endpoints will be tested, first in the Efficacy Population and then in the ITT Population in the order specified below for each endpoint. Statistical significance will only be declared for secondary endpoints if the primary endpoint and previous secondary endpoints are also statistically significant.

The key secondary endpoints and the testing order are listed below:

1. ORR by RECIST Version 1.1;
2. DOR by RECIST Version 1.1;
3. ORR by RECIST Version 1.1 and CA-125 response; and
4. PRO as assessed by the EORTC QLQ-C30 Global Health Status score.

Safety Analyses

Adverse events, clinical laboratory results, vital signs, ECOG performance status, body weight, and concomitant medications/ procedures will be tabulated and summarized. Adverse events will be summarized overall and separately for serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to death, and NCI CTCAE Version 4.0 Grade 3 or higher AEs. Body weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG performance status will be summarized categorically.

Independent Data Monitoring Committee (IDMC)

An IDMC will meet to review the efficacy and safety data from this study. The IDMC will review efficacy and safety of rucaparib versus chemotherapy to ensure the study remains beneficial to patients.

The IDMC may recommend that the study be stopped if the data indicate that the invPFS benefit will very likely not be achieved or there is excessive toxicity observed in the rates of serious and/or Grade 3 and 4 AEs. Details regarding the IDMC will be documented in a committee charter.

Date of Protocol Amendment 2 Approval

23 October 2020

TABLE OF CONTENTS

1 SYNOPSIS 5
2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 24
3 INTRODUCTION 28
3.1 Investigational Product 28
3.2 Background and Rationale for PARP Inhibition 28
3.3 Ovarian Cancer 29
3.3.1 Treatment of Ovarian Cancer 29
3.3.2 PARP Inhibitors in Ovarian Cancer 31
3.4 Prior Experience with Rucaparib 31
3.4.1 Nonclinical Experience with Rucaparib 31
3.4.2 Clinical Experience with Rucaparib 32
3.5 Rationale for this Study of Rucaparib 37
4 STUDY OBJECTIVES 38
4.1 Primary Objective 38
4.2 Secondary Objectives 38
4.3 Exploratory Objectives 38
5 INVESTIGATIONAL PLAN 40
5.1 Overall Study Design and Plan 40
5.1.1 Screening Phase 40
5.1.2 Assignment / Randomization 41
5.1.3 Treatment Phase 41
5.1.4 Post-treatment Phase 43
5.2 Study Schema 44
5.3 End of Study 46
5.4 Rationale for Study Design and Control Group 46
6 STUDY POPULATION SELECTION 48
6.1 Number of Patients and Sites 48
6.2 Inclusion Criteria 48
6.3 Exclusion Criteria 49
6.4 Criteria for Rucaparib Crossover Treatment Eligibility Following Radiological Progression on or after Comparator Arm Therapy 51
6.5 Patients or Partners of Patients of Reproductive Potential 52
6.6 Waivers of Inclusion/Exclusion Criteria 53
7 STUDY TREATMENT(S) 54
7.1 Description of Treatment(s) and Storage 54
7.1.1 Investigational Drug Product - Rucaparib 54
7.1.2 Chemotherapeutic Drug Products 54

7.2 Packaging and Labeling 54
7.2.1 Rucaparib 54
7.2.2 Chemotherapy 55
7.3 Blinding 55
7.4 Method of Assigning Patients to Treatment Groups 55
7.5 Preparation and Administration of Protocol-specified Treatment 56
7.5.1 Rucaparib 56
7.5.2 Single-agent Weekly Paclitaxel Preparation, Administration, and Restrictions 59
7.5.3 Single-agent Cisplatin and Carboplatin Preparation, Administration, and Restrictions 59
7.5.4 Platinum-based Doublet Chemotherapy Preparation, Administration, and Restrictions 60
7.5.5 Re-treatment and Dose Modification for All Chemotherapy 60
7.5.6 Treatment with Rucaparib beyond Progression 60
7.6 Treatment Compliance 61
7.6.1 Rucaparib Treatment Compliance 61
7.6.2 Chemotherapy Treatment Compliance 62
7.7 Accountability of Protocol-specified Treatment 62
7.8 Prior and Concomitant Therapy 62
7.8.1 Anticancer or Experimental Therapy 63
7.8.2 Hematopoietic Growth Factors and Blood Products 63
7.8.3 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates 63
7.8.4 Transporter Inhibitors, Inducers, and Substrates 63
7.8.5 Bisphosphonates 63
7.8.6 Anticoagulants 63
7.8.7 Other Concomitant Medications 64
8 STUDY PROCEDURES AND ACTIVITIES BY VISIT 65
8.1 Schedule of Assessments 65
8.2 Informed Consent 74
8.3 Initial Study Screening Prior to Randomization 74
8.3.1 Within 60 Days Prior to Randomization 74
8.3.2 Up to 28 Days Prior to Randomization 75
8.3.3 Up to 14 Days Prior to Randomization 76
8.3.4 Up to 3 Days Prior to First Dose of Study Drug 76
8.4 Treatment Phase (Day 1 to Day 28 per Cycle) 76
8.4.1 Day 1 of Every Cycle (Rucaparib and Chemotherapy Arms, Including Continuation of Rucaparib Treatment after Radiologic Disease Progression) 76

8.4.2 Days 8 and 15 of Every Cycle (Weekly Paclitaxel Arm) 78
8.4.3 Intra-Cycle (Single-agent Platinum or Doublet Chemotherapy of Investigator's Selection) 79
8.4.4 Day 15 of Cycles 1 and 2 (Rucaparib Arm) 80
8.5 Post-treatment Phase 80
8.5.1 Randomized Treatment Discontinuation 80
8.5.2 28-Day Safety Follow-up Visit (Randomized Treatment/ Cross Over to Rucaparib) 82
8.5.3 Long-term Follow-up (Randomized Treatment/Cross Over to Rucaparib) 83
8.6 Informed Consent for Patients Who Cross Over to Rucaparib after Disease Progression on Study Chemotherapy 84
8.7 Screening Prior to Cross Over to Rucaparib 84
8.7.1 Up to 14 Days Prior to the First Dose of Rucaparib for Crossover Patients: 84
8.7.2 Up to 3 Days Prior to First Dose of Rucaparib for Crossover Patients: 85
8.8 Treatment with Rucaparib in Patients Who Cross Over from Chemotherapy (Day 1 to Day 28 per Cycle) 85
8.8.1 Day 1 of Every Cycle (Crossover to Rucaparib) 85
8.8.2 Day 15 of Cycles 1 and 2 (Crossover to Rucaparib) 86
8.9 Post-treatment for Patients Who Cross Over to Rucaparib 87
8.9.1 Treatment Discontinuation for Patients Who Cross Over to Rucaparib 87
9 METHODS OF DATA COLLECTION 89
9.1 Medical History and Demographic/ Baseline Characteristics 89
9.2 Prior and Concomitant Medication Assessments 89
9.3 Efficacy Evaluations 89
9.3.1 Disease/ Tumor Assessments 89
9.3.2 Tumor Markers 90
9.4 Safety Evaluations 90
9.4.1 Adverse Event Assessment 90
9.4.2 Clinical Laboratory Investigations 90
9.4.3 Vital Signs 91
9.4.4 12-Lead Electrocardiogram 92
9.4.5 Body Weight and Height 92
9.4.6 Physical Examinations 92
9.4.7 ECOG Performance Status 92
9.5 Biomarker Analysis – FFPE Tumor Tissue 92
9.6 Biomarker Analysis – Blood 93
9.7 Pharmacokinetics Evaluation 93

9.8 Patient Reported Outcomes (Health and Quality of Life Questionnaires) 94
10 ADVERSE EVENT MANAGEMENT 95
10.1 Definition of an Adverse Event 95
10.2 Definition of a Serious Adverse Event 95
10.3 Definition of an Adverse Event of Special Interest 96
10.4 Events or Outcomes Not Qualifying as Serious Adverse Events 96
10.5 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events 96
10.6 Pregnancy or Drug Exposure during Pregnancy 97
10.7 Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest 97
10.7.1 Onset Date of Adverse Events 98
10.7.2 Resolution Date of Adverse Events 98
10.7.3 Intensity of Adverse Events 98
10.7.4 Causal Relationship of Adverse Events to Study Drug 98
10.7.5 Outcome and Action Taken 99
10.8 Follow-Up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest 100
10.9 Potential Drug-induced Liver Injury 100
10.10 Regulatory Aspects of Serious Adverse Event and Adverse Events of Special Interest Reporting 100
11 PLANNED STATISTICAL METHODS 102
11.1 General Considerations 102
11.2 Determination of Sample Size 102
11.3 Analysis Populations 103
11.4 Patient Disposition 103
11.5 Demographics and Baseline Characteristics 103
11.6 Efficacy Analyses 104
11.6.1 Primary Efficacy Analyses 104
11.6.2 Secondary Efficacy Analyses 104
11.6.3 Exploratory Efficacy Analyses 105
11.6.4 Exploratory Pharmacokinetic Analyses 106
11.7 Safety Analyses 106
11.7.1 Adverse Events 107
11.7.2 Clinical Laboratory Evaluations 108
11.7.3 Vital Sign Measurements 108
11.8 Interim Analysis 109
12 PATIENT DISPOSITION 110
12.1 Removal of Patients from the Study or Study Drug 110

13 STUDY ADMINISTRATION 111
13.1 Regulatory and Ethical Considerations 111
13.1.1 Regulatory Authority Approvals 111
13.1.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval 111
13.2 Patient Information and Consent 112
13.3 Patient Confidentiality 112
13.4 Study Monitoring 113
13.5 Case Report Forms and Study Data 113
13.6 Independent Data Monitoring Committee 114
13.7 Study Termination and Site Closure 114
13.8 Modification of the Study Protocol 115
13.9 Retention of Data 115
13.10 Quality Control and Assurance 116
13.10.1 Changes to the Protocol and Deviations 116
13.10.2 Study Site Training and Ongoing Monitoring 116
13.10.3 Direct Access to Source Data/ Documents for Audits and Inspections 117
13.11 Clinical Study Report 117
13.12 Publication and Disclosure Policy 117
13.13 Investigator Oversight 117
14 REFERENCE LIST 118
15 APPENDICES 123
15.1 Appendix 1 123
15.2 Appendix 2 128
15.3 Appendix 3 129
15.4 Appendix 4 130
15.5 Appendix 5 131

LIST OF IN-TEXT TABLES

Table 1. Treatments by Progression-free Interval after Most Recent Platinum 42
Table 2. Rucaparib Formulation and Storage 54
Table 3. Rucaparib Dose Reduction Steps.....59
Table 4. Schedule of Assessments for All Patients (Randomization to Therapy at Study Initiation) 66
Table 5. Schedule of Assessments for Patients Who Cross Over to Rucaparib After Being Randomized to and Receiving Chemotherapy 71

LIST OF IN-TEXT FIGURES

Figure 1. Study Schema 45

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ALCOA+	attributable, legible, contemporaneous, original or certified copy, accurate, and complete, consistent, enduring, and available
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BCRP	breast cancer resistance protein
BER	base excision repair
BICR	blinded independent central review
BID	twice a day
bp	base-pair
BRCA	breast cancer 1 or breast cancer 2
BRCA 1/2	breast cancer gene 1 or breast cancer gene 2
CI	confidence interval
CL	clearance
CL/F	apparent total clearance of drug after oral administration
cm	centimeter
C_{max}	maximum plasma concentration
CR	complete response
CRF	case report form
CRM	continual reassessment model
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating cell-free tumor DNA
CV	coefficient of variation
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose-limiting toxicities
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	concentration producing 50% of maximum effect

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
EORTC QLQ-OV28	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module OV28
EQ-5D	Euro-Quality of Life 5D
ESMO	European Society for Medical Oncology
F	bioavailability
FD & C	colorants that have been approved by the Food and Drug Administration for use in food, drugs and cosmetics
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FMI	Foundation Medicine, Inc.
gBRCA	germline breast cancer gene 1 or 2 mutation
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
H & E	hematoxylin and eosin
HDPE	high-density polyethylene
HPMC	hydroxypropyl methylcellulose
HGSOC	high-grade serous ovarian cancer
HNSTD	highest non-severely toxic dose
HPLC	high-performance liquid chromatography
hr	hour
HR	hazard ratio
HRD	homologous recombination deficiency
HRR	homologous recombination repair
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation
IRR	independent radiology review
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
K_i	inhibition constant
K_{ic}	inhibition constant competitive
LOH	loss of heterozygosity
LTFU	long-term follow-up

MATE	multidrug and toxin extrusion transporter
MDR1	multidrug resistance protein 1
MDS	myelodysplastic syndrome
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MS	mass spectrometry
MTD	maximum tolerated dose
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NCCN	National Comprehensive Cancer Network
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect-level
OAT	organic ion transporter
OCT	organic cation transporter
ORR	objective response rate
P_{app}	apparent permeability coefficient
PARPi	poly(ADP-ribose) polymerase inhibitor
PD	progressive disease (in context of disease monitoring)
PD	pharmacodynamic (in context of pharmacology discussion)
PDX	patient-derived xenograft
PEG	polyethylene glycol
PFS	progression-free survival
PFS2	the second event of PFS, in subsequent line of treatment
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PLD	pegylated liposomal doxorubicin
PO	orally
PR	partial response
PRO	patient-reported outcome
PV	pharmacovigilance
QD	once a day
RAD51C	RAD51 homolog C
RAD51D	RAD51 homolog D
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
sBRCA	somatic breast cancer gene 1 or 2 mutation

SD	stable disease (in context of disease monitoring)
SD	standard deviation (in context of biostatistics)
SOC	system organ class
$t_{1/2}$	terminal half-life
tBRCA	tumor tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA
TK	toxicokinetics
T_{max}	time of occurrence of C_{max}
TMZ	Temozolomide
UGT	uridine diphosphate-glucuronosyl transferase
UK	United Kingdom
ULN	upper limit of normal
US	United States
USAN	United States Adopted Name
USP	US Pharmacopeia
V_{ss}	volume of distribution at steady-state
WBC	white blood cell
wt	wild-type

3 INTRODUCTION

3.1 Investigational Product

Rucaparib (CO-338) is a small molecule inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) being developed for the treatment of ovarian cancer associated with homologous recombination deficiency (HRD). Rucaparib has been shown to potently inhibit PARP-1, PARP-2, and PARP-3 and has demonstrated activity in a background of breast cancer gene 1 and 2 (BRCA1 and BRCA2) mutations in both clinical and nonclinical studies.

Clovis Oncology, Inc. (Clovis) is developing rucaparib for oral administration in patients with relapsed ovarian cancer who have a BRCA mutation based on analysis of tumor tissue DNA. The therapeutic rationale for PARP inhibition with rucaparib in the presence of HRD is induction of synthetic lethality.

3.2 Background and Rationale for PARP Inhibition

Normal cells repair single-strand breaks in DNA primarily through base excision repair (BER). While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP-1 is the best characterized. Single-strand breaks that are not repaired result in stalled replication forks and the development of double-strand breaks, which are primarily repaired by homologous recombination repair (HRR) of DNA, a complex process involving multiple proteins, including those encoded by BRCA1 and BRCA2, as well as RAD51, Fanconi anemia core complex, ataxia telangiectasia mutated (ATM), and ataxia telangiectasia and RAD3-related (ATR) protein, among others.

Defects in the HRR pathway (ie, HRD), either as an initiating or late event in carcinogenesis, may be responsible for the genetic instability observed in many cancers. It has been estimated that approximately 50% of high-grade serous ovarian cancer (HGSOC) has alterations in the HRR pathway.[12] Germline mutations in the BRCA1 and BRCA2 genes (gBRCA1/2) are the strongest known hereditary factors for epithelial ovarian cancer (EOC), accounting for up to 15% of all EOC.[13, 14] Epithelial ovarian cancer patients carry heterozygous deleterious mutations in their germline DNA and develop tumors when the remaining wild-type functional allele is inactivated (ie, “second hit”). Approximately 6% to 8% of HGSOC patients have somatic mutations in BRCA1 or BRCA2 (sBRCA1/2).[12, 15] However, HRD is not limited to mutations of BRCA1/2. Approximately 27% of HGSOC patients have an alteration in an HRR gene other than BRCA1/2 or due to other molecular alteration or modification (eg, epigenetic silencing).

Inhibition of DNA damage repair in cancer cells, which are intrinsically genetically unstable, represents an attractive opportunity for therapeutic development. Given the overlap in various DNA repair pathways, inhibition of a single pathway is unlikely to have a significant effect. Inhibition of multiple DNA repair pathways in parallel, such as having a deleterious mutation in a critical BER gene in the presence of a PARP inhibitor, may lead to cell death, a concept known as synthetic lethality. Normal cells, with only one DNA repair pathway affected by inhibition of PARP, still have an intact DNA repair pathway that can compensate

for the defect. This concept of synthetic lethality has been demonstrated in key in vitro and in vivo studies, as well as in several clinical trials with PARP inhibitors.[16-21]

While up to 15% of patients may have a hereditary form of ovarian cancer (based on germline mutations), approximately 6% to 8% of HGSOC patients have sBRCA1/2 mutations.[12, 15] Both gBRCA1/2 and sBRCA1/2 mutations result in HRD, and patients whose tumors harbor these mutations derive clinical benefit from PARP inhibitor therapy.[22] Collectively, these mutations comprise a group known as tumor $BRCA^{mut}$ ($tBRCA^{mut}$). Patients without evidence of a gBRCA1/2 or sBRCA1/2 mutation also derive benefit from PARP inhibitor treatment.[22, 23] The molecular signature associated with PARP inhibitor response in a BRCA wild-type ($BRCA^{wt}$) setting is not yet fully understood, but may be linked to other mechanisms of HRD.

3.3 Ovarian Cancer

Globally, ovarian cancer is the eighth most common cancer and the seventh leading cause of cancer death among women, responsible for approximately 140,000 deaths each year.[1] Additionally, it is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer.[2, 3] Unfortunately because of delayed presentation and diagnosis, almost 75% of women with ovarian cancer are diagnosed with stage III/IV disease and 75% of women with advanced stage disease ultimately relapse or die from their disease despite treatment.[1]

After initial therapy, most women will have a progression-free interval of approximately 1.5 to 2 years, depending on the extent of post-operative residual disease and response to chemotherapy.[24] Relapse still occurs; however, in the majority of cases, and only 10% to 30% of women experience long-term survival.[24] Advanced stage disease is associated with a 5 year survival rate of only 30% to 40%.[2]

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.[24] The site of origin of EOC remains unclear. Some studies suggest that serous EOC and primary peritoneal cancer (PPC) arise from the fallopian tube epithelium; however, other studies suggest an origin within stem cells of the ovarian surface epithelium.[24-28] EOC, PPC and fallopian tube cancer behave very similarly and are therefore treated in the same way.

The median age at presentation of EOC is 60 years. Due to the non-specific nature of symptoms, many women present with advanced disease and therefore have a poor prognosis.

3.3.1 Treatment of Ovarian Cancer

The standard approach to treatment of advanced HGSOC is cytoreductive surgery (either at time of diagnosis or interval debulking), with the goal of minimizing residual tumor to no visible residual disease, a major prognostic indicator for improved survival. Six to 8 cycles of platinum- and taxane-based chemotherapy is the global standard of care. If initial cytoreduction is not performed, interval debulking surgery is considered. This surgery may

be carried out after 3 or 4 cycles of primary chemotherapy, followed by 3 further cycles of chemotherapy. Platinum analogues, such as carboplatin and cisplatin, are the most active agents, mediating their effects through the formation of inter- and intra-strand cross-links with DNA.[24, 29]

Despite a 70-80% initial response rate, most women have disease relapse.[3-5] 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.[30] 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. However, 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 (ie, HRD such as BRCA1/2 mutations) and thus are used as a guide to define platinum status in this study.

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.[3-5] Patients with platinum-resistant disease receive single-agent treatment with pegylated liposomal doxorubicin (PLD), topotecan, gemcitabine, or weekly paclitaxel, or a combination of bevacizumab and chemotherapy (paclitaxel, PLD, or topotecan).[31-33] However, these agents have limited utility due to poor efficacy (objective response rates ranging 20-30% with median progression-free survival [PFS] < 6 months) and significant toxicities. 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).

As many patients experience multiple relapses, prognosis and response to therapy decreases as the interval between last chemotherapy exposure and disease relapse shortens. The treatment-free, or specifically the platinum-free interval, provides further prognostic information for patients, as therapeutic options lessen and survival shortens as a patient's tumor becomes less responsive to repeated courses of platinum-based therapy. Patients who have received several prior lines of treatment are known to have strongly diminished treatment-free intervals and response rates and the benefits of continued treatment with conventional chemotherapy often does not outweigh the risk of hypersensitivity and additional, intolerable toxicity. This patient population is a group with limited treatment options, so the development of therapies that offer improved benefit-risk is critically needed that could benefit from treatment with a targeted agent that takes the molecular characteristics of their disease into account.[34, 35]

3.3.2 PARP Inhibitors in Ovarian Cancer

Refer to current Investigator's Brochure for comprehensive information on PARP inhibitors.

PARP inhibitors have demonstrated clinical activity in patients with BRCA1/2-mutant tumors, and have emerged as a new treatment option for relapsed ovarian cancer. In the United States (US), olaparib was approved 19 December 2014 for treatment of patients with gBRCA1/2 ovarian cancer who had received ≥ 3 prior chemotherapy regimens (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf) based on results of a Phase 2 study.[36] Rucaparib was subsequently approved in the US for use in women with a BRCA mutation (germline or somatic) who had received at least 2 prior chemotherapy regimens, based on a response rate of 54%.

PARP inhibitor maintenance therapy has also been established as an effective strategy for improving outcomes in recurrent, second-line and beyond, platinum-sensitive ovarian cancer. As of January 2019, rucaparib, niraparib, and olaparib were all approved as second-line switch maintenance therapies for ovarian cancer patients in the US[37-39] and Europe.[40-42] Three randomized, double-blind studies demonstrated statistically significant improvements in median progression-free survival (PFS) as compared to placebo in the ITT Population regardless of BRCA1/2 mutation or HRD status (Study 19, NOVA, and ARIEL3).[43-45] Study 19 was the first study to show that the outcomes of somatic BRCA (sBRCA)-mutant + gBRCA-mutant patients were the same as gBRCA-mutant patients alone, suggesting that it is appropriate to not differentiate between germline and somatic mutations. These switch maintenance studies also demonstrated statistically significant benefit in the overall unselected patient population. Recently, olaparib[38, 41] and niraparib[39, 42] were also approved as front-line switch maintenance for ovarian cancer patients in US and Europe.

In the European Union (EU), olaparib is approved as maintenance treatment following a response to platinum-based chemotherapy in patients with BRCA1/2-mutant (germline or somatic) relapsed ovarian cancer who received at least 2 prior platinum-based regimens. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003726/human_med_001831.jsp&mid=WC0b01ac058001d124). Olaparib has also demonstrated clinical activity in patients without a BRCA1/2 mutation[21, 46, 47]; however, the molecular signature associated with olaparib response in those trials was not fully understood.

3.4 Prior Experience with Rucaparib

Refer to the current Investigator's Brochure for comprehensive nonclinical and clinical information for rucaparib.

3.4.1 Nonclinical Experience with Rucaparib

The results from nonclinical studies are consistent with the anticipated mechanism of action and pharmacological effects of PARP inhibition. Further information can be found in the rucaparib IB.

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 enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and dogs. Rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UDP-glucuronosyltransferase 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1), and may inhibit P-gp and BCRP in the gut.

Oral dosing of rucaparib in single and repeat dose toxicity studies in rats and dogs resulted in toxicity to the hematopoietic, lymphopoietic, and gastrointestinal (GI) 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.[48-51]

3.4.2 Clinical Experience with Rucaparib

Information regarding clinical studies with rucaparib is available in the current Investigator's Brochure.

Rucaparib is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer who have evidence of HRD. Rucaparib clinical studies have/are evaluating patients with relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer in both the treatment and maintenance settings.

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

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

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

Additional information on the clinical studies is provided in the rucaparib IB.

3.4.2.1 Overview of Pharmacokinetics and Drug-Drug Interactions

Assessment of rucaparib PK in cancer patients showed an approximate dose proportional exposure after once a day (QD) or twice a day (BID) dosing, rapid absorption with maximum plasma 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.

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 AUC_{0-24h} of rucaparib by 20% and 38%, respectively, as compared with that under fasted conditions.

In vitro, CYP enzymes were shown to contribute to rucaparib metabolism. In a preliminary assessment of rucaparib metabolism in patients, rucaparib biotransformation pathways included hydroxylation or oxidation, N-demethylation, deamination, and phase II methylation. A carboxylic acid metabolite (M324) and a phase II N-methylated metabolite of M324 (M338) were identified as major metabolites.

Drug interactions with rucaparib as a substrate were assessed in a population PK (Pop PK) analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultra-rapid 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 CYP1A2 or CYP2D6 inhibitors.

No clinically significant effect of concomitant administration of strong P-gp inhibitors on rucaparib PK was observed. Concomitant treatment with proton pump inhibitors did not show clinically significant effect on rucaparib PK. No dose modification is recommended based on concomitant use of P-gp inhibitors or PPIs.

In a “cocktail” DDI study (CO-338-044), the effects of steady-state rucaparib at 600 mg BID on CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp were evaluated with single oral doses of sensitive probes (caffeine [CYP1A2], S-warfarin [CYP2C9], omeprazole [CYP2C19], midazolam [CYP3A4], and digoxin [P-gp], respectively). Data suggest that rucaparib is a moderate inhibitor of CYP1A2, a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Rucaparib also marginally inhibits P-gp, and the effect is unlikely to be clinically significant.

In another DDI study (Study CO-338-095) in cancer patients, effects of rucaparib on oral rosuvastatin as BCRP substrate and oral contraceptives were determined following 14 days of dosing at 600 mg BID. Rucaparib weakly inhibited BCRP and caused mild increases in plasma exposures to ethinylestradiol and levonorgestrel.

In Study CO-338-078, PK of a single-dose rucaparib was compared between cancer patients with normal hepatic function and moderate hepatic impairment. Patients with moderate hepatic impairment showed an approximately 46% increase in area under the concentration-time curve from 0 to infinity ($AUC_{0\text{-}inf}$) without apparent change in C_{max}.

Details of these clinical DDI studies are provided in the rucaparib IB.

3.4.2.2 Overview of Efficacy

Evaluation of rucaparib efficacy has largely focused on patients with advanced ovarian cancer in both the treatment and maintenance settings. A summary of efficacy data from two fully-enrolled, ongoing single-arm Phase 2 studies (Study CO-338-010 Part 2A; Study CO-338-017 Parts 1 and 2) evaluating rucaparib efficacy in the treatment setting of ovarian cancer, and from one fully-enrolled, ongoing Phase 3 study (Study CO-338-014) evaluating rucaparib efficacy compared to placebo in the maintenance setting of ovarian cancer is provided below.

Additional efficacy data for rucaparib in ovarian cancer, in other tumors, and in combination with chemotherapy (completed studies in early development) are provided in the rucaparib IB.

In both the treatment and maintenance setting of advanced ovarian cancer, rucaparib administered at the starting dose of 600 mg BID demonstrated robust clinical activity.

Ovarian Cancer Treatment Indication

On 19 December 2016, FDA granted accelerated approval for the marketing of rucaparib (Rubraca®) for monotherapy treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥ 2 chemotherapies. The recommended dose of rucaparib is 600 mg BID.

The basis for the approval of rucaparib as monotherapy for the treatment of ovarian cancer are the datasets and analyses for patients with EOC, FTC, or PPC comprising the primary efficacy analysis population. The primary efficacy analysis population included 106 patients pooled from the open-label, single-arm Phase 2 studies, Study CO-338-010 (Study 10) Part 2A and Study CO-338-017 (ARIEL2) Parts 1 and 2, with BRCA-mutant ovarian cancer [EOC, FTC, or PPC], who had received ≥ 2 prior chemotherapy regimens, at least 2 of which were platinum-based, and who had received at least 1 dose of 600 mg rucaparib.[6]

The primary outcome measure on which approval was based is investigator-assessed ORR per RECIST v1.1, with ORR by central independent radiological review (IRR) conducted as a supportive analysis. ORR by investigator was 53.8%, while ORR IRR was 41.5%, confirming the results of investigator assessment for this endpoint.[52] Responses were durable,

indicated by a duration of response (DOR) by investigator assessment of approximately 9.2 months.

Ovarian Cancer in the Maintenance Setting

In the maintenance setting of rucaparib monotherapy for treatment of patients with EOC, FTC, or PPC, the results of Study CO-338-014 (ARIEL3) clearly demonstrate that rucaparib offers significant benefit compared to placebo. For the primary endpoint of investigator-assessed (invPFS), the median PFS was significantly prolonged by rucaparib compared to placebo; a result demonstrated across the tBRCA, HRD (tBRCA + non-tBRCA LOH^{high}), and ITT populations ($p < 0.0001$ for each population). [53] The median invPFS for the 3 analysis populations ranged from 10.8 months to 16.6 months following rucaparib treatment and was consistently 5.4 months for the placebo group, regardless of the population analyzed, with a hazard ratio (HR) = 0.231 for the tBRCA subpopulation ($p < 0.0001$), HR = 0.317 for the HRD subpopulation ($p < 0.0001$), and HR = 0.365 for the ITT population ($p < 0.0001$). The benefit of rucaparib in terms of tumor response was observed early in treatment. The invPFS results were confirmed by a key, stand-alone secondary endpoint analysis of PFS assessed by blinded independent central review (BICR; bicrPFS); each population receiving rucaparib had a statistically significant prolonged median bicrPFS compared to placebo.

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

Results of the exploratory endpoint of ORR, along with that of invPFS in the non-nested populations, support the clinically meaningful impact of delaying disease recurrence in women with advanced ovarian cancer, and show a further response to rucaparib treatment in patients with measurable disease.

3.4.2.3 Overview of Safety

Consistent with the efficacy evaluation of rucaparib, evaluation of rucaparib safety has largely focused on patients with advanced ovarian cancer in both the treatment and maintenance settings. A summary of safety data from 2 fully-enrolled, ongoing single-arm Phase 1/2 studies (Study CO-338-010 Part 2A and Part 2B; Study CO-338-017 Part 1 and Part 2) evaluating rucaparib safety in the treatment setting of ovarian cancer, and from one fully-enrolled, ongoing Phase 3 study (Study CO-338-014) evaluating rucaparib efficacy compared to placebo in the maintenance setting of ovarian cancer is provided below. Additional safety data for rucaparib in ovarian cancer, in other tumors, and in combination with chemotherapy (completed studies in early development) are provided in the rucaparib IB.

The safety profile of rucaparib is similar in ovarian cancer patients treated with rucaparib in either the treatment or maintenance setting.

Integrated Safety Analysis in Ovarian Cancer

The most recent integrated safety information for the treatment indication is provided in the rucaparib IB. Pooled safety data are provided as of the 01 September 2017 cut-off date for the ongoing Studies CO-338-010 (Parts 2A and 2B) and CO-338-017 (ARIEL2; Parts 1 and 2), in which 545 patients with relapsed ovarian cancer received 600 mg BID rucaparib. Safety data in the maintenance setting are provided as of the 15 April 2017 cut-off date for Study CO-338-014 (ARIEL3), in which a total of 561 patients have been treated (372 patients in the rucaparib group and 189 patients in the placebo group).

Patients with ovarian cancer who received 600 mg BID rucaparib in treatment setting as well as in the maintenance setting), the most common 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 ANC, and asthenia/fatigue.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin (and associated increase in mean corpuscular volume and mean corpuscular hemoglobin), increased ALT, increased AST, and increased serum creatinine, being most common. Decreased platelets, neutrophils, leukocytes, lymphocytes and increased cholesterol were observed to a lesser extent. The reported elevations in ALT/AST with rucaparib treatment in either the treatment or maintenance settings were not associated with any events of drug-induced liver injury (DILI).

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

Photosensitivity was initially reported in the Phase 1 dose-escalation part of Study CO-338-010 (n=6; 10.7%) and based on these reports of photosensitivity, guidance for sun protection was included in rucaparib clinical studies. In the recent integrated safety analysis from 917 patients treated with rucaparib in either placebo-controlled Study CO-338-014 (ARIEL3) and two open-label, single-arm trials (Studies CO-338-010 and CO-338-017 [ARIEL2]), 118 patients (12.9%]) experienced All Grade photosensitivity and 2 patients (0.2%) experienced ≥ Grade 3 (Clovis, data on file). Patients should use typical precautions when going outside, such as applying sunscreen (sun protection factor 50 or greater) and/or covering exposed skin with clothing and wearing a hat and sunglasses.

3.4.2.4 Adverse Events of Special Interest

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESI), as these events have been observed in patients exposed to cytotoxic chemotherapy (eg, platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib.

Exposure to DNA-damaging therapies for ovarian and breast cancer present an increased risk of developing MDS or AML.[54] In addition, the patients who have developed MDS and AML have/had significant confounding risk factors, including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation presenting a higher risk of developing one or more malignancy(ies).[54, 55] Based upon the above confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib.

Adverse events (AEs) of pneumonitis have been reported with PARP inhibitor treatment, including in clinical trials evaluating rucaparib. Currently, however, there is a lack of understanding of a mechanistic link between pneumonitis and PARP inhibitor treatment, and causality assessment is often confounded by lack of a consistent clinical pattern as well as other pre-disposing factors, such as cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy. Clovis is seeking to understand whether or not there is a relationship between pneumonitis and rucaparib treatment; thus, Clovis is designating pneumonitis as an AESI to gather data to enable a thorough evaluation and assessment of the event and associated terms specified in Section 10.7.

More information on AESIs is provided in the rucaparib IB.

3.5 Rationale for this Study of Rucaparib

PARPi, including rucaparib, have demonstrated consistent robust clinical activity in patients with deleterious BRCA1/2-mutant tumors, including in patients with relapsed deleterious BRCA1/2-mutant (germline or somatic) ovarian cancer. Clinical activity of PARPi versus standard of care chemotherapy has not yet been extensively evaluated in prospective trials enrolling only patients with known deleterious BRCA1/2 mutant tumors (germline or somatic). Assessment of chemotherapy response in patients with BRCA1/2 mutant tumors has been primarily examined in small retrospective analyses.

The primary purpose of this Phase 3 study is to compare the efficacy and safety of rucaparib versus chemotherapy as treatment for relapsed ovarian cancer patients with deleterious BRCA1/2 mutation in their tumor.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is:

- To determine investigator-assessed progression-free survival (invPFS) by RECIST Version 1.1 of rucaparib versus chemotherapy.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate PFS by RECIST Version 1.1, as assessed by BICR (bicrPFS)
- To compare efficacy of rucaparib versus chemotherapy as measured by overall survival (OS)
- To compare efficacy of rucaparib versus chemotherapy as measured by ORR using RECIST Version 1.1 by investigator assessment
- To compare efficacy of rucaparib versus chemotherapy as measured by DOR by investigator assessment
- To compare efficacy of rucaparib versus chemotherapy as measured by ORR using RECIST Version 1.1 by investigator assessment and Gynecologic Cancer InterGroup (GCIG) cancer antigen-125 (CA-125) response criteria
- To evaluate patient-reported outcome (PRO) for rucaparib versus chemotherapy as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and ovarian cancer module QLQ-OV28
- To evaluate the safety and tolerability of rucaparib versus chemotherapy.

4.3 Exploratory Objectives

Exploratory objectives in this study are:

- To evaluate the second event of PFS, in subsequent line of treatment (PFS2), both by investigator assessment
- To evaluate disease control rate (RECIST Version 1.1 CR, PR, and prolonged SD $\geq$ 12 weeks, by investigator assessment)
- To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D)
- To assess molecular changes in tumor samples over time in matched pairs

- To assess circulating cell-free tumor DNA (ctDNA) as a molecular marker of efficacy
- To evaluate the impact of gene expression molecular subgroups on PFS and OS
- To assess efficacy in BRCA-mutation subgroups (ie, germline/somatic and BRCA1/BRCA2)
- To characterize steady-state trough concentrations of rucaparib
- To explore the relationship between rucaparib exposure and responses (safety and efficacy)

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

This is a Phase 3 multicenter, randomized study evaluating rucaparib versus chemotherapy for treatment of relapsed, high-grade epithelial serous or Grade 2 or 3 endometrioid ovarian, fallopian tube, or primary peritoneal cancer. The study will enroll patients with a deleterious BRCA1/2 mutation in their tumor. All patients will be required to have received at least 2 prior chemotherapy regimens, with at least one that includes a platinum. Patients with platinum-refractory disease (ie, progression during or within 4 weeks after last dose of the most recent platinum-based therapy) and patients who have received prior PARPi treatment will be excluded.

5.1.1 Screening Phase

All patients will undergo screening assessments within 60 days prior to randomization. Informed consent may be completed outside the 60-day screening window as informed consent does not expire, except as required by applicable regulatory requirements, or if withdrawn by the patient.

All patients, with the exception of those known to harbor a deleterious BRCA1/2 mutation (germline or somatic), will be required to provide archival tumor tissue or a screening biopsy for central laboratory analysis prior to enrollment. Patients with a known deleterious BRCA1/2 mutation (germline or somatic) must also submit archival tumor tissue for central laboratory testing; however, enrollment is not contingent upon the central laboratory analysis of tissue. A local BRCA1/2 mutation result from previous testing will be adequate for enrollment. Patients with a deleterious BRCA1/2 mutation who meet all other entry criteria will be eligible for the study. If archival tumor tissue is not available, the patient may undergo a screening biopsy.

Tumor analysis will be performed using a next-generation sequencing (NGS) test by Foundation Medicine Inc (FMI). Results of the FMI panel test will be provided to patients who consent to receive this information. In the event a BRCA1/2 is identified in tumor tissue, the patient may be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline testing, this result will be entered in the clinical trial database for this study.

Additional screening assessments will include demographics and medical history, prior treatments for serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (and other malignancies, if applicable), prior and current medications and procedures, 12-lead ECG, ECOG performance status, local laboratory hematology, serum chemistry, and CA-125 measurement, serum pregnancy (for women of childbearing potential only), urinalysis, physical examination, height, weight, and vital signs measurements, blood samples for ctDNA and genomic analyses, adverse events, and radiologic assessment by computed tomography (CT) or magnetic resonance imaging (MRI). Patient-reported outcomes (PRO) will be collected using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate.

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

- local BRCA1/2 test result if patient has previously been tested;
- number of prior chemotherapy regimens, including treatment-free interval after first platinum-containing regimen and progression-free interval after most recent platinum-containing regimen;
- if known deleterious BRCA1/2 mutation (germline or somatic), confirmation that a sufficient quantity of tumor tissue is available and will be submitted to the central laboratory.

5.1.2 Assignment / Randomization

Patients classified as having a deleterious BRCA1/2 mutation by FMI (central laboratory) analysis or documented local results for deleterious germline or somatic BRCA1/2 mutation, with confirmation of adequate tumor tissue availability for known deleterious BRCA1/2 mutant patients, and confirmation of all other eligibility criteria in the screening phase, patients will be randomized 2:1 to receive rucaparib or chemotherapy. Randomization will occur by a central randomization procedure using interactive response technology (IRT), which is described in more detail in Section 7.4. Study treatment must be initiated within 3 days after randomization.

5.1.3 Treatment Phase

During the treatment phase (continuous 28-day treatment cycles), patients will receive rucaparib or chemotherapy and be monitored for safety and efficacy. Patients randomized to chemotherapy will receive treatment based upon the progression-free interval after their most recent platinum therapy and also Investigator selection for platinum-sensitive patients. Treatments available to patients by progression-free interval after most recent platinum are displayed in Table 1.

Table 1. Treatments by Progression-free Interval after Most Recent Platinum

Progression-free Interval after Most Recent Platinum	Treatments		
	Rucaparib	**or**	**Chemotherapy**
Platinum-resistant (≥ 1 to < 6 months)	Rucaparib	or	Weekly paclitaxel
Partially platinum-sensitive (≥ 6 to < 12 months)	Rucaparib	or	Weekly paclitaxel
Platinum-sensitive (≥ 12 months)	Rucaparib	or	Platinum-based chemotherapy per investigator choice of the following[a]: • Monotherapy cisplatin; • Monotherapy carboplatin; • Carboplatin and paclitaxel; • Carboplatin and gemcitabine; or • Cisplatin and gemcitabine

Abbreviations: ESMO = European Society for Medical Oncology; NCCN = National Comprehensive Cancer Network.

[a] Chemotherapy listed for platinum-sensitive patients is based on NCCN and ESMO guidelines.[8, 10]

Rucaparib will be administered as 600 mg BID. Weekly paclitaxel 60 to 80 mg/m^2 (dose per institutional standard of care), will be administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle (with a week break from dosing on Day 22 in each cycle). The dose and administration of monotherapy cisplatin or carboplatin or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine infusion will follow institutional guidelines for each agent. No more than 8 cycles of platinum monotherapy or doublet therapy are to be administered in this study. Patients will receive the same chemotherapy in 21-day or 28-day cycles, as appropriate, throughout the study.

Assessments and procedures during the study will include AEs; physical examinations; vital signs, 12-lead ECGs, and weight measurements; local laboratory hematology, serum chemistry, and CA-125 measurements; serum pregnancy for women of childbearing potential; blood samples for ctDNA and genomic analyses; plasma samples for PK analysis; concomitant medications, therapies, and procedures; disease/ tumor assessment; study drug administration and accountability; and PRO. During treatment, urinalysis will be performed as clinically indicated.

Patients will be assessed for disease status per RECIST Version 1.1 at baseline (screening), at the end of every 8 calendar weeks relative to Cycle 1 Day 1 (within 5 days before is

permitted) until radiologically confirmed disease progression by RECIST Version 1.1, as assessed by the investigator, or death. Tumor assessments should be performed at the time of treatment discontinuation if the reason was other than radiologically-confirmed disease progression or it has been ≥ 8 weeks since the last assessment. Patients experiencing disease progression by RECIST Version 1.1, as assessed by the investigator, will be discontinued from treatment and enter follow-up, unless a patient on rucaparib is still receiving benefit and, jointly, the investigator and Sponsor agree with continued rucaparib treatment. Patients initially receiving chemotherapy have the option to cross over to rucaparib treatment. Patients with rising CA-125 should not be discontinued based on this result alone, but should have a radiologic assessment and be assessed for disease progression by RECIST Version 1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST Version 1.1 per the protocol schedule of assessments. Patients who have been on study at least 18 months will decrease the frequency of tumor assessments to every 16 weeks (within 5 days before is permitted). All CT scans (and other imaging, as appropriate) performed at baseline, during the treatment period, and at treatment discontinuation will be collected for bicrPFS, which will constitute a supportive analysis. BICR will review CT scans for a given patient in batches throughout the conduct of the study, but not necessarily in real-time. All treatment decisions will be made by the investigator based on local radiology results.

Patients will be continuously monitored for safety and efficacy. An Independent Data Monitoring Committee (IDMC) with multidisciplinary representation will evaluate safety and efficacy data in compliance with a prospective charter. The IDMC will have access to study data including treatment assignments.

Patients randomized to chemotherapy have the option to cross over to receive rucaparib upon radiological progression per RECIST Version 1.1, provided that disease progression is confirmed with supporting documentation and approval is obtained from the Sponsor (or designee). If clinical progression is diagnosed, then confirmation of disease progression by radiologic assessment per RECIST Version 1.1 is required along with Sponsor (or designee) approval of the radiology report confirming disease progression before a patient is considered eligible to cross over to rucaparib.

If a patient randomized to rucaparib has radiologic progression, but continues to derive clinical benefit per the investigator, then continuation of rucaparib treatment beyond progression will be permitted. In such cases, the documented decision to continue will be made jointly between the investigator and the Sponsor (or designee), it must be documented in the patient's chart, and the patient must provide consent within a reasonable timeframe of the documented decision to continue treatment with rucaparib. Patients will continue to have all protocol-required assessments specified in Table 4.

5.1.4 Post-treatment Phase

Upon treatment discontinuation, patients will have a treatment discontinuation visit. The following assessments will be performed at the discontinuation of treatment to the extent possible: PRO; ECOG performance status; concomitant medications and procedures; 12-lead ECG; physical examination; vital signs and weight measurements; hematology and serum

chemistry; serum pregnancy for women of childbearing potential; blood samples for ctDNA and genomic analyses; CA-125 measurement; disease/ tumor assessment; study drug accountability; and AE monitoring. Concomitant medications and procedures, AE monitoring, and PRO will also be collected following the last dose of study drug at the 28 (± 3) days Safety Follow-up Visit. Ongoing serious adverse events (SAEs), AEs of special interest (AESIs), and treatment-related Grade 3/4 AEs will be followed until either resolution or stabilization has been determined or until lost to follow-up. An optional tumor biopsy will be collected from patients who experience disease progression/discontinue treatment and provide appropriate consent. The Sponsor (or designee) should be notified of all study terminations as soon as possible. The date and reason for cessation of study drug must be documented in the electronic case report form (eCRF) and source documents.

After the 28-day Safety Follow-up Visit, only SAEs considered as potentially related to study drug should be reported per Clovis Pharmacovigilance (PV) requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or similar events (ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia), if considered to be related to study drug.

After the 28-day Follow-up Visit, AESIs of MDS and AML, irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or similar events should only be reported up to, but not beyond, the 28-Day Follow-up Visit (28 days after the last dose of rucaparib).

Disease/ tumor assessment will continue (using the same methodology as was used at initial study screening [eg, CT scan]) if reason for treatment discontinuation was other than death or disease progression based on radiologic assessment. Disease/ tumor assessments should continue to be performed every 8 calendar weeks (within 5 days before is permitted) relative to Cycle 1 Day 1 until radiologic disease progression by RECIST Version 1.1, as assessed by the investigator, death, loss to follow-up, withdrawal, study closure, or initiation of subsequent treatment. PRO assessments should also be collected at every cycle for all patients through disease progression in association with the radiologic assessments for disease progression.

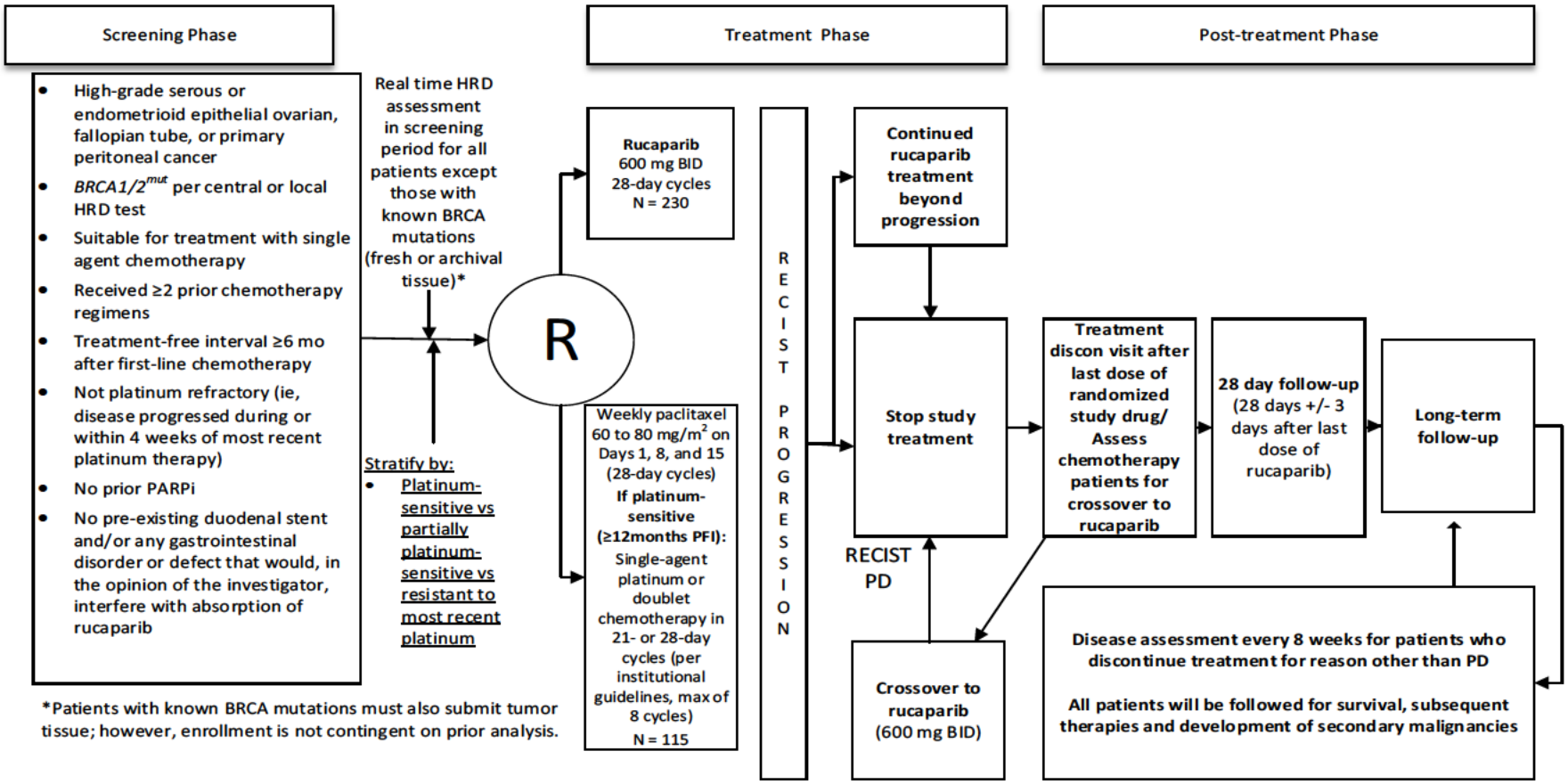
All patients will be followed for survival, subsequent treatments, and monitoring for secondary malignancy every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent, or study closure.

If a patient begins subsequent anti-cancer therapy, the Sponsor will terminate collection of SAEs, with the exception of AESIs MDS and AML.

5.2 Study Schema

The study schema is provided in Figure 1.

Figure 1. Study Schema



Abbreviations: BID = twice a day; BRCA = breast cancer gene; HRD = homologous recombination deficiency; PARPi = poly(ADP-ribose) polymerase inhibitor; PD = progressive disease; PFI = progression-free interval; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors.

5.3 End of Study

The study is monitored on an ongoing basis by an IDMC for the number of PFS events required for the primary endpoint and for safety signals. Upon formal closure of the study, individual patients who are continuing to benefit from treatment with rucaparib at the time of study closure, and who do not meet any of the criteria for withdrawal, will have the option of receiving rucaparib via another access mechanism. In addition, individuals who are continuing in long-term follow-up (LTFU) may transition to have their LTFU and scans, if applicable, captured via another mechanism.

The Sponsor may discontinue the study early for any reason as noted in Section 13.7.

5.4 Rationale for Study Design and Control Group

This study will evaluate the efficacy and safety of rucaparib versus chemotherapy as treatment for relapsed high-grade serous or endometrioid ovarian cancer in patients who have received two or more prior lines of chemotherapy and have evidence of HRD. There is unmet need in the third-line treatment setting for a therapy that provides benefit and does not add to the cumulative toxicity of prior chemotherapy regimens.

This study will directly compare the PFS of treatment with rucaparib versus chemotherapy in patients with a deleterious BRCA1/2 mutation. Patients with platinum-resistant disease (ie, progressed ≥ 1 to < 6 months after the last dose of platinum) or with partially platinum-sensitive disease (ie, progressed ≥ 6 to < 12 months after the last dose of platinum) will be randomized 2:1 to receive either rucaparib or weekly paclitaxel. Patients with platinum-sensitive disease (ie, progressed ≥ 12 months after the last dose of platinum) will be randomized 2:1 to receive either rucaparib or platinum-based chemotherapy. The choice of platinum-based chemotherapy will be per Investigator's discretion; options include monotherapy (carboplatin or cisplatin) or combination therapy (carboplatin and paclitaxel, carboplatin and gemcitabine, or cisplatin and gemcitabine). These chemotherapy options are among the recommended standard-of-care treatments (per National Comprehensive Cancer Network [NCCN] and European Society for Medical Oncology [ESMO] guidelines) for patients with relapsed, platinum-sensitive ovarian cancer.[8, 10]

A 2:1 randomization to receive either rucaparib or chemotherapy will allow for statistical comparison of PFS, OS, and ORR between the treatment arms and provide access to rucaparib for a larger number of patients who would otherwise receive standard chemotherapy. Stratification by progression-free interval after most recent platinum-containing therapy will occur upon study entry to maintain balance between treatment groups.

The study drug is open label. Blinding of the Investigators and patients is not possible because rucaparib is a tablet taken orally and chemotherapy in this study will be administered via IV infusion. Additionally, the dosing regimens differ, making it impossible to blind the patients to treatment. Rucaparib will be administered as 600 mg BID based upon supportive Phase 1/2 clinical efficacy and safety. Paclitaxel will be administered as 60 to 80 mg/m^2 (dose per institutional standard of care) on Days 1, 8, and 15 of a 28-day cycle (with a week

break from dosing on Day 22 in each cycle) via IV infusion. This regimen of paclitaxel was selected instead of the conventional 3-weekly schedule as studies have shown that weekly administration provides clinical benefit similar to the 3-weekly schedule and causes less neutropenia and peripheral neuropathy.[56-61] Other single-agent and doublet chemotherapy dosage and administration will follow institutional guidelines/Prescribing Information for each agent in 28-day cycles.

There is limited data regarding the activity of weekly paclitaxel in patients with BRCA1/2 mutated ovarian cancer, but the data that are available support the use of this schedule of paclitaxel in this patient population. A retrospective study has shown that single-agent paclitaxel is active in patients with relapsed ovarian cancer harboring a deleterious BRCA1/2 mutation, with ORRs of 60% and 27%, in platinum-sensitive and platinum-resistant disease, respectively. Notably, of the platinum-sensitive patients who received single-agent paclitaxel (15/26), the ORR observed with weekly paclitaxel (60%) was identical to the ORR (60%) observed with standard 3-weekly paclitaxel.[57] In addition, a study conducted by Ang et al, demonstrated a 50% (5/10) RECIST ORR in heavily pretreated patients with BRCA1/2 mutations who had been treated with olaparib and subsequently re-challenged with weekly paclitaxel.[62]

Overall, the chemotherapy agents that were selected as comparators for this study have demonstrated activity in advanced ovarian cancer. Weekly paclitaxel has robust clinical activity, a favorable safety profile, and is recommended by NCCN and ESMO guidelines for the treatment of relapsed ovarian cancer.[8-10] Cisplatin and carboplatin are effective single-agent therapies as well as in combination (doublet therapy) with paclitaxel or gemcitabine for treatment of ovarian cancer in patients with platinum-sensitive disease as recommended by NCCN and ESMO guidelines.[8, 10, 11] Therefore, these chemotherapies are appropriate comparators to confirm rucaparib benefit for the planned patient population.

6 STUDY POPULATION SELECTION

6.1 Number of Patients and Sites

The enrollment planned for this study is approximately 345 patients at approximately 100 study sites worldwide, with 230 patients randomized to rucaparib and 115 patients randomized to chemotherapy (ie, comparator).

Patients will be randomized 2:1 to receive rucaparib or chemotherapy.

6.2 Inclusion Criteria

Eligible patients must meet the following inclusion criteria. Unless otherwise specified, the criteria below apply to all patients.

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form prior to any study-specific evaluation
2. Be ≥ 18 years of age at the time the informed consent form is signed
3. Have a histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer
    a. If mixed histology, > 50% of the primary tumor must be confirmed to be high-grade serous or endometrioid upon review by local pathology
    b. Patients with a histology of other than serous or endometrioid are also eligible if they are known to harbor a deleterious germline or somatic BRCA1/2 mutation
4. Received ≥ 2 prior chemotherapy regimens, with at least 1 regimen including a platinum, and have relapsed or progressive disease as confirmed by radiologic assessment
    a. Had documented treatment-free interval of ≥ 6 months following the first chemotherapy regimen received
    b. Hormonal agents (eg, tamoxifen, letrozole, etc.), anti-angiogenic agents (eg, bevacizumab, pazopanib, cediranib, etc.), and other non-chemotherapy agents will not be counted as a chemotherapy regimen for the purpose of determining patient eligibility
    c. Agents administered in the maintenance setting will not be counted as a separate regimen
5. Have a deleterious BRCA1/2 mutation as confirmed by the central laboratory. Note: patients known to harbor a deleterious germline or somatic BRCA1/2 mutation based on local assessment may be enrolled without central tissue analysis provided there is confirmation that tumor tissue is available to be provided to the central laboratory.
    a. Sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue must be available for planned analyses; cytospin blocks from ascites are not acceptable.

i. The most recently obtained tumor tissue that is of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content) should be submitted.

b. In the event archival tumor tissue is not available a screening biopsy sample may be collected and provided to the central laboratory

6. Have evaluable disease: ie at least 1 target or non-target lesion that can be assessed per RECIST Version 1.1 (Appendix 1)
7. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to randomization:
    a. Bone Marrow Function
        i. Absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/L
        ii. Platelets $> 100 \times 10^9$/L
        iii. Hemoglobin > 10 g/dL
    b. Hepatic Function
        i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ upper limit of normal (ULN); if liver metastases, then $\leq 5 \times$ ULN
        ii. Bilirubin $\leq 1.5 \times$ ULN; $< 2 \times$ ULN if hyperbilirubinemia is due to Gilbert's syndrome
        iii. Serum albumin $\geq$ 30 g/L (3.0 g/dL)
    c. Renal Function
        i. Serum creatinine $\leq$ 1.5 x ULN or estimated glomerular filtration rate (GFR) $\geq$ 45 mL/min using the Cockcroft-Gault formula
8. Women of childbearing potential must have a negative serum pregnancy test $\leq$ 3 days prior to administration of the first dose of study drug
9. Have an ECOG performance status of 0 or 1 (Appendix 2).

6.3 Exclusion Criteria

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

1. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment
    a. Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/ or bone marrow transplant > 2 years prior to first dose of study drug. Ongoing hormonal treatment for previously treated breast cancer is permitted.
2. Prior treatment with any PARP inhibitor, including rucaparib, regardless of duration
3. Prior treatment with single-agent paclitaxel or nab-paclitaxel
4. Prior known clinically significant hypersensitivity (per investigator judgement despite implementation of a desensitization protocol) to:

   a. paclitaxel treatment for patients with a progression-free interval of < 12 months after last platinum-based regimen, or
   b. platinum treatment for patients with a progression-free interval of ≥ 12 months after last platinum-based regimen

5. Platinum refractory disease: disease progressed by radiologic assessment during or within 4 weeks after completing treatment with most recent platinum-based therapy
6. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously-treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks after completion of therapy
7. Pre-existing duodenal stent and/ or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib
8. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C, with the exception of patients with a sustained virologic response after completion of treatment for hepatitis C
9. Women who are pregnant or breast feeding
10. 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
11. Ongoing toxicity from prior cancer treatment ≥ Grade 2 by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (ongoing Grade 2 non-hematologic toxicity, with the exception of peripheral neuropathy, may be permitted with prior advanced approval from Sponsor)
12. Non study-related minor surgical procedure ≤ 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
13. Requires regular blood transfusions, granulocyte colony-stimulating factor, or platelet transfusions
14. Drainage of ascitic fluid 2 or more times in the 4 weeks prior to the first dose of study drug, uncontrolled pleural effusion, or permanent drain in place (eg, PleurX®) for ascites or pleural effusion
15. Hospitalization for bowel obstruction within 3 months prior to randomization
16. 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

6.4 Criteria for Rucaparib Crossover Treatment Eligibility Following Radiological Progression on or after Comparator Arm Therapy

To be eligible for participation in the crossover part of the study, patients must fulfill the following criteria and initiate treatment with rucaparib ≤ 8 weeks after radiologic disease progression:

1. Have documented radiological progression per RECIST Version 1.1 during or following completion of comparator arm chemotherapy
2. Receive Sponsor approval to cross over from chemotherapy to rucaparib treatment
3. Have adequate hematological and biological function, confirmed by the following local laboratory values ≤ 14 days prior to first dose of rucaparib:
    a. Bone Marrow Function
        i. ANC ≥ 1.5×10^9/L
        ii. Platelets > 100×10^9/L
        iii. Hemoglobin > 10 g/dL
    b. Hepatic Function
        i. AST and ALT ≤ 3 × ULN; if liver metastases, then ≤ 5 × ULN
        ii. Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome
        iii. Serum albumin ≥ 30 g/L (3.0 g/dL)
    c. Renal Function
        i. Serum creatinine ≤ 1.5 x ULN or estimated GFR ≥ 45 mL/minute using the Cockcroft-Gault formula
4. All Grade 3 and 4 hematologic and non-hematologic toxicities (except alopecia, nausea, vomiting, or adequately controlled diarrhea) improved to baseline or ≤ CTCAE Grade 1
5. Women of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to administration of the first dose of rucaparib in the crossover
6. Have an ECOG performance status of 0 to 1 (Appendix 2).
7. Written consent on an IRB/IEC-approved ICF

In addition, any of the following will exclude patients from receiving rucaparib in the crossover part:

1. Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment
    a. Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to continue in the trial provided all prior chemotherapy was completed > 6 months prior and/ or bone marrow transplant > 2 years prior to first dose of study drug (non-melanoma skin cancer excepted)

2. Received treatment with chemotherapy, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs after discontinuation of study chemotherapy
3. Non study-related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of rucaparib in crossover patients; in all cases, the patient must be sufficiently recovered and stable before treatment administration
4. Women who are pregnant or breast feeding
5. Withdrawal of consent during treatment with the comparator arm chemotherapy
6. Presence of any other condition that may increase the risk associated with study participation and, in the opinion of the investigator, would make the patient inappropriate (including general noncompliance with study procedures during treatment with the comparator arm chemotherapy, per investigator judgement) for continuing in the study with crossover to rucaparib treatment

6.5 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Female patients are considered to be of childbearing potential unless 1 of the following applies:

- 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: or

- Considered to be permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy.

Female patients of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to administration of the first dose of study drug. 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.

Female patients of reproductive potential and their male partners must practice highly effective methods (failure rate < 1% per year) of contraception during treatment and for 6 months following the last dose of study drug. Highly effective contraception includes:

- Ongoing use of progesterone-only injectable or implantable contraceptives (eg, Depo Provera, Implanon, Nexplanon);
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Bilateral tubal occlusion;

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

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

6.6 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.

7 STUDY TREATMENT(S)

7.1 Description of Treatment(s) and Storage

This study will assess the investigational drug rucaparib compared to chemotherapy using a parallel-group study design.

7.1.1 Investigational Drug Product - Rucaparib

Rucaparib camsylate (also known as CO-338) is an oral formulation. Rucaparib tablets for oral administration will be supplied to the study sites by the Sponsor. A brief description of the investigational product is provided below with details in the Pharmacy Guidelines.

Table 2. Rucaparib Formulation and Storage

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

7.1.2 Chemotherapeutic Drug Products

Single-agent chemotherapy will consist of paclitaxel, cisplatin, or carboplatin. Doublet platinum-based chemotherapy will consist of carboplatin and paclitaxel, carboplatin and gemcitabine, or cisplatin and gemcitabine. Each of these individual drugs will either be procured by the study site or supplied by the Sponsor. Each product will be stored according to the manufacturer's prescribing information/ product packaging and as described in the Pharmacy Guidelines.

Single-agent weekly paclitaxel will be assigned to patients per study randomization. Single-agent cisplatin or carboplatin or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine will be selected by the Investigator for treatment of platinum-sensitive patients randomized to chemotherapy. The selected chemotherapy should be based on what is appropriate for the patient and the Investigator must have experience with the single-agent or doublet chemotherapy that is selected.

7.2 Packaging and Labeling

7.2.1 Rucaparib

All tablets are provided in high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers between 15° and 30° C (59 and 86° F).

Patients will be dispensed one or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28 days treatment per cycle, including a small overage.

Study drug containers containing rucaparib tablets will be labeled in accordance with local regulatory requirements.

7.2.2 Chemotherapy

Depending on local health authority guidelines, the chemotherapy agents will be obtained through commercial supply, the site pharmacy, or from the Sponsor. The packaging and labeling will vary depending on the source of the supply.

Products will be labeled to meet local country requirements. Where sites source their own chemotherapy, they are responsible for the quality and security of the supply and for ensuring it is appropriately labeled and dispensed in compliance with local regulations.

7.3 Blinding

This is an open-label study; the study drugs will not be blinded or masked to the Investigator or patient, so each will know the treatment being administered. A plan will be put in place to limit bias for Sponsor personnel.

7.4 Method of Assigning Patients to Treatment Groups

The following will be included as a randomization stratification factor at study entry to ensure treatment groups are balanced:

- Platinum resistant: patients who progressed ≥ 1 to < 6 months after the last dose of platinum-based chemotherapy;
- Partially platinum-sensitive: patients who progressed ≥ 6 months to < 12 months after last dose of platinum-based chemotherapy; and
- Platinum sensitive: patients who progressed ≥ 12 months after last dose of platinum-based chemotherapy;

Platinum-resistant patients and partially platinum-sensitive patients will be randomized 2:1 to receive rucaparib or weekly paclitaxel.

Platinum-sensitive patients will be randomized 2:1 to receive rucaparib or platinum-based chemotherapy. The investigator will select an appropriate monotherapy platinum (carboplatin or cisplatin) or platinum-based doublet (carboplatin and paclitaxel, carboplatin and gemcitabine, or cisplatin and gemcitabine). The Investigator should have experience using the chemotherapy that is selected and prior to randomization must notify the Sponsor (or designee) which platinum chemotherapy a platinum-sensitive patient will receive if randomized to the chemotherapy arm.

Study treatment must be initiated within 3 days after randomization.

7.5 Preparation and Administration of Protocol-specified Treatment

The investigator or designee will be responsible for distributing study drug to all patients. Study drug (ie, rucaparib or chemotherapy) will be assigned by IRT according to the patient's randomization assignment. The Investigator will select the most appropriate monotherapy platinum or platinum-based doublet for platinum-sensitive patients randomized to chemotherapy (see Section 7.1.2).

The IRT will manage all study drug supplied by the Sponsor. The system should be accessed to record each dispensation of rucaparib and each administration of chemotherapy comparators according to the patient's randomized treatment. Guidelines for the use of the IRT will be provided to study sites. Study sites should follow local guidelines for the handling of cytotoxic chemotherapy.

7.5.1 Rucaparib

The starting dose of rucaparib is 600 mg ingested BID. Patients may take rucaparib with or without food. Each dose should be taken with at least 8 oz. (240 mL) of water. Tablets should be swallowed whole without crushing or chewing.

Patients should take rucaparib doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (ie, does not take it within 4 hours of the scheduled time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up.

Dosing with rucaparib may be held or reduced as described in Section 7.5.1.1.

Each treatment cycle of rucaparib is 28 days. 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 rucaparib tablets and all containers (empty, partially used, and/or unopened) to the next scheduled visit for reconciliation by site personnel. After the last dose of rucaparib is taken (initial or crossover treatment), the patient will be followed for 28 (± 3) days for safety and efficacy data.

7.5.1.1 Rucaparib Dose Modification Criteria

Treatment with rucaparib should be held if any of the following are observed and a dose reduction should be considered or implemented.

- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below.
- At the discretion of the investigator, oral study drug may be interrupted or continued if new or worsening unexplained pulmonary symptoms suggestive of pneumonitis

(including, but not limited to, dyspnea) occur and while evaluation to rule out pneumonitis or confirm such a diagnosis as well as etiology are ongoing; these events should be managed as described below.

- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

MANAGEMENT OF ANEMIA

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

- Refer to Sections 10.3 and 10.7 of the protocol for additional information regarding classification and reporting of MDS or AML as an AESI.

MANAGEMENT OF RUCAPARIB TREATMENT-EMERGENT ALT/AST ELEVATIONS

- Grade 4 ALT/AST elevations: hold rucaparib until values have returned to Grade 2 or better, then resume rucaparib with a dose reduction. Monitor liver function tests weekly for 3 weeks after rucaparib has been restarted.

- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:

  – Monitor liver function tests weekly until improvement to ≤ Grade 2.

  – Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN and alkaline phosphatase is < 3 x ULN.

  – If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before rucaparib can be resumed, either at the current dose or at a reduced dose.

Treatment with rucaparib should be held until the toxicity resolves to ≤ CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, the dose should be reduced following resolution 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. If a patient continues to experience toxicity despite dose reduction steps to 300 mg BID, or if dosing with rucaparib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and the Sponsor.

DILI is described in the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation [63] and should be referenced when managing treatment-emergent ALT/AST elevations.

Rucaparib treatment must be interrupted if biochemical criteria for suspected DILI are met, according to presence of the following laboratory abnormalities:

ALT or AST > 3x ULN AND bilirubin > 2x ULN.

While treatment is interrupted, the patient should be evaluated for the presence of confounding factors including malignant disease in the liver, co-administration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as monitoring of international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, rucaparib must be permanently discontinued.

All cases of possible DILI must be reported as SAEs (see Section 10.9) and will be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin.

Management of New or Worsening Pulmonary Symptoms

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

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

Refer to Sections 10.3 and 10.7 of the protocol for additional information regarding classification and reporting of pneumonitis (and associated events) as an AESI.

DOSE REDUCTION STEPS

Dose reduction steps are presented in Table 3.

Dose escalation upon resolution 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 eCRF.

Table 3. Rucaparib Dose Reduction Steps

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

Abbreviation: BID = twice a day.

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

7.5.2 Single-agent Weekly Paclitaxel Preparation, Administration, and Restrictions

The starting dose of weekly paclitaxel is 60 to 80 mg/m^2 (dose per institutional standard of care) administered via IV infusion on Days 1, 8, and 15 in each 28-day cycle (with a week break from dosing on Day 22 in each cycle). Body surface area (BSA) will be determined before the start of each cycle, based on baseline height and most recent weight, or as determined by institutional guidelines. All patients should be pre-medicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such pre-medication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel. Pre-medications should be recorded in the appropriate eCRF.

Handling, preparation, administration, precautions, and restrictions for the use of paclitaxel are to follow Prescribing Information provided in the Pharmacy Guidelines or approved institutional or local guidelines. Paclitaxel must be diluted prior to infusion.

7.5.3 Single-agent Cisplatin and Carboplatin Preparation, Administration, and Restrictions

Body surface area will be determined before the start of each cycle, based on baseline height and most recent weight, or as determined by institutional guidelines. The dosage, dosing schedule, and administration of single-agent cisplatin or carboplatin will follow institutional guidelines for each agent. Appropriate site personnel should prepare and administer study drug. A maximum of 8 cycles of single-agent cisplatin or carboplatin are to be administered.

Caution should be exercised in handling the aqueous solution. Procedures for proper handling and disposal of anticancer drugs should be utilized. Qualified personnel (eg, pharmacist) should be designated to prepare cisplatin or carboplatin. **Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin or carboplatin should not be used for preparation or administration. Aluminum reacts with these drugs, causing precipitate formation and a loss of potency.**

Handling, preparation, administration, precautions, restrictions and other information for the use of each drug are in the Prescribing Information provided in the Pharmacy Guidelines or approved institutional or local guidelines.

7.5.4 Platinum-based Doublet Chemotherapy Preparation, Administration, and Restrictions

Body surface area will be determined before the start of each cycle, based on baseline height and most recent weight, or as determined by institutional guidelines. The dosage, dosing schedule, and administration of doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine IV infusion will follow institutional guidelines for each agent. A maximum of 8 cycles of platinum doublet therapy are to be administered in this study. Appropriate site personnel should prepare and administer study drug.

Caution should be exercised in handling and preparing chemotherapeutic agents. Procedures for proper handling and disposal of anticancer drugs should be utilized. Qualified personnel (eg, pharmacist) should be designated to prepare chemotherapy.

Handling, preparation, administration, precautions, restrictions and other information for the use of each drug are in the Prescribing Information provided in the Pharmacy Guidelines or approved institutional or local guidelines.

7.5.5 Re-treatment and Dose Modification for All Chemotherapy

In the event of toxicities, dose delays and modifications should occur in accordance with the highest toxicity observed per the recommendations and guidelines provided in the approved Prescribing Information provided in the Pharmacy Guidelines or according to institutional guidelines or local dose reduction protocols. Dose modifications must be recorded for each patient in the appropriate section of the eCRF.

7.5.6 Treatment with Rucaparib beyond Progression

Patients will receive the study drug to which they are randomized (rucaparib or chemotherapy) until radiologic disease progression by investigator-assessed RECIST Version 1.1; unacceptable toxicity or inability to tolerate further treatment, as assessed by the investigator; pregnancy; death; loss to follow-up; withdrawal of consent, or other appropriate clinical reason.

If a patient receiving study drug has met criteria for confirmed radiologic disease progression by RECIST Version 1.1 criteria, but continues to derive clinical benefit per the investigator, continuation of treatment will be permitted. In such cases, the documented decision to

continue rucaparib treatment will be provided to the Sponsor (or designee) and the investigator's decision to continue treatment must be documented in the source documents. The patient must provide additional consent that should be obtained within reasonable timeframe of the documented decision to continue treatment with rucaparib. 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 rucaparib will continue to have all protocol required assessments as described in Section 8.

7.5.6.1 Crossover to Rucaparib Treatment

Patients initially randomized to chemotherapy have the option to cross over to rucaparib treatment upon radiologic disease progression with Sponsor (or designee) approval of the radiology report confirming disease progression, signed consent for crossover, and meeting eligibility for the crossover as listed in Section 6.4. Patients who cross over to receive rucaparib will continue to have all protocol-required assessments as described in Section 8. Crossover to rucaparib can occur after toxicities related to chemotherapy have resolved or sufficiently stabilized and patient meets all criteria for initiation of treatment with rucaparib. Initiation of treatment with rucaparib should occur within 8 weeks following radiologic disease progression.

7.5.6.2 Continuation of Rucaparib

If a patient receiving rucaparib (either initial randomization or as crossover treatment) has met criteria for radiologic disease progression by RECIST Version 1.1, but the patient continues to derive clinical benefit per the investigator, then continuation of treatment will be permitted. In such cases, the documented decision to continue will be made jointly between the investigator and the Sponsor (or designee) (see Section 7.5.6). The patient must provide additional consent that should be obtained within reasonable timeframe following the decision to continue treatment with rucaparib. Patients continuing to receive rucaparib will continue to have all protocol-required assessments as described in Section 8.

7.6 Treatment Compliance

7.6.1 Rucaparib Treatment Compliance

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. Study site personnel will record compliance information on the electronic case report form (eCRF).

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.

7.6.2 Chemotherapy Treatment Compliance

Chemotherapy will be administered by study-site personnel as an infusion during study-site visits. Drug dosing and administration will be managed by the study-site for each patient following the institutional guidelines or Prescribing Information for each agent.

7.7 Accountability of Protocol-specified Treatment

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

The site is responsible for the return or destruction of study drug supplied by the Sponsor as required. 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. Any study drug supplied by the Sponsor accidentally or deliberately destroyed must be accounted for. All study drug containers must be accounted for prior to their destruction at the study center, according to institutional procedures for disposal of cytotoxic chemotherapeutic drugs. Unused study drug containers should be destroyed on-site if possible. If destruction on site is not possible, supply should be returned to the drug depot.

During the course of the study and at completion of the study, the number of study drug containers received, dispensed, returned, and destroyed must be reconciled.

For comparator chemotherapy that is sourced locally, the study site should follow local drug accountability practices.

7.8 Prior and Concomitant Therapy

Patients who have received prior treatment with a PARP inhibitor including IV or oral rucaparib or with single-agent paclitaxel or nab-paclitaxel are not eligible to participate in this study.

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.

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

7.8.1 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 hormonal treatment for prior breast cancer. Prior treatment with such excluded anticancer therapies must have been completed > 14 days prior to the first dose of study drug.

7.8.2 Hematopoietic Growth Factors and Blood Products

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

7.8.3 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo CYP interaction study (CO-338-044), rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used in patients taking concomitant medicines that are sensitive substrates of CYP1A2, CYP2C9, and/or CYP3A (Appendix 3).

Patients taking phenytoin, a CYP2C9 substrate with a narrow therapeutic window, should have therapeutic drug level monitored while using concomitantly with rucaparib.

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.

7.8.4 Transporter Inhibitors, Inducers, and Substrates

Based on the results from Study CO-338-095, rucaparib weakly inhibited BCRP. Caution should be used for concomitant use of BCRP substrates (eg, rosuvastatin, sulfasalazine).

7.8.5 Bisphosphonates

Bisphosphonates are permitted.

7.8.6 Anticoagulants

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

7.8.7 Other Concomitant Medications

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

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

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

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

8 STUDY PROCEDURES AND ACTIVITIES BY VISIT

8.1 Schedule of Assessments

Table 4 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 4. Schedule of Assessments for All Patients (Randomization to Therapy at Study Initiation)

Procedure[a]	Screening Phase			Randomization	Treatment Phase (21- or 28-day Cycles)			Post-treatment Phase		
	Day -60 to Day -1	Day -28 to Day -1	Day -14 to Day -1		Day 1[b]	Day 8 (weekly paclitaxel) (intra-cycle for platinum therapy)	Day 15[c] (weekly paclitaxel; rucaparib Cycles 1 and 2) (intra-cycle for platinum therapy)	Treatment Discontinuation	28-day Safety Follow-up	Long-term Follow-up
Medical/Oncology History[d]	X									
Demographic Information/Smoking Status	X									
Tumor Tissue Sample (Archival or Screening Biopsy)[e]	X									
Patient-reported outcome (EORTC QLQ-30 and QLQ-OV28, EQ-5D)[f]		X			X			X	X	
Physical Examination[g], Height[g], Weight[g]		X			X	X	X	X	X	
Vital Signs[h]		X			X	X	X	X	X	
12-lead ECG[i]		X			X	(X)	(X)	X	X	
Prior/Concomitant Medications/Procedures[j]		X			X	X	X	X	X	
Disease Assessment/Tumor Scans[k, l, m]		X			Every 8 weeks after C01D01[l]			X	X[m]	X[m]
ECOG Performance Status[n]		X			X	X	X	X	X	
Hematology[o]			X		X	X	X	X	X	
Serum Chemistry[p] (fasting not required)			X		X	(X)	X	X	X	
Serum Pregnancy Test (women of childbearing potential only)[q]			X		X			X		
Urinalysis[r]			X							
CA-125 Measurement[s]			X		X			X	X	
Randomization to Study Treatment[t]				X						

Table 4. Schedule of Assessments for All Patients (Randomization to Therapy at Study Initiation)

Procedure[a]	Screening Phase			Randomization	Treatment Phase (21- or 28-day Cycles)			Post-treatment Phase		
	Day. -60 to Day -1	Day -28 to Day -1	Day -14 to Day -1		Day 1[b]	Day 8 (weekly paclitaxel) (intra-cycle for platinum therapy)	Day 15[c] (weekly paclitaxel; rucaparib Cycles 1 and 2) (intra-cycle for platinum therapy)	Treatment Discontinuation	28-day Safety Follow-up	Long-term Follow-up
Blood Sample for ctDNA Analysis[u]		X			X			X		
Blood Sample for Germline/Somatic BRCA Status[u]					X					
Plasma PK Sample[v]					X					
Study Drug Administration (weekly paclitaxel)[w, x]					X	X	X			
Study Drug Administration (single-agent platinum or platinum-based doublet chemotherapy)[w, x]					X	[X]	[X]			
Study Drug Dispensation (rucaparib)[y]					X					
Adverse Events[z, aa]	(X)	(X)	(X)		X	X	X	X[z]	X[z]	
Post-treatment Tumor Tissue Biopsy (optional)[bb]								X		
Subsequent Treatments, Secondary Malignancy Monitoring, and Overall Survival[cc, dd]									X	X

Abbreviations: AE = adverse event, AESI = adverse event of special interest, ALP = alkaline phosphatase, ALT = alanine transaminase, AML = acute myeloid leukemia, ANC = absolute neutrophil count, AST = aspartate transaminase, BRCA1/2 = breast cancer gene, BUN = blood urea nitrogen, CA-125 = cancer antigen 125, bicarbonate=CO_2/HCO_3-, CT = computed tomography, ctDNA = circulating cell-free tumor DNA, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, EORTC QLQ-OV28 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module OV28, EQ-5D = Euro-QoL 5D, QoL= quality of life, GCIG = gynecologic cancer intergroup, GFR = glomerular filtration rate, g/s = germline/somatic, Hct = hematocrit, HDL= high density lipoprotein, Hgb = hemoglobin, HRD = homologous recombination deficiency, IRT = interactive response technology, LDL= low density lipoprotein, LTFU = long-term follow-up, MCH = mean corpuscular hemoglobin, MCHC, = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MDS = myelodysplastic syndrome, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetic, PRO = patient-reported outcome, RBC= red blood cell count, RECIST = Response Evaluation Criteria in Solid Tumors, SAE = serious adverse event, WBC = white blood cell.

Table 4. Schedule of Assessments for All Patients (Randomization to Therapy at Study Initiation)

[a] = The study visit window in the treatment phase is ± 3 days, unless noted otherwise for a particular assessment.

[b] = First dose of study drug in Cycle 1 must be administered within 3 days after randomization. All procedures on Day 1 of any cycle are to be performed before administration of paclitaxel, monotherapy cisplatin, monotherapy carboplatin, or platinum-based doublet therapy. Procedures required on Cycle 1 Day 1 may be omitted, if completed successfully ≤ 3 days prior to first dose of study drug during the screening period.

[c] = Patients randomized to rucaparib will visit the study site on Day 15 of Cycles 1 and 2 for study procedures. Beginning with Cycle 3, patients receiving rucaparib will only need to visit the study site on Day 1 of each cycle.

[d] = Patient's medical record must include prior surgeries/treatments received, dates of administration, date of progression and how assessed, radiology reports, best response achieved, and progression-free interval after last platinum regimen. If known, BRCA1/2 mutation status will also be recorded on the appropriate case report form.

[e] = Adequate archival tumor tissue sample or a new sample, if needed, must be provided to the central laboratory to enable determination of HRD status for eligibility, randomization, determination of HRD status prior to final analysis (if required), and storage for potential bridging to the final companion diagnostic test. Patients with a known deleterious BRCA1/2 mutation (germline or somatic) must also have sufficient quantity of archival tumor tissue for central laboratory testing; however, may enroll based upon previous documented local laboratory results. The most recently collected sample available of adequate quality and quantity must be provided or a new sample acquired. Tumor tissue content ≥ 20% with ≥ 80% nucleated cellular content is required. If archival tumor tissue is not available, patients may undergo a screening biopsy. A sufficient quantity of archival tumor tissue or tumor tissue from a screening biopsy must be submitted to the central laboratory **at least 3 weeks prior to planned randomization** for determination of eligibility.

[f] = PRO instruments must be completed before other scheduled study procedures and dosing (if applicable) at Screening, on Day 1 of each treatment cycle, at treatment discontinuation, and at the 28-day Safety Follow-up Visit (randomized treatment discontinuation and/or crossover rucaparib treatment discontinuation) for all patients.

[g] = Height at screening only. Weight at screening, Day 1 of each cycle, during each visit before administration of chemotherapy, at randomized treatment discontinuation, and at the 28-day Safety Follow-up Visit. Chemotherapy will be administered after completion of the physical examination during a study visit.

[h] = Vital signs (blood pressure, pulse, and body temperature) after the patient has been resting for at least 5 minutes. For patients receiving chemotherapy, vital signs will be assessed before administration.

[i] = Heart rate, PR, QRS, QT, QTc, and rhythm. Investigator to review results and assess as normal or abnormal, and if abnormal whether clinically significant or not clinically significant. ECGs are to be completed on Day 1 of each cycle for patients receiving rucaparib and chemotherapy. ECGs on intracycle visits (Day 8 and Day 15) may be performed if clinically indicated per investigator judgement. An ECG is not performed at Day 15 in Cycles 1 and 2 of rucaparib treatment. ECG assessments may be repeated as clinically indicated.

[j] = Concomitant medications/procedures will be reviewed with patients at each study visit and updated as needed.

[k] = Disease/ tumor assessments to consist of clinical examination and appropriate imaging techniques (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline (ie, initial study screening) 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 by CT scan at each required assessment time.

Table 4. Schedule of Assessments for All Patients (Randomization to Therapy at Study Initiation)

[l] = Disease/ tumor assessments to be performed at baseline (screening) and at the end of every 8 calendar weeks relative to Cycle 1 Day 1 after randomization (within 5 days before is permitted). Disease progression will only be determined by RECIST Version 1.1. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST Version 1.1. If the radiologic assessment does not confirm GCIG CA-125 disease progression, patients should continue on treatment and continue to be assessed by RECIST Version 1.1 per the protocol schedule of assessments.

[m] = Disease/ tumor assessments to be performed at the end of every 8 calendar weeks relative to Cycle 1 Day 1 (within 5 days before is permitted) until investigator-assessed radiologic disease progression by RECIST Version 1.1 for any patient who discontinued from study treatment for reason other than disease progression or death (scans occur at treatment discontinuation or 28-day safety follow-up if it has been ≥ 8 weeks since last scan or disease progression was noted on the last scan). Patients who cross over to with rucaparib will have tumor assessments every 8 calendar weeks relative to Day 1 of initiation of treatment with rucaparib.

[n] = ECOG performance status is to be completed before administration of chemotherapy during a study visit.

[o] = Includes RBC and parameters (Hgb, Hct, MCV, MCH, MCHC) and reticulocyte count, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory. The hematology blood sample is to be collected before administration of chemotherapy during a study visit. Additional and more frequent tests may be performed at the investigator's discretion.

[p] = Includes total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, and lipid panel (total cholesterol, LDL, HDL, and triglycerides). Blood will be analyzed by a local laboratory. The serum chemistry blood sample is to be collected before administration of chemotherapy during a study visit, except at Day 8 visits where serum chemistry may be performed at investigator's discretion. Additional and more frequent tests may be performed at the investigator's discretion.

[q] = Women of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to the first dose of study drug. A serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the treatment phase and at the treatment discontinuation visit. All tests will be performed by a local laboratory.

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

[s] = CA-125 measurement should be performed at screening, on Cycle 1 Day 1, at the start of every 2nd cycle thereafter (ie, Day 1 of Cycles 3, 5, 7, etc.), at randomized treatment discontinuation, at the 28-day Safety Follow-up Visit, and as clinically indicated. All CA-125 measurements will be performed by a local laboratory.

[t] = Randomization will occur by a central randomization procedure using IRT. Patients will be stratified at study entry based on the interval between completion of the most recent platinum regimen and disease progression by radiologic assessment. Platinum-resistant and partially platinum-sensitive patients will be randomized 2:1 to receive rucaparib or weekly paclitaxel. Platinum-sensitive patients will be randomized 2:1 to receive rucaparib or chemotherapy. The investigator will select an appropriate single-agent or doublet chemotherapy from those offered in the study, which include single-agent cisplatin or carboplatin or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine. No more than 8 cycles of platinum monotherapy or doublet therapy are to be administered.

[u] = Blood for germline/somatic (g/s) BRCA status: Blood samples will be collected from all enrolled patients for g/sBRCA mutation analysis on Day 1 of Cycle 1. If sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter.

Blood sample for ctDNA analysis: Blood samples for ctDNA analysis will be collected for all patients at screening, before dosing on Day 1 of Cycles 1 to 6, and at treatment discontinuation. Refer to the Laboratory Manual for details.

Table 4. Schedule of Assessments for All Patients (Randomization to Therapy at Study Initiation)

[v] = Plasma samples for PK analysis are to be collected in patients randomized to receive rucaparib. Samples should be collected before the morning dose on Day 1 of Cycles 2 to 6 as close to 12 hours after the previous dose as possible. If the start of the next treatment cycle is delayed, the PK sample should still be collected during this visit instead of on Day 1 of the delayed start of the next treatment cycle. Samples are not to be collected in patients receiving chemotherapy or crossing over to rucaparib. Refer to the Laboratory Manual for sample collection details.

[w] = Study procedures are to be completed before administration of chemotherapy.

[x] = Paclitaxel treatment visits occur on Days 1, 8, and 15 of each 28-day cycle (with a break from dosing on Day 22 in each cycle). Single-agent platinum or doublet chemotherapy will be administered in 21- or 28-day cycles, per institutional guidelines. Treatment visits may vary dependent upon the chemotherapy selected and patients should return to the study site for treatment according to the appropriate institutional schedule for each respective chemotherapy. No more than 8 cycles of platinum monotherapy or doublet therapy are to be administered.

[y] = Study visits should take into account the patient's rucaparib supply. A quantity of rucaparib sufficient to complete 1 cycle will be dispensed to the subject on Day 1 of each cycle. Each treatment cycle is 28 days.

[z] = AEs that occur after first administration of study drug through to 28 days after last dose of study drug will be recorded. SAEs that are deemed related to a screening procedure will be recorded/submitted. All treatment-related SAEs, and the AESIs myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) of any causality, are to be reported, even if they occur after the 28-day safety follow-up.

[aa] = Ongoing SAEs, AESIs, and treatment-related Grade 3/4 AEs will be followed until resolution, stabilization, or lost to follow up. SAEs/AESIs are collected per Clovis PV guidelines and reported in the Clovis PV database through the 28-day Follow-up Visit after the last dose of rucaparib. After this visit, only SAEs considered as potentially related to study drug (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML irrespective of causality, will be reported. If a patient discontinues from treatment and begins a subsequent anti-cancer therapy, the Sponsor will terminate collection of SAEs, with the exception of AESIs MDS and AML.

[bb] = An optional tumor biopsy may be collected from patients from time of radiographic disease progression/randomized treatment discontinuation until the start of the next treatment. The option will also be available to patients allowed by the investigator and Sponsor to continue rucaparib after radiologic disease progression at the time of first disease progression. Additional consent is required. Refer to the Pathology Charter for detailed sample handling instructions. If disease progression is caused by appearance of a new lesion(s), the lesion(s) should be prioritized for the optional biopsy.

[cc] = Patients will have 28-day (±3 days) safety follow-up after the last dose of study drug (initial treatment or rucaparib as crossover treatment, as applicable). Patients randomized to rucaparib or who cross over to receive rucaparib will have the safety follow-up visit at 28-days after discontinuation of rucaparib. Patients randomized to chemotherapy will have a safety follow-up visit 28 (±3) days after the last dose of chemotherapy and continue with long-term follow-up (LTFU) until disease progression.

[dd] = Following disease progression or other reason for treatment discontinuation, patients will be followed for subsequent treatments, secondary malignancy, and survival 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 specified in Section 10.10.

Table 5. Schedule of Assessments for Patients Who Cross Over to Rucaparib After Being Randomized to and Receiving Chemotherapy

Procedure[a]	Screening	Treatment with Rucaparib (28-day Cycles)		Post-Crossover Treatment Phase		
	Day -14 to Day -1	Day 1[b]	Day 15[c] (Cycles 1 and 2)	Treatment Discontinuation	28-day Safety Follow-up	Long-term Follow-up
Patient-reported outcome (EORTC QLQ-30 and QLQ-OV28,, EQ-5D)[d]	X	X		X	X	
Physical Examination[e], Weight[e]	X	X	X	X	X	
Vital Signs[f]	X	X	X	X	X	
12-lead ECG[g]	X	X		X	X	
Concomitant Medications/Procedures[h]	X	X	X	X	X	
Disease Assessment/Tumor Scans[i, j, k]	X[j]	Every 8 weeks after C01D01[j]		X	X[k]	X[k]
ECOG Performance Status	X	X	X	X	X	
Hematology[l]	X	X	X	X	X	
Serum Chemistry[m] (fasting not required)	X	X	X	X	X	
Serum Pregnancy Test (women of childbearing potential only)[n]	X	X		X		
Urinalysis[o]	X					
CA-125 Measurement[p]	X	X		X	X	
Blood Sample for ctDNA Analysis[q]	X	X		X		
Study Drug Dispensation (rucaparib)[r]		X				
Adverse Events[s, t]	X	X	X	X[s]	X[s]	
Post-treatment Tumor Tissue Biopsy (optional)[u]	(X)			X		
Subsequent Treatments, Secondary Malignancy Monitoring, and Overall Survival[v, w]					X	X

Table 5. Schedule of Assessments for Patients Who Cross Over to Rucaparib After Being Randomized to and Receiving Chemotherapy

Abbreviations: AE = adverse event, AESI = adverse event of special interest, ALP = alkaline phosphatase, ALT = alanine transaminase, AML = acute myeloid leukemia, ANC = absolute neutrophil count, AST = aspartate transaminase, BRCA1/2 = breast cancer gene, BUN = blood urea nitrogen, CA-125 = cancer antigen 125, CT = computed tomography, ctDNA = circulating cell-free tumor DNA, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, EORTC QLQ-OV28 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module OV28, EQ-5D = Euro-QoL 5D, QoL= quality of life, GCIG = gynecologic cancer intergroup, GFR = glomerular filtration rate, Hct = hematocrit, HDL= high density lipoprotein, Hgb = hemoglobin, HRD = homologous recombination deficiency, IRT = interactive response technology, LDL= low density lipoprotein, MCH = mean corpuscular hemoglobin, MCHC, = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MDS = myelodysplastic syndrome, MRI = magnetic resonance imaging, PET = positron emission tomography, PRO = patient-reported outcome, RBC= red blood cell count, RECIST = Response Evaluation Criteria in Solid Tumors, SAE = serious adverse event, WBC = white blood cell

[a] = The study visit window in the treatment phase is ± 3 days, unless noted otherwise for a particular assessment.

[b] = First dose of rucaparib in Cycle 1 of the crossover treatment must be administered ≤ 8 weeks after radiologic disease progression on chemotherapy.

[c] = Patients will visit the study site on Day 15 of Cycles 1 and 2 for study procedures. Beginning with Cycle 3, patients will only need to visit the study site on Day 1 of each cycle.

[d] = PRO instruments must be completed before other scheduled study procedures and dosing (if applicable) at Screening, on Day 1 of each treatment cycle, at treatment discontinuation, and at the 28-day Safety Follow-up Visit for rucaparib crossover patients.

[e] = Weight at screening, Day 1 of each cycle, at cross over to rucaparib treatment discontinuation, and at the 28-day Safety Follow-up Visit.

[f] = Vital signs (blood pressure, pulse, and body temperature) after the patient has been resting for at least 5 minutes.

[g] = Heart rate, PR, QRS, QT, QTc, and rhythm. Investigator to review results and assess as normal or abnormal, and if abnormal whether clinically significant or not clinically significant. ECGs are to be completed at screening, Day 1 of each cycle and repeated as clinically indicated.

[h] = Concomitant medications/procedures will be updated at each study visit.

[i] = Disease/ tumor assessments to consist of clinical examination and appropriate imaging techniques (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline (ie, initial study screening) 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 by CT scan at each required assessment time.

[j] = Disease/ tumor assessments to be performed at screening (if it has been ≥ 6 weeks since last scan or disease progression was noted on the last scan), at the end of every 8 calendar weeks after Cycle 1 Day 1 in the crossover period, relative in timing to Cycle 1 Day 1 (within 5 days before is permitted) of rucaparib treatment in the crossover period. Disease progression will only be determined by RECIST Version 1.1. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST Version 1.1. If the radiologic assessment does not confirm GCIG CA-125 disease progression, patients should continue on treatment and continue to be assessed by RECIST Version 1.1 per the protocol schedule of assessments.

[k] = Disease/ tumor assessments to be performed at the end of every 8 calendar weeks relative to Cycle 1 Day 1 (within 5 days before is permitted) of rucaparib in the crossover period until investigator-assessed radiologic disease progression by RECIST Version 1.1 for any patient who discontinued from study treatment for reason other than disease progression, death, or initiation of subsequent treatment (scans occur at treatment discontinuation or 28-day safety follow-up if it has been ≥ 8 weeks since last scan or disease progression was noted on the last scan).

Table 5. Schedule of Assessments for Patients Who Cross Over to Rucaparib After Being Randomized to and Receiving Chemotherapy

[l] = Includes RBC and parameters (Hgb, Hct, MCV, MCH, MCHC) and reticulocyte count, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory. Additional and more frequent tests may be performed at the investigator's discretion.

[m] = Includes total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, and lipid panel (total cholesterol, LDL, HDL, and triglycerides). Blood will be analyzed by a local laboratory. Additional and more frequent tests may be performed at the investigator's discretion.

[n] = Women of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to the first dose of crossover rucaparib treatment. A serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the treatment with rucaparib and at the treatment discontinuation visit. All tests will be performed by a local laboratory.

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

[p] = CA-125 measurement should be performed during the rucaparib crossover period at screening, on Cycle 1 Day 1, at the start of every 2nd cycle thereafter (ie, Day 1 of Cycles 3, 5, 7, etc.), at crossover rucaparib treatment discontinuation, at the 28-day Safety Follow-up Visit, and as clinically indicated. All CA-125 measurements will be performed by a local laboratory.

[q] = Blood samples will be collected from all patients for ctDNA analysis during the rucaparib crossover period at screening, before the rucaparib dose on Day 1 of Cycles 1 to 6, and at crossover rucaparib treatment discontinuation. Refer to the Laboratory Manual for details.

[r] = Study visits should take into account the patient's rucaparib supply. A quantity of rucaparib sufficient to complete 1 cycle will be dispensed to the subject on Day 1 of each cycle. Each treatment cycle is 28 days.

[s] = AEs that occur after first administration of study drug through to 28 days after last dose of study drug will be recorded. In addition, AEs/SAEs that were related to a screening procedure will also be recorded. All treatment-related SAEs, and the AESIs of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) of any causality, are to be reported, even if they occur after the 28-day safety follow-up.

[t] = Ongoing SAEs, AESIs, and treatment-related Grade 3/4 AEs will be followed until resolution, stabilization, or lost to follow up. SAEs/AESIs are collected per Clovis PV guidelines and reported in the Clovis PV database through the 28-day Follow-up Visit after the last dose of rucaparib. After this visit, only SAEs considered as potentially related to study drug (including serious reports of pneumonitis or similar events, if considered to be related to study drug), and AESIs of MDS and AML irrespective of causality, will be reported. If a patient discontinues from treatment and begins a subsequent anticancer therapy, the Sponsor will terminate collection of SAEs, with the exception of AESIs MDS and AML.

[u] = An optional tumor biopsy may be collected from patients any time after radiographic disease progression, cross over to rucaparib, or treatment discontinuation until the start of the next non-study treatment. Additional consent is required. Refer to the Pathology Charter for detailed sample handling instructions. If disease progression is caused by appearance of a new lesion(s), the lesion(s) should be prioritized for the optional biopsy.

[v] = Patients will have 28-day (±3 days) safety follow-up after the last dose of rucaparib in the crossover part.

[w] = Patients discontinued from cross over to rucaparib treatment, regardless of reason, are to be followed for subsequent treatments, secondary malignancy, and survival 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 an SAE.

8.2 Informed Consent

The investigator or their designee shall discuss with each patient the nature of the study and its requirements. To participate in the study, informed consent must be obtained from each potential patient prior to any study activities. The information on the IRB/ ERC-approved consent form should be translated and communicated in the language the patient (or legally authorized representative) can understand. Obtaining written informed consent does not signify the start of the Screening Phase. The first study-specific, screening activity performed after signature of the informed consent form begins the Screening Phase. Informed consent does not expire unless specifically withdrawn by the patient.

Analysis of tumor tissue for a deleterious BRCA1/2 mutation (germline or somatic) will be performed using Foundation Medicines NGS test. Results of the FMI test 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 the patient chooses to have germline testing, this result will be entered in the clinical trial database for this study.

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

Patients who cross over to treatment with rucaparib after radiologic disease progression per RECIST Version 1.1 by investigator assessment must provide additional consent to continue treatment, as well as Sponsor (or designee) approval of the radiology report confirming disease progression. Details regarding crossover to rucaparib begin in Section 8.6.

Patients randomized to rucaparib with radiologic disease progression who are still receiving benefit and are allowed to continue rucaparib treatment must also provide consent for continued treatment.

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

8.3 Initial Study Screening Prior to Randomization

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to randomization within the allowable windows of time as indicated below. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable 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.

8.3.1 Within 60 Days Prior to Randomization

- Medical/oncology history, including demographic information (birth date, race, gender, etc.), smoking status, and oncology history, including date of diagnosis for epithelial

ovarian, primary peritoneal, or fallopian tube cancer (and other malignancy, if applicable), prior surgeries/ treatments received for cancer, dates of treatment administration, best response achieved, date of progression and how assessed, progression-free interval after last platinum regimen, radiology reports, and BRCA1/2 mutation status (if known);

- FFPE archival tumor tissue or screening biopsy sample. Sufficient archival FFPE tumor tissue (enough for 1 x 4 µm section for H&E and approximately 8 to 12 x 10 µm sections [unstained], or equivalent) for planned analyses should be provided. Refer to Section 9.5 for more information and to the Pathology Charter for detailed sample handling instructions.
    - The most recently collected tumor tissue sample available that is of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content) must be provided or a new sample acquired;
    - Sample must be submitted to the central laboratory **at least 3 weeks prior to planned randomization** for determination of HRD status to assess eligibility. A documented local BRCA1/2 result from previous testing will be adequate for enrollment of patients with known deleterious BRCA1/2 mutation (germline or somatic); however, these patients must provide tumor tissue for central laboratory testing during the study (archival tumor tissue or biopsy)
    - Another sample may be obtained and testing repeated if the tumor tissue sample is determined to be inadequate for analysis. In those patients, it may take more than 60 days to complete screening assessments.
- AE monitoring (only record if related to screening procedures).

8.3.2 Up to 28 Days Prior to Randomization

- PRO collected using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate (complete before other procedures);
- Physical examination by body system, including height and weight;
- Vital signs (blood pressure, pulse, and body temperature);
- 12-lead ECG;
- Prior and concomitant medications, any surgical/ medical procedures, and update medical history;
- Disease/tumor assessment: assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1); other studies (magnetic resonance imaging [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;
- ECOG performance status (Appendix 2);

- Blood sample for ctDNA analysis (all patients); and
- AE monitoring (only record if related to screening procedure).

8.3.3 Up to 14 Days Prior to Randomization

- Hematology: includes RBC and parameters (hemoglobin, hematocrit, MCV, MCH, and MCHC) and reticulocyte count, WBC and differential (with ANC), and platelet count;
- Serum chemistry: includes total protein, albumin, creatinine, or estimated GFR using the Cockcroft Gault formula, blood urea nitrogen (BUN) or urea, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, and lipid panel (total cholesterol, LDL, HDL, and triglycerides). Note: fasting is not required;
- Urinalysis (performed on freshly voided clean sample): includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings;
- CA-125 measurement (Appendix 4);
- Update medical history; and
- AE monitoring (only record if related to screening procedure).

8.3.4 Up to 3 Days Prior to First Dose of Study Drug

- Serum pregnancy test for women of childbearing potential;
- Update medical history; and
- AE monitoring (only record if related to screening procedure)

8.4 Treatment Phase (Day 1 to Day 28 per Cycle)

Patients are to be randomized to receive either rucaparib or chemotherapy (Section 5.1.2) after meeting eligibility criteria (Sections 6.2 and 6.3) and having completed screening assessments (Section 8.3).

The first dose of study drug must be administered ≤ 3 days after randomization. Procedures required on Cycle 1 Day 1 may be omitted if successfully completed during the screening period within ≤ 3 days prior to first dose of study drug.

Serum pregnancy testing for women of childbearing potential must occur ≤ 3 days prior to the first dose of study drug (Section 8.3.4).

8.4.1 Day 1 of Every Cycle (Rucaparib and Chemotherapy Arms, Including Continuation of Rucaparib Treatment after Radiologic Disease Progression)

The following procedures/assessments will be completed for all patients before initiation of randomized treatment on Cycle 1 Day 1 and on Day 1 of every cycle thereafter, including

patients randomized to rucaparib who are allowed by the Investigator and Sponsor and consent to continue treatment after radiologic disease progression.

Patients initially randomized and treated with chemotherapy who have crossed over to rucaparib following radiographic progression per RECIST Version 1.1 will follow the procedures/assessments beginning in Section 8.6. Patients who cross over to rucaparib will be required to sign a crossover ICF, meet eligibility criteria for the crossover described in Section 6.4, and have Sponsor (or designee) approval prior to crossing over to rucaparib treatment.

Patients will be instructed to refrain from taking their first dose of rucaparib at home on the day of their Day 1 visits for Cycles 2 to 6 to collect blood/plasma samples for PK and/or ctDNA testing.

- PRO using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate (complete before other procedures and dosing; Appendix 5);
- Physical examination;
- Weight;
- Vital Signs;
- 12-lead ECG;
- Concomitant medications and procedures;
- Disease/ tumor assessment (using the same methodology as was used at screening [eg, CT scan]) every 8 calendar weeks (within 5 days before is permitted) relative to start of treatment on Day 1 of Cycle 1 through to 18 months on study, then every 16 calendar weeks (within 5 days before is permitted) relative to the start of treatment on Day 1 of Cycle 1. Timing of disease/tumor assessments is relative to Day 1 of Cycle 1 after randomization;
- ECOG performance status (Appendix 2);
- Hematology;
- Serum chemistry (fasting is not required);
- Serum pregnancy for women of childbearing potential; (≤ 3 days prior to start of every cycle);
- CA-125 measurement (Cycle 1 and every 2nd cycle thereafter [ie, Cycles 3, 5, 7, etc.]);
- Blood sample for ctDNA analysis (all patients – sampling before the dose on Day 1 of Cycles 1 to 6);
- Blood sample for g/sBRCA analysis (one sample per randomized patient – sampling on Day 1 of Cycle 1 [preferred]). If sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter. This sample is a requirement for all patients;

- Plasma samples for PK analysis are to be collected in all patients receiving rucaparib (not in cross-over patients). Samples should be collected before the morning dose on Day 1 of Cycles 2 to 6 as close to 12 hours after the previous dose as possible. If the start of the next treatment cycle is delayed, the PK sample should still be collected during this visit instead of on Day 1 of the delayed start of the next treatment cycle;
- AE monitoring; and
- Study drug administration (weekly paclitaxel, single-agent, or doublet chemotherapy) or dispensation (rucaparib).

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until Day 1 of the next treatment cycle. Patients will ingest rucaparib BID at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of water with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 7.5.1).

Paclitaxel will be prepared and administered by study site personnel after study procedures are completed. Weekly paclitaxel is to be administered at a starting dose of 60 to 80 mg/m^2 (dose per institutional standard of care) via IV infusion. Additional information on paclitaxel preparation and administration is in Section 7.5.2. In the event of toxicities, re-treatment or dose modification will be according to the approved Prescribing Information provided in the Pharmacy Guidelines or according to institutional guidelines or local dose reduction protocols (see Section 7.5.5).

Single-agent platinum or doublet chemotherapy for platinum-sensitive patients will be prepared and administered by study site personnel after study procedures are completed and according to institutional guidelines. Additional information on preparation and administration is in Sections 7.5.3 and 7.5.4. In the event of toxicities, re-treatment or dose modification will be according to the approved Prescribing Information provided in the Pharmacy Guidelines or according to institutional guidelines or local dose reduction protocols (see Section 7.5.5).

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

8.4.2 Days 8 and 15 of Every Cycle (Weekly Paclitaxel Arm)

The following procedures/assessments will be completed before weekly paclitaxel is administered:

- Physical examination;
- Weight
- Vital Signs;
- 12-lead ECG (as clinically indicated per investigator judgement);
- Concomitant medications and procedures;

- ECOG performance status (Appendix 2);
- Hematology;
- Serum chemistry (fasting is not required) (Day 8 serum chemistry may be omitted based on investigator judgement);
- AE monitoring; and
- Study drug administration.

Paclitaxel will be prepared and administered by study site personnel. Weekly paclitaxel is to be administered as 60 to 80 mg/m^2 (dose per institutional standard of care) via IV infusion. There will be a week break from dosing on Day 22 in each 28-day cycle. In the event of toxicities, re-treatment or dose modification will be according to the approved Prescribing Information provided in the Pharmacy Guidelines or according to institutional guidelines or local dose reduction protocols (see Section 7.5.5).

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

8.4.3 Intra-Cycle (Single-agent Platinum or Doublet Chemotherapy of Investigator's Selection)

Based on the dosing schedule, per institutional guidelines, for the single-agent platinum or doublet chemotherapy that was selected by the investigator, the patient may need to return to the study site for dosing/procedures during a treatment cycle. Minimally, the following procedures/assessments are to be completed before the single-agent platinum or doublet chemotherapy is administered. If there are other procedures and laboratory assessments required per institutional guidelines for the selected treatment, they should also be completed at the appropriate times during each cycle:

- Physical examination;
- Weight
- Vital Signs;
- 12-lead ECG (as clinically indicated per investigator judgement);
- Concomitant medications and procedures;
- ECOG performance status (Appendix 2);
- Hematology;
- Serum chemistry (fasting is not required);
- AE monitoring; and
- Study drug administration.

Single-agent platinum or platinum-based doublet chemotherapy for platinum-sensitive patients will be prepared and administered by study site personnel after study procedures are

completed and according to institutional guidelines. Additional information on preparation and administration is in Sections 7.5.3.and 7.5.4. In the event of toxicities, re-treatment or dose modification will be according to the approved Prescribing Information provided in the Pharmacy Guidelines or according to institutional guidelines or local dose reduction protocols (see Section 7.5.5).

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

8.4.4 Day 15 of Cycles 1 and 2 (Rucaparib Arm)

The following procedures/assessments will be completed:

- Physical examination;
- Vital Signs;
- Concomitant medications and procedures;
- ECOG performance status (Appendix 2);
- Hematology;
- Serum chemistry (fasting is not required);
- AE monitoring; and
- Study drug continuation.

Patients will continue BID dosing with rucaparib with or without food, taking doses at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz. (240 mL) of water. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treat or dose modify according to the criteria described in Section 7.5.1).

8.5 Post-treatment Phase

8.5.1 Randomized Treatment Discontinuation

Upon randomized treatment discontinuation, regardless of the reason, patients will have a treatment discontinuation visit. However, patients receiving rucaparib with radiologic disease progression by RECIST Version 1.1, as assessed by the investigator, but still receiving benefit, per the investigator, may be considered for treatment continuation. A joint, documented decision between the investigator and Sponsor (or designee) may allow for continued rucaparib treatment with patient consent. If the patient does continue to receive rucaparib, then the patient will continue cycles of rucaparib as described starting in Section 8.4.1 and a treatment discontinuation visit as described in Section 8.5.1 will occur at the end of all rucaparib treatment. Patients who continue treatment with rucaparib after radiologic disease progression and thus do not have a treatment discontinuation visit will have the option of tumor tissue biopsy collection at time of first disease progression on study

(requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions.

Patients randomized and treated with chemotherapy will have the following procedures performed when chemotherapy is discontinued for any reason. These patients may be eligible to cross over to treatment with rucaparib upon radiologic disease progression by RECIST Version 1.1, as assessed by the investigator. Following an additional consent to cross over to rucaparib treatment (Section 8.6), these patients may be evaluated for eligibility to cross over to treatment as described in Sections 6.4 and 8.7.

The following procedures will be performed when treatment to which the patient is randomized has been completed or is discontinued:

- PRO using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate (complete before other procedures; Appendix 5);
- Physical examination;
- Weight;
- Vital Signs;
- 12-lead ECG;
- Concomitant medications and procedures;
- Disease/ tumor assessment (using the same methodology as was used at screening [eg, CT scan]) if reason for treatment discontinuation was other than death or disease progression based on radiologic assessment and it has been ≥ 8 weeks since last scan or disease progression was noted on the last scan;
- ECOG performance status (Appendix 2);
- Hematology;
- Serum chemistry (fasting is not required);
- Serum pregnancy for women of childbearing potential;
- CA-125 measurement (Appendix 4);
- Blood sample for ctDNA analysis (all patients);
- AE monitoring; and
- Optional tumor tissue biopsy collection from the time of disease progression/ randomized treatment discontinuation until the start of the next treatment (requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions.

8.5.2 28-Day Safety Follow-up Visit (Randomized Treatment/ Cross Over to Rucaparib)

The following procedures will be performed for all patients at 28 (±3) days after the last dose of randomized study drug and/or cross over to rucaparib.

Patients initially randomized to rucaparib and patients who cross over to receive rucaparib after chemotherapy will have a safety follow-up visit 28 (±3) days after the last dose of rucaparib.

Patients randomized to chemotherapy who do not cross over to receive rucaparib will have a safety follow-up visit 28 (±3) days after the last dose of randomized chemotherapy and continue with LTFU (Section 8.5.3).

- PRO using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate (complete before other procedures; Appendix 5);
- Physical examination;
- Weight;
- Vital Signs;
- 12-lead ECG;
- Concomitant medications and procedures;
- If applicable, disease/ tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan]) when the reason for treatment discontinuation was other than death or disease progression based on radiologic assessment and it has been ≥ 8 weeks since last scan or disease progression was noted on the last scan. Disease/ tumor assessment should continue to be performed every 8 calendar weeks relative to Cycle 1 Day 1 (within 5 days before is permitted) until radiologic disease progression by RECIST Version 1.1, as assessed by the investigator, death, loss to follow-up, withdrawal of consent, study closure, or initiation of subsequent treatment;
- ECOG performance status (Appendix 2);
- Hematology;
- Serum chemistry (fasting is not required);
- CA-125 measurement (Appendix 4);
- AE monitoring (Note: all SAEs, AESIs, and treatment-related Grade 3/4 AEs are to be followed to outcome, if longer than the 28-day follow-up period); and
- Any pregnancy is to be followed to outcome (Section 10.6).
- Information collected for subsequent treatments and/or secondary malignancy. Diagnosis of any secondary malignancy will require appropriate documentation (ie, laboratory and/ or pathology reports) and should be reported as indicated in Section 10.10.

Patients who do not withdraw from the study at this visit will continue with LTFU as described in Section 8.5.3.

8.5.3 Long-term Follow-up (Randomized Treatment/Cross Over to Rucaparib)

Patients randomized to rucaparib who complete a safety follow-up visit 28 (±3) days after the last dose of rucaparib will continue in LTFU as described below.

Patients randomized to chemotherapy who discontinue treatment due to radiologic disease progression and are ineligible or do not consent to cross over to rucaparib treatment will continue in LTFU as described below, after a safety follow-up visit.

Patients randomized to chemotherapy who discontinue treatment before radiologic disease progression and complete a safety follow-up visit 28 (±3) days after the last dose of randomized chemotherapy will continue in LTFU as described below. At the time of radiologic disease progression, the patient may be eligible and consent to cross over to treatment with rucaparib. The patient may also be ineligible or not consent to cross over to rucaparib treatment and will continue in LTFU.

Patients who cross over to rucaparib treatment will follow the procedures beginning in Section 8.6. These patients will have appropriate follow-up visits after discontinuation of cross over rucaparib treatment.

- If applicable, disease/ tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan]) when the reason for treatment discontinuation was other than death or disease progression based on radiologic assessment and it has been ≥ 8 weeks since last scan or disease progression was noted on the last scan. Disease/ tumor assessment should continue to be performed every 8 calendar weeks relative to Cycle 1 Day 1 (within 5 days before is permitted), every 16 weeks (±5 days before is permitted) for patients who have been on study (including cross over to rucaparib in patients randomized to chemotherapy) for at least 18 months, until radiologic disease progression by RECIST Version 1.1, as assessed by the investigator, death, loss to follow-up, withdrawal, study closure, or initiation of subsequent non-study treatment
- All patients discontinued from treatment, regardless of reason, will be followed and information collected for subsequent treatments, secondary malignancy, and survival every 12 weeks (± 14 days) after treatment discontinuation 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 will require appropriate documentation (ie, laboratory and/ or pathology reports) and should be reported as indicated in Section 10.10.
- SAEs assessed as potentially related to study drug (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and the AESIs of MDS and AML, irrespective of causality, are to be reported as specified in Section 10.10.

AESIs of pneumonitis or similar events should only be reported up to, but not beyond, the 28-Day Follow-up Visit (28 days after the last dose of rucaparib).

8.6 Informed Consent for Patients Who Cross Over to Rucaparib after Disease Progression on Study Chemotherapy

Patients who initially received chemotherapy and then cross over to treatment with rucaparib after radiologic disease progression per RECIST Version 1.1 by investigator assessment must provide additional consent to receive rucaparib treatment, as well as Sponsor (or designee) approval. Patients who are eligible to cross over as described in Section 6.4 and receive approval must receive the first dose of rucaparib ≤ 8 weeks following radiographic progression on chemotherapy. Ineligible patients will continue with a 28-day Safety Follow-up Visit and LTFU as in Sections 8.5.2 and 8.5.3.

Additionally, patients participating in the optional tumor tissue biopsy at the time of radiographic disease progression/treatment discontinuation after cross over to rucaparib 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.

8.7 Screening Prior to Cross Over to Rucaparib

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to initiating treatment with rucaparib within the allowable windows of time as indicated below. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care. Assessments performed at treatment discontinuation and/or at the 28-day safety follow-up following discontinuation of chemotherapy may be utilized, provided they were within the allowable windows of time as indicated below.

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.

8.7.1 Up to 14 Days Prior to the First Dose of Rucaparib for Crossover Patients:

- PRO collected using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate (complete before other procedures; Appendix 5);
- Physical examination;
- Weight;
- Vital signs (blood pressure, pulse, and body temperature);
- 12-lead ECG;
- Concomitant medications and procedures;

- Disease/ tumor assessment (using the same methodology as was used at screening [eg, CT scan]) if it has been ≥ 6 weeks since last scan or disease progression was noted on the last scan;
- ECOG performance status (Appendix 2);
- Hematology;
- Serum Chemistry (fasting is not required);
- Urinalysis (freshly voided sample);
- CA-125 measurement (Appendix 4);
- Blood sample for ctDNA analysis; and
- AE monitoring.

8.7.2 Up to 3 Days Prior to First Dose of Rucaparib for Crossover Patients:

- Serum pregnancy test for women of childbearing potential.

8.8 Treatment with Rucaparib in Patients Who Cross Over from Chemotherapy (Day 1 to Day 28 per Cycle)

Patients will begin to receive rucaparib after approval by the Sponsor/designee to cross over, meeting eligibility criteria (Sections 6.4), and having completed screening assessments (Section 8.7).

The first dose of rucaparib must be administered ≤ 8 weeks after radiologic disease progression on chemotherapy.

Serum pregnancy testing for women of childbearing potential must occur ≤ 3 days prior to the first dose of study drug (Section 8.3.4).

8.8.1 Day 1 of Every Cycle (Crossover to Rucaparib)

Patients initially randomized and treated with chemotherapy who have crossed over to rucaparib following radiographic progression per RECIST Version 1.1 will have these assessments on Day 1 of every cycle of treatment with rucaparib.

Patients will also be instructed to refrain from taking their first dose of rucaparib at home on the day of their Day 1 visits for Cycles 1 through 6 to collect blood samples for ctDNA testing.

- PRO using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate (complete before other procedures and dosing; Appendix 5);
- Physical examination;
- Weight;

- Vital Signs;
- 12-lead ECG;
- Concomitant medications and procedures;
- Disease/ tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan]) every 8 calendar weeks (within 5 days before is permitted) relative to the start of treatment on Day 1 of Cycle 1 in the crossover period through to18 months in crossover period of the study, then every 16 calendar weeks (within 5 days before is permitted) thereafter. The first disease/ tumor assessment on the crossover part of the study should be performed approximately 8 weeks after the last assessment was performed.
- ECOG performance status (Appendix 2);
- Hematology;
- Serum chemistry (fasting is not required);
- Serum pregnancy for women of childbearing potential; (≤ 3 days prior to start of every cycle);
- CA-125 measurement (Cycle 1 and every 2nd cycle thereafter [ie, Cycles 3, 5, 7, etc.]);
- Blood sample for ctDNA analysis (sampling before the rucaparib dose on Day 1 of Cycles 1 through 6);
- AE monitoring; and
- Study drug dispensation (rucaparib).

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until Day 1 of the next treatment cycle. Patients will ingest rucaparib BID at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of water with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 7.5.1).

Site personnel will account for study drug that is dispensed to the patient during the study visit and document appropriately.

8.8.2 Day 15 of Cycles 1 and 2 (Crossover to Rucaparib)

The following procedures/assessments will be completed:

- Physical examination;
- Vital Signs;
- Concomitant medications and procedures;
- ECOG performance status (Appendix 2);
- Hematology;

- Serum chemistry (fasting is not required);
- AE monitoring; and
- Study drug continuation.

Patients will continue BID dosing with rucaparib with or without food, taking doses at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz. (240 mL) of water. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treat or dose modify according to the criteria described in Section 7.5.1).

8.9 Post-treatment for Patients Who Cross Over to Rucaparib

8.9.1 Treatment Discontinuation for Patients Who Cross Over to Rucaparib

Upon discontinuation of rucaparib treatment in patients who crossed over from chemotherapy, regardless of the reason, there will be a treatment discontinuation visit.

The following procedures will be performed:

- PRO using the EORTC QLQ-C30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate (complete before other procedures; Appendix 5);
- Physical examination;
- Weight;
- Vital Signs;
- 12-lead ECG;
- Concomitant medications and procedures;
- Disease/ tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan]) if reason for treatment discontinuation was other than death or disease progression based on radiologic assessment and it has been ≥ 8 weeks since last scan or disease progression was noted on the last scan;
- ECOG performance status (Appendix 2);
- Hematology;
- Serum chemistry (fasting is not required);
- Serum pregnancy for women of childbearing potential;
- CA-125 measurement (Appendix 4);
- Blood sample for ctDNA analysis;
- AE monitoring; and
- Optional tumor tissue biopsy collection any time after disease progression, cross over to rucaparib, or treatment discontinuation until the start of the next non-study treatment

(requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions.

Patients will continue to be followed for 28 (±3) days after discontinuation of rucaparib as crossover treatment in the 28-day follow-up visit as described in Section 8.5.2 and in LTFU as described in Section 8.5.3.

9 METHODS OF DATA COLLECTION

9.1 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, progression-free interval after last platinum regimen, radiology reports, and gBRCA mutation status (if known).

9.2 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 28-day Safety Follow-up Visit after treatment discontinuation. Medications information will be entered in the appropriate eCRF after it is obtained at each study visit.

9.3 Efficacy Evaluations

9.3.1 Disease/ Tumor Assessments

Disease/ tumor assessments will be performed during screening (baseline), at the end of every 8 calendar weeks after Cycle 1 Day 1 (within 5 days before is permitted) during treatment, and continue post-treatment every 8 calendar weeks, relative to Cycle 1 Day 1, until radiologically confirmed disease progression by RECIST Version 1.1, as assessed by the investigator, or death (unless these were the reasons for treatment discontinuation), or initiation of subsequent treatment. Tumor assessments should be performed at the time of treatment discontinuation if the reason was other than death or radiologically-confirmed disease progression and it has been ≥ 8 weeks since the last assessment. Patients who have been on study at least 18 months, may decrease the frequency of tumor assessments to every 16 weeks (within 5 days before is permitted).

Tumor response will be interpreted using RECIST Version 1.1 (Appendix 1). Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST Version 1.1. If the radiologic assessment does not confirm GCIG CA-125 disease progression, patients should continue on treatment and continue to be assessed by RECIST Version 1.1 per the protocol schedule of assessments.

Disease/ tumor assessments should consist of clinical examination and appropriate imaging techniques (ie, computed tomography [CT] scans of the chest, abdomen, and pelvis with

appropriate slice thickness per RECIST Version 1.1); other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET], and ultrasound) may also 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 time.

Copies of CT scans (and other imaging, as appropriate) will be collected from all patients for Independent Radiology Review (IRR).

9.3.2 Tumor Markers

Blood samples to assess CA-125 will be collected at screening, on Day 1 of Cycle 1, at the start of every 2nd cycle thereafter (ie, Day 1 of Cycles 3, 5, 7, etc.), at treatment discontinuation, and as clinically indicated. All CA-125 tests will be performed by a local laboratory.

CA-125 < ULN will be required to designate a CR.

9.4 Safety Evaluations

9.4.1 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. Patients will be monitored for AEs during study participation (beginning at the time informed consent is obtained) and until 28 days after the last dose of study drug. After the 28-day window, only treatment-related SAEs assessed as potentially related to study drug (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and the AESIs of MDS and AML irrespective of causality, need to be reported. In the time after informed consent is provided but before study drug is administered, AEs/ SAEs are to be recorded if they are the result of a study-related procedure. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (Version 4.03) and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 10.

If a patient discontinues from treatment and begins subsequent anti-cancer therapy, the Sponsor will terminate collection of SAEs, with the exception of the AESIs of MDS and AML.

9.4.2 Clinical Laboratory Investigations

Samples for hematology, serum chemistry, urinalysis, and serum pregnancy will be analyzed by a local laboratory. Fasting is not required before blood sampling. The panels of laboratory tests to be performed are shown below:

Hematology: red blood cells (RBC) and parameters (hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]) and reticulocyte count, white blood cells (WBC) and differential (with ANC), and platelet count will be assessed at screening, during treatment at each study visit, and at the treatment discontinuation visit for all patients. Hematology results must be reviewed by the investigator before the start of treatment with study drug and ongoing at times testing occurs. Additional and more frequent tests may be performed at the investigator's discretion.

Serum Chemistry: total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, glucose, sodium, potassium, chloride, bicarbonate (optional), calcium, phosphorus, and lipid panel (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], and triglycerides), at screening, during treatment at each study visit, and at the treatment discontinuation visit for all patients. Testing of bicarbonate is optional and should be performed when clinically indicated or evaluated through arterial blood gas at the investigator's judgement. With the exception of bicarbonate, phosphorus, and the lipid panel, serum chemistry results must be reviewed by the investigator before the start of treatment with study drug and ongoing at times testing occurs.

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

Serum Pregnancy: for women of childbearing potential only. A serum pregnancy test must be performed ≤ 3 days prior to first dose of study drug (a negative result is required before dosing can begin) and at the treatment discontinuation visit. A serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Treatment Phase, and a serum pregnancy test performed at Treatment Discontinuation. A positive serum pregnancy test during study participation must be reported to the Sponsor. Refer to Section 10.6 for details.

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 10.5 for guidelines on reporting of abnormal laboratory values as AEs.

9.4.3 Vital Signs

Vital signs will include blood pressure, heart rate, and body temperature and will be taken after the patient has been resting for at least 5 minutes during screening, at study visits during the Treatment Phase, and at the treatment discontinuation visit.

9.4.4 12-Lead Electrocardiogram

For all patients, 12-lead ECGs will be performed at the following times:

- Screening (within 28 days prior to randomization)
- At each study visit
- Treatment discontinuation

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

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

9.4.5 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, at each study visit prior to chemotherapy administration, and at the treatment discontinuation visit.

9.4.6 Physical Examinations

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

9.4.7 ECOG Performance Status

ECOG performance status (Appendix 2) will be assessed during screening, at study visits during the Treatment Phase, and at the treatment discontinuation visit. 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.

9.5 Biomarker Analysis – FFPE Tumor Tissue

All patients, with the exception of those known (ie, documented) to harbor a deleterious BRCA1/2 mutation (germline or somatic), will be required to provide sufficient quantity of archival tumor tissue or a screening biopsy for central laboratory analysis prior to enrollment.

A sufficient quantity of archival tumor tissue or tumor tissue from a screening biopsy must be submitted directly to the central laboratory **at least 3 weeks prior to the planned randomization** for determination of HRD status.

Patients with a known deleterious BRCA1/2 mutation (germline or somatic) must also submit archival tumor tissue for central laboratory testing; however, enrollment is not contingent upon the central laboratory analysis of tissue. A local BRCA1/2 mutation result from

previous testing will be adequate for enrollment. Sufficient quantity of archival tumor tissue must be confirmed by central laboratory testing in these patients during the study. If archival tumor tissue of sufficient quantity is not available, the patient may undergo a screening biopsy.

Patients with a deleterious BRCA1/2 mutation who meet all other entry criteria will be eligible for the study.

Sufficient archival FFPE tumor tissue (enough for 1 x 4 µm section for H&E and approximately 8 to 12 x 10 µm sections [unstained], or equivalent) for planned analyses should be provided. In addition to determining HRD status, gene expression profiling on extracted RNA will be analyzed to classify tumors into gene expression molecular subtypes, which have been shown to associate with patient survival in HGSOC.[64] Refer to the Pathology Charter for details. The most recently collected tumor tissue sample available that is of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content) must be provided or a new sample acquired.

An optional tumor tissue biopsy sample is requested any time after disease progression, crossover to rucaparib, or treatment discontinuation until the start of the next non-study treatment. 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 Pathology Charter.

9.6 Biomarker Analysis – Blood

Blood samples will be collected as specified in the Schedule of Assessments during screening, before dosing on Day 1 of Cycles 1 to 6, and at treatment discontinuation from all patients entered in the study for plasma ctDNA and genomic (g/sBRCA) analyses. Blood samples will also be collected at the same times in patients who cross over to rucaparib treatment. Genomic DNA will be extracted from the cellular portion of these blood samples and analyzed to determine whether the BRCA1/2 mutation is germline or somatic prior to final data analysis. Sample collection details are provided in the Laboratory Manual.

9.7 Pharmacokinetics Evaluation

For patients receiving rucaparib, plasma samples are to be collected for trough level PK analysis of rucaparib before the morning dose on Day 1 of Cycles 2 to 6 as close to 12 hours after the previous dose as possible. If the start of the next treatment cycle is delayed, the PK sample should still be collected during this visit instead of on Day 1 of the delayed start of the next treatment cycle. Samples are not to be collected in patients receiving chemotherapy or crossing over to rucaparib. Refer to the Laboratory Manual for sample collection details for PK samples.

9.8 Patient Reported Outcomes (Health and Quality of Life Questionnaires)

Patient reported outcomes (PROs) consisting of the EORTC QLQ-30/ QLQ-OV28, and EQ-5D instruments, or other collection format as appropriate (see Appendix 5), will be assessed during screening, on Day 1 of every treatment cycle, at treatment discontinuation, and at the 28-day Safety Follow-up Visit. Patients should complete the instruments before any other scheduled study procedures are performed and dosing occurs (if applicable).

PRO assessments should be collected at every cycle for all patients through disease progression in association with the radiologic assessments for disease progression.

10 ADVERSE EVENT MANAGEMENT

10.1 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, not on the physical examination eCRF, which is reserved for physical signs or findings).

10.2 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) 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.

10.3 Definition of an Adverse Event of Special Interest

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

Details on the Sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to the Sponsor within 24 hours of knowledge of the event (see Section 10.10 for reporting instructions).

10.4 Events or Outcomes Not Qualifying as Serious Adverse Events

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

- Pre-planned or elective hospitalization including social and/ or convenience situations (eg, respite care)
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward)
- Overdose of either Clovis study drug or concomitant medication unless the event meets SAE criteria (eg, hospitalization). 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 SAE.
- Events that meet the SAE criteria (as outlined in Section 10.2) and occur after informed consent, but before the first dose of study drug that are considered unrelated to protocol-mandated screening procedures.

10.5 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in lab 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

10.6 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a study patient or partner of a study patient 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 an SAE.

A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form should 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.

10.7 Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

Events that occur after signing of informed consent but prior to initiation of study drug, unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF; however, events are to be reported as SAEs if serious and related to a protocol-mandated procedure during this time. Any AE that occurs after first dose of study drug through 28 days after receiving the last dose of [study drug] will be recorded on the AE eCRF.

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

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

SAEs and AESIs that occur during the study or within 28 days after receiving the last dose of study drug, 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. After the 28-day reporting window after discontinuation of randomized treatment and/or cross over to rucaparib for patients randomized to chemotherapy, only SAEs assessed as potentially related to study drug need to be reported. This includes serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis,

hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug.

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

- AESIs of pneumonitis or similar events should only be reported up to, but not beyond, the 28-day Follow-up Visit (28 days after the last dose of rucaparib).

Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 10.8.

10.7.1 Onset Date of Adverse Events

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

10.7.2 Resolution Date of Adverse Events

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

10.7.3 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, Version 4.03 grading scale (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).[65]

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 those that led to the patient's death

10.7.4 Causal Relationship of Adverse Events to Study Drug

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

Not Related To Study Drug	• An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.) • 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.

10.7.5 Outcome and Action Taken

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

Action Taken with Study Drug (note all that apply)

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

Outcome

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

10.8 Follow-Up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

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

10.9 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria,[63] must be reported as SAEs (see Section 10.7 for reporting details).

Potential drug induced liver injury is defined as:

1. ALT or AST elevation > 3 × upper limit of normal (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.

10.10 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 U.S. Food and Drug Administration (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.

11 PLANNED STATISTICAL METHODS

11.1 General Considerations

All efficacy analyses will be performed at a two-sided 0.05 significance level. All efficacy analyses will be analyzed for the Efficacy Population and for the ITT Population. The Efficacy Population is defined as all randomized patients with a deleterious BRCA mutation, excluding those patients identified to have a BRCA reversion mutation. The methodology used to identify patients with a BRCA reversion mutation based on analysis of a blood sample obtained prior to randomization will be detailed in a separate document.

All safety analyses will be summarized for all patients who received at least one dose of protocol-specified treatment.

This study has a randomized part and a crossover part, and all efficacy, disposition, demographics and baseline, and safety will be presented separately for these study parts.

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

The Kaplan-Meier methodology will be used to summarize time-to-event variables. If estimable, the 50th (median) percentile with the 95% confidence interval (CI) will be summarized for each randomized treatment group. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

The number of patients with events and the number of censored patients will also be presented.

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

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

11.2 Determination of Sample Size

The enrollment planned for this study is approximately 345, with 230 patients randomized to rucaparib and 115 patients to chemotherapy.

The median PFS is assumed to be 12 months for rucaparib and 8 months for the comparator. Assuming an accrual over about 3 years; a dropout rate of 2%; with a hazard ratio of 0.65; and at least 275 events, a sample size of 345 patients (230 patients randomized to rucaparib

and 115 patients randomized to chemotherapy) would yield at least 80% power at a two-sided 0.05 significance level.

11.3 Analysis Populations

The following analysis populations are defined for the treatment part of the study:

Safety Population – Patients who received at least one dose of protocol-specified treatment.

ITT population – All randomized patients.

Efficacy Population – All randomized patients with a deleterious BRCA mutation, excluding those identified to have a BRCA reversion mutation.

The crossover part will only be summarized for the Safety Population, which is defined as all patients who crossed over to rucaparib treatment and received at least one dose of rucaparib.

11.4 Patient Disposition

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

11.5 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 baseline variables will be summarized with frequency tabulations:

- Time since diagnosis of primary tumor (months): 0 to 12, > 12 to 24, > 24;
- The randomization factor or progression-free interval for the most recent prior platinum-based regimen:
  - Platinum resistant: patients who progressed ≥ 1 to < 6 months after the last dose of platinum-based chemotherapy;
  - Partially platinum-sensitive: patients who progressed ≥ 6 to < 12 months after last dose of platinum-based chemotherapy; and
  - Platinum sensitive: patients who progressed ≥ 12 months after last dose of platinum-based chemotherapy
- The following BRCA1/2 mutation characteristics will also be summarized:
  - BRCA1/2 mutation status (germline or somatic)
  - BRCA mutation gene (BRCA1 or BRCA2)

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

11.6 Efficacy Analyses

All efficacy analyses will be performed both in the Efficacy Population and in the ITT Population. The primary endpoint and key secondary endpoints will be tested using a hierarchical step-down procedure starting with the primary efficacy endpoint in the Efficacy Population then testing the primary endpoint for the ITT Population.

If the primary endpoint is statistically significant, then the secondary efficacy endpoints will be tested in the order specified below where for each endpoint, first in the Efficacy Population, and then in the ITT Population. In order to preserve the overall Type 1 error rate, statistical significance will only be declared for the secondary endpoints, listed below, if the primary endpoint and previous secondary endpoints are also statistically significant;

1. ORR by RECIST Version 1.1;
2. DOR by RECIST Version 1.1;
3. ORR by RECIST Version 1.1 and CA-125 response; and
4. PRO as assessed by the EORTC QLQ-C30 Global Health Status score.

The stratification factor used for randomization is the progression-free interval after most recent platinum-containing therapy (ie, platinum-resistant, partially platinum-sensitive, or platinum-sensitive). All efficacy analyses will be based on the randomization strata given at randomization, however, a sensitivity analysis of invPFS may be performed using the actual strata if patients have been allocated incorrectly.

11.6.1 Primary Efficacy Analyses

The primary efficacy endpoint for the study is disease progression according to RECIST Version 1.1 as assessed by the Investigator, or death from any cause for the treatment part. Patients without a documented event of progression will be censored on the date of their last tumor assessment (ie, radiologic assessment) or date of randomization if no tumor assessments have been performed. Patients who withdraw from treatment prior to progression will be followed for disease status and survival whenever possible.

The primary endpoint of invPFS will be analyzed using the stratified Cox proportional hazard methodology. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

11.6.2 Secondary Efficacy Analyses

The secondary endpoint of bicrPFS by RECIST Version 1.1 is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by BICR, or death due to any cause, whichever occurs first. Only tumor scans prior to start of any subsequent anti-cancer treatment are included.

OS will be analyzed using Cox proportional hazard methodology. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

ORR by RECIST Version 1.1 as assessed by the investigator: The proportion of responders will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test.

Duration of Response (DOR) as assessed by the investigator: DOR is defined as the time from the first response (RECIST Version 1.1 CR or PR) until the first date that PD is documented. Duration of response will be summarized and analyzed using the same methodology as described for the primary endpoint.

ORR by RECIST Version 1.1 as assessed by the investigator and CA-125 response: The proportion of responders will be analyzed using a stratified chi-square test.

Change from baseline during the first 6 treatment cycles for PRO endpoints by EORTC QLQ-C30 Global Health Status score.

PRO endpoints by EORTC QLQ-C30 and QLQ-OV28 will be summarized according to the scoring manual.

Analyses of changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for each subscale and total score. Patients that do not have both a baseline measurement and at least one post-baseline measurement will not be included.

At a given visit, the change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment and stratification variable as a categorical factor and baseline measurement for the parameter as a continuous covariate. In addition, further analyses using repeated measures modeling or time to event might be used and will be described in the SAP.

11.6.3 Exploratory Efficacy Analyses

The endpoints for exploratory analyses are:

- To evaluate PFS of study treatment followed by the subsequent line of treatment (PFS2), defined as the time from randomization to the second event of disease progression or death, as assessed by the investigator;
- To evaluate PRO utilizing the EQ-5D;
- To assess molecular changes in tumor samples over time in matched pairs;
- To assess circulating ctDNA as a molecular marker of efficacy;
- To assess efficacy in BRCA-mutation subgroups (ie, germline/somatic and BRCA1/BRCA2)
- To evaluate the impact of gene expression molecular subgroups on PFS and OS;
- To evaluate disease control rate (RECIST Version 1.1 CR, PR, and prolonged SD > 12 weeks, by investigator assessment).

11.6.3.1 Progression-free Survival 2 (PFS2)

The second event of PFS, PFS2, is defined as the time from randomization to the second event of disease progression as assessed by the investigator, or death due to any cause. The first event of disease progression will be captured as the primary endpoint in this study and thus the second event will be the next event of disease progression as assessed by the investigator. This second event of PFS may be a documented event per RECIST Version 1.1 guidelines or may be an event of symptomatic progression. Progression-free survival 2 will be analyzed using Cox proportional hazard method. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

11.6.3.2 Patient-reported Outcome EQ-5D

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

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

11.6.3.3 Changes in Tumor Samples and Changes in Circulating Cell-free Tumor DNA

Changes in the molecular profile of tumor samples over time in matched pairs of pre- and post-treatment tissue, if available, will be evaluated in addition to the circulating ctDNA.

11.6.3.4 Disease Control Rate

Disease control rate is defined as RECIST Version 1.1 evaluation of CR, PR or SD > 12 weeks and SD > 24 weeks as assessed by the investigator. The number and percent of patients meeting the criteria for disease control rate for each treatment group will be summarized. The proportion of patients will be analyzed using a stratified chi-square test.

11.6.4 Exploratory Pharmacokinetic Analyses

In all patients with at least one PK sample collected, the trough plasma rucaparib PK data (C_{min}) and summary statistics (N, mean, SD, minimum, median, max, CV%) will be reported. The PK data and selected safety and efficacy endpoints will be included in exploratory population PK and exposure-response analyses, if data allow, and the results will be reported separately.

11.7 Safety Analyses

All safety analyses will be summarized by randomization treatment group for the randomized part and for all patients in the crossover part.

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

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

11.7.1 Adverse Events

AEs will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 or later. Only treatment-emergent adverse events (TEAEs) will be collected: Treatment-emergent during the treatment part is defined as safety data with an onset date on or after the date of first dose of randomized study medication until the date of the last study medication plus 28 days, or up to the date of first dose of rucaparib for those patients who cross over from chemotherapy, whichever is first.

Safety data will be presented for the crossover part separately, using the safety assessment before or on the date of first dose of rucaparib as the baseline value for the crossover part for the patients who cross over. The data that is deemed treatment emergent for the crossover part is defined as safety data with an onset date on or after the date of first dose of rucaparib in the crossover part until the date of the last study medication plus 28 days.

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

Separate tables will be presented as follows:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs;
- Serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study medication;
- TEAEs resulting in interruption/delay of study medication; and
- TEAEs resulting in dose reduction of study medication.

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

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

11.7.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will be presented in SI units. The on-treatment period for the treatment part will be defined as data with an onset date on or after the date of first dose of study medication until the date of the last dose of study medication plus 28 days, or date of first dose of rucaparib for those patients who cross over from chemotherapy, whichever is first. The on-treatment period for the laboratory values for cross-over part will be defined as all laboratory values on or after first dose of rucaparib in the crossover until the date of the last dose of rucaparib plus 28 days.

Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

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

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

11.7.3 Vital Sign Measurements

The on-treatment period for the treatment part will be defined as the time from first dose of study drug to 28 days after the last dose of study drug, or start of first dose of rucaparib for those patients who cross over from chemotherapy, whichever is first. The on-treatment period for the vital signs for crossover part will be defined as all vital sign values on or after first dose of rucaparib in the crossover until the date of the last dose of rucaparib plus 28 days. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

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

and maximum) of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given.

11.8 Interim Analysis

No formal interim efficacy analyses are planned; however, ongoing review of data will occur.

An IDMC will meet to review the efficacy and safety data from this study. The IDMC will review efficacy and safety of rucaparib versus chemotherapy to ensure the study remains beneficial to patients.

The IDMC will have access to study data including patient treatment.

Individual patient treatment assignments will not be available to the Sponsor during an IDMC review. A plan will be put in place to limit bias for Sponsor personnel.

The IDMC may recommend that the study be stopped if the data indicate that the invPFS benefit will very likely not be achieved and/or there is excessive toxicity observed in the rates of serious and/or Grade 3 and 4 AEs.

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

12 PATIENT DISPOSITION

12.1 Removal of Patients from the Study or Study Drug

A patient must be discontinued from protocol-prescribed therapy if any of the following apply:

- Consent withdrawal for any reason at the patient's own request or at the request of their legally authorized representative;
- Progression of patient's underlying cancer per RECIST Version 1.1 (unless, in the opinion of the investigator, the patient continues to derive clinical benefit; treatment beyond progression must be approved by the Sponsor);
- 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;
- Non-compliance by the patient with protocol-mandated procedures; or
- A positive pregnancy test at any time during the study.

Discontinuation of treatment does not necessarily indicate study discontinuation for a patient. Samples collected for research will continue to be used unless the patient explicitly withdraws consent for their use. If patient samples are tested before consent is withdrawn, the information collected up to the point of the withdrawn consent may still be used. If the patient withdraws consent to continue in the study or discontinues the study for another reason it will be documented on the appropriate eCRF. A patient may withdraw consent to participate in an additional part of a study that has an additional consent (ie, optional tumor biopsy) yet continue to participate and be treated/ followed in the main part of the study.

The Sponsor may discontinue the study early for any of the reasons noted in Section 13.7.

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Council for Harmonisation (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 and the ethical principles underlying the European Union Directive 2001/20/EC and the US CFR, Title 21, Part 50 (21CFR50) and applicable local requirements.

13.1.1 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.

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

13.1.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, drug dosing diaries, 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 informed consent form will be transmitted to the Sponsor. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

No patient will be admitted to the study until appropriate IEC/ IRB approval of the study protocol has been received, the investigator has obtained the signed and dated informed consent form, 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.

13.2 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 E6(R2) GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed ICFs from each patient 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.

The patient will have the option to provide additional consent to allow or not allow the Sponsor to retain residual samples for future unspecified research.

13.3 Patient Confidentiality

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient identifiers such as initials, year of birth, and an identification code (ie, not names) should be recorded on any form submitted to the Sponsor and the IRB/ IEC. The investigator must record all 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 Investigator's Brochure, 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.

13.4 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. Visits may also be conducted by Sponsor personnel.

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.

13.5 Case Report Forms and Study Data

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.

Clinical data, including AEs, concomitant medications, and laboratory data will be entered into Medidata RAVE, a 21 CFR Part 11-compliant data capture system. The data system

includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.6 Independent Data Monitoring Committee

An IDMC will be established to review safety and efficacy data in compliance with a prospective charter. The IDMC will be comprised of medical oncologists with experience in treating patients with the cancer being studied and a statistician, all of whom are not otherwise involved in the study as investigators. The IDMC responsibilities, authorities, and procedures for this study will be documented in the IDMC charter, which will be endorsed and signed by the IDMC prior to the first data review meeting.

Following data review, the IDMC will recommend continuation, revision, or termination of the study and/ or continuing or halting enrollment into a particular subgroup. The IDMC will also ensure the study is beneficial to patients (see Section 11.8). The IDMC will meet at least semi-annually after sufficient data has been collected. The IDMC chairperson may convene a formal IDMC meeting if there are safety concerns. The Sponsor can also request an IDMC review of safety data. Details regarding the IDMC will be in the committee charter.

13.7 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. Refer to Section 5.3 for additional details.

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 any of the following apply:

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

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

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).

13.8 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.

13.9 Retention of Data

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, drug accountability records, correspondence with the IEC/ IRB and the Sponsor, and other study-related documents.

The investigator should have control of all essential documents generated by the site. Source documents must be maintained and meet standard criteria of source documentation practices to ensure data is attributable, legible, contemporaneous, original or certified copy, accurate, and complete, consistent, enduring, and available (ALCOA+), and any changes to 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 trial 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 informed consent forms, 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 that are used for source document verification should fulfill the requirements for certified copies. Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location. The Sponsor will inform the investigator, in writing, when the trial-related records are no longer needed.

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

13.10 Quality Control and Assurance

The Sponsor will implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) 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 trial results should be the focus of these procedures.

13.10.1 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 subject having to be withdrawn from the study and rendering that subject non-evaluable. Any deviation must be documented in the source documents and reported to the Sponsor.

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

13.10.2 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 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.

13.10.3 Direct Access to Source Data/ Documents for Audits and Inspections

The study 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 purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate clinical study conduct and compliance with the protocol, SOPs, ICH GCPs, and the applicable regulatory requirements. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. The investigator and the Sponsor may also be subject to an inspection by FDA, European Regulatory authorities, or other applicable regulatory authorities at any time. The auditor and regulatory authorities will require authority from the investigator to have direct access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files are available, if requested. It is important that the investigator(s) and their staff cooperate with the auditor or regulatory authorities during an audit or inspection.

13.11 Clinical Study Report

A CSR will be prepared, regardless of whether the trial is completed, under the responsibility and supervision of the Sponsor and signed by the Sponsor's Chief Medical Officer, thereby indicating their agreement with the analyses, results, and conclusions of the CSR. The CSR will be provided to the regulatory agency(ies) as required by the applicable regulatory requirements.

13.12 Publication and Disclosure Policy

All data generated from this study are the property of the Sponsor and shall be held in strict confidence along with all information furnished by the Sponsor. 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. Written permission to the investigator will be contingent on the review by the Sponsor of the statistical analysis and manuscript, and will provide for nondisclosure of the Sponsor confidential or proprietary information. In all cases, the parties agree to provide all manuscripts or abstracts to all other parties 30 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.

13.13 Investigator Oversight

The investigator has a responsibility for supervising any individual or party to whom they delegate trial related duties or functions conducted at the trial 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 and data generated.

14 REFERENCE LIST

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277-300.
2. US Cancer Statistics Working Group. United States Cancer Statistics: 1999–2009 Incidence and Mortality Web-based Report: Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2013 [Available from: http://www.cdc.gov/uscs.
3. Morgan RJ, Jr., Alvarez RD, Armstrong DK, Boston B, Burger RA, Chen LM, et al. NCCN Clinical Practice Guidelines in Oncology: epithelial ovarian cancer. Journal of the National Comprehensive Cancer Network. 2011;9(1):82-113.
4. Pfisterer J, Ledermann JA. Management of platinum-sensitive recurrent ovarian cancer. Semin Oncol. 2006;33(2 Suppl 6):S12-6.
5. Naumann RW, Coleman RL. Management strategies for recurrent platinum-resistant ovarian cancer. Drugs. 2011;71(11):1397-412.
6. Clovis Oncology, Inc. RUBRACA (Rucaparib) [prescribing information] December 2016 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf.
7. Oza AM, Tinker AV, Oaknin A, Shapira-Frommer R, McNeish IA, Swisher EM, et al. Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2. Gynecol Oncol. 2017.
8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer: J Natl Compr Canc Netw; 2014 [Version 2.2015]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
9. Bristol-Myers Squibb Company. TAXOL (paclitaxel) Prescribing Information April 2011 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf.
10. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi24-32.
11. Bristol-Myers Squibb Company. PARAPLATIN (carboplatin) Prescribing Information July 2010 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020452s005lbl.pdf.
12. TCGA. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609-15.
13. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654-63.
14. Pruthi S, Gostout BS, Lindor NM. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. Mayo Clinic Proceedings. 2010;85(12):1111-20.
15. Hennessy BTJ, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD, et al. Somatic Mutations in BRCA1 and BRCA2 Could Expand the Number of Patients That Benefit

From Poly (ADP Ribose) Polymerase Inhibitors in Ovarian Cancer. J Clin Oncol. 2010;28(22):3570-6.
16. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434(7035):913-7.
17. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917-21.
18. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009;361(2):123-34.
19. Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet. 2010;376(9737):245-51.
20. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376(9737):235-44.
21. Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol. 2011;12(9):852-61.
22. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin GJS, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a BRCA mutation (BRCAm). J Clin Oncol. 2013:31(15_suppl):abstract 5505.
23. Kristeleit RS, Shapiro G, LoRusso P, Infante JR, Flynn M, Patel MR. A phase I dose-escalation and PK study of continuous oral rucaparib in patients with advanced solid tumors. J Clin Oncol. 2013;31(suppl):2585.
24. Cannistra SA. Cancer of the ovary. N Engl J Med. 2004;351(24):2519-29.
25. Cannistra SA. Is there a "best" choice of second-line agent in the treatment of recurrent, potentially platinum-sensitive ovarian cancer? J Clin Oncol. 2002;20(5):1158-60.
26. Salvador S, Rempel A, Soslow RA, Gilks B, Huntsman D, Miller D. Chromosomal instability in fallopian tube precursor lesions of serous carcinoma and frequent monoclonality of synchronous ovarian and fallopian tube mucosal serous carcinoma. Gynecol Oncol. 2008;110(3):408-17.
27. Levanon K, Crum C, Drapkin R. New insights into the pathogenesis of serous ovarian cancer and its clinical impact. J Clin Oncol. 2008;26(32):5284-93.
28. Flesken-Nikitin A, Hwang CI, Cheng CY, Michurina TV, Enikolopov G, Nikitin AY. Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche. Nature. 2013;495(7440):241-5.
29. Reed E, Dabholkar M, Chabner BA. Platinum Analogues. In: Chabner BA, Longo DL, editors. Cancer Chemotherapy and Biotherapy. Philadelphia: Lippincott-Raven Publishers; 1996. p. 357-78.
30. Parkinson CA, Brenton JD. Predictive Biology of Ovarian Cancer. In: Kehoe S, editor. Gynaecological Cancers: Biology and Therapeutics. London: RCOG; 2011. p. 41-54.

31. Roche Registration Limited. AVASTIN (bevacizumab) SmPC 19 July 2016 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf.
32. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32(13):1302-8.
33. AVASTIN (bevacizumab) [package insert]. South San Francisco, CA: Genentech, Inc; May 2015 [Available from: http://www.gene.com/download/pdf/avastin_prescribing.pdf.
34. Bruchim I, Jarchowsky-Dolberg O, Fishman A. Advanced (>second) line chemotherapy in the treatment of patients with recurrent epithelial ovarian cancer. European journal of obstetrics, gynecology, and reproductive biology. 2013;166(1):94-8.
35. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. 2012;23(10):2605-12.
36. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib Monotherapy in Patients With Advanced Cancer and a Germline BRCA1/2 Mutation. J Clin Oncol. 2014.
37. Clovis Oncology Inc. RUBRACA (rucaparib) Prescribing Information October 2020 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s008lbl.pdf.
38. AstraZeneca Pharmaceuticals LP. LYNPARZA (olaparib) Prescribing Information May 2020 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf.
39. GlaxoSmithKline. ZEJULA (niraparib) Prescribing Information April 2020 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf.
40. Clovis Oncology UK Ltd. RUBRACA (rucaparib) SmPC March 2019 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004272/WC500249806.pdf.
41. AstraZeneca AB. LYNPARZA (olaparib) SmPC November 2019 [Available from: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf.
42. Tesaro Bio Netherlands BV. ZEJULA (niraparib) SmPC February 2020 [Available from: https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf.
43. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014;15(8):852-61.
44. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-64.
45. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy

(ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10106):1949-61.
46. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. The New England Journal of Medicine. 2012.
47. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. The Lancet Oncology. 2014;15(8):852-61.
48. Mukhopadhyay A, Elattar A, Cerbinskaite A, Wilkinson SJ, Drew Y, Kyle S, et al. Development of a functional assay for homologous recombination status in primary cultures of epithelial ovarian tumor and correlation with sensitivity to poly(ADP-ribose) polymerase inhibitors. Clin Cancer Res. 2010;16(8):2344-51.
49. Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996;56(23):5360-4.
50. Pellegata NS, Sessa F, Renault B, Bonato M, Leone BE, Solcia E, et al. K-ras and p53 gene mutations in pancreatic cancer: ductal and nonductal tumors progress through different genetic lesions. Cancer Res. 1994;54(6):1556-60.
51. Drew Y, Plummer R. The emerging potential of poly(ADP-ribose) polymerase inhibitors in the treatment of breast cancer. Current Opinion in Obstetrics and Gynecology. 2010;22(1):67-71.
52. Oza AM, Lorusso D, Oaknin A, Safra T, Swisher EM, Bondarenko IM, et al., editors. ARIEL4: An International, Multicenter Randomized Phase 3 Study of the PARP Inhibitor Rucaparib vs Chemotherapy in Germline or Somatic BRCA1- or BRCA2-Mutated, Relapsed, High-Grade Ovarian Carcinoma [abstract]. 2017 ASCO Annual Meeting; 2017; Chicago, IL.
53. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2017.
54. Fulcher N, Shenolikar RA, Durden E, Moore KN, editors. Incidence of secondary myelodysplastic syndrome and acute myeloid leukemia in patients with ovarian and breast cancer in real-world setting in the U.S. 2017 ASCO Annual Meeting: J Clin Oncol 35, 2017 (suppl; abstr 5574).
55. Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer. 2007;7:152.
56. Rosenberg P, Andersson H, Boman K, Ridderheim M, Sorbe B, Puistola U, et al. Randomized trial of single agent paclitaxel given weekly versus every three weeks and with peroral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. Acta Oncol. 2002;41(5):418-24.
57. Tan DS, Yap TA, Hutka M, Roxburgh P, Ang J, Banerjee S, et al. Implications of BRCA1 and BRCA2 mutations for the efficacy of paclitaxel monotherapy in advanced ovarian cancer. European Journal of Cancer. 2013;49(6):1246-53.

58. du Bois A, Luck HJ, Buser K. Extended phase II study of paclitaxel as a 3-h infusion in patients with ovarian cancer previously treated with platinum. Eur J Cancer Clin Oncol. 1997;;33(379-84).
59. Gore ME, Levy V, Rustin G, Perren T, Calvert AH, Earl H, et al. Paclitaxel (Taxol) in relapsed and refractory ovarian cancer: the UK and Eire experience. British journal of cancer. 1995;72(4):1016-9.
60. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, Gianni L, Myles J, van der Burg ME, et al. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. J Clin Oncol. 1994;12(12):2654-66.
61. Budd GT, Barlow WE, Moore HCF, Hobday TJ, Stewart JA, Isaacs C, et al., editors. Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer. 2013 ASCO Annual Meeting: J Clin Oncol 31:18s, 2013 (suppl; abstr CRA1008).
62. Ang JE, Gourley C, Powell CB, High H, Shapira-Frommer R, Castonguay V, et al. Efficacy of chemotherapy in BRCA1/2 mutation carrier ovarian cancer in the setting of PARP inhibitor resistance: a multi-institutional study. Clin Cancer Res. 2013;19(19):5485-93.
63. US Department of Health and Human Services, Food and Drug Administration, CDER, CBER. Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation 2009 [Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf.
64. Leong HS, Galletta L, Etemadmoghadam D, George J, Köbel M, Ramus SJ, et al. Efficient molecular subtype classification of high-grade serous ovarian cancer. The Journal of pathology. 2015;236(3):272-7.
65. National Cancer Institute. Common Terminology Criteria for Adverse Events, Version 4.03 14 June 2010 [Available from: http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
66. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer. 2009;45(2):228-47.
67. Services UDoHaH, Administration FaD, CDER. Guidance for Industry: In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions January 2020 [Available from: https://www.fda.gov/media/134582/download
68. Rustin GJS, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21(2):419-23.

15 APPENDICES

15.1 Appendix 1

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS CRITERIA

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009) and at http://www.eortc.be/Recist/Default.htm.[66] A short summary is given below.

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 LD of target lesions, taking as reference the baseline sum LD.
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 LD 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. The appearance of one or more new lesions is also considered progression.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
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	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

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
Abbreviations: CR = complete response; NE = nonevaluable; PD = progressive disease; stable disease = stable disease.			

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

Abbreviations: CR = complete response; NE = nonevaluable; PD = progressive disease; SD = stable disease.

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

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Duration of Response

CT scans are required for this study at screening and every 8 calendar weeks (within 5 days before is permitted) thereafter. Patients who have been on study at least 18 months, may decrease the frequency of disease/ tumor assessments to every 16 weeks (within 5 days before is permitted).

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.

15.2 Appendix 2

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.

In the event performance status is assessed by the Karnofsky Performance Status scale, the following conversion chart applies.

Karnofsky Performance Status			**ECOG Performance Status**
General Description	**Score**	**Specific Description**	**Score**
Able to carry on normal activity and to work; no special care needed	100	Normal; no complaints; no evidence of disease	0
	90	Able to carry on normal activity; minor signs or symptoms of disease	1
	80	Normal activity with effort; some signs or symptoms of disease	
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do active work	2
	60	Requires occasional assistance, but is able to care for most of personal needs	
	50	Requires considerable assistance and frequent medical care	3
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance	
	30	Severely disabled; hospital admission is indicated although death not imminent	4
	20	Very sick; hospital admission necessary; active supportive treatment necessary	
	10	Moribund; fatal processes progressing rapidly	
	0	Dead	5

15.3 Appendix 3

EXAMPLES OF SENSITIVE CLINICAL CYTOCHROME P450 (CYP) SUBSTRATES

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

Source: FDA Guidance on Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-mediated Drug Interactions, January 2020.[67] Refer to this website for updated list of sensitive and moderate sensitive substrates. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1

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

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

15.4 Appendix 4

MODIFIED GYNECOLOGICAL CANCER INTERGROUP (GCIG) GUIDELINES FOR RESPONSE USING CA-125

Adapted from Rustin et al., Int J Gynecol Cancer. 2011.[68]
GCIG CA-125 definitions are available at http://gcig.igcs.org/CA-125.html.

To be evaluable for response by CA-125 requires an elevated baseline value of at least twice the upper limit of normal and at least two additional samples after the start of treatment.

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

1. in a sample collected after initiation of study treatment AND

2. that is confirmed in a subsequent sample collected ≥ 21 days after the prior sample. The absolute value of this confirmatory sample must be ≤ 110% of the prior sample.

The date when the first sample with a 50% decrease from baseline is observed is the date of the CA-125 response.

In patients who have measureable disease by RECIST Version 1.1 and CA-125, the date of response will be the date of the earlier of the two events. When assessing progression, the objective change in tumor size should be used for treatment decisions. For example, if a patient has a reduction in measurable disease, but an increase in CA-125 that suggests progression, treatment should continue.

15.5 Appendix 5

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, EORTC Ovarian Cancer Module QLQ-OV28, and Euro-Quality of Life 5D (EQ-5D) Patient Reported Outcomes

Sample forms for the EORTC QLQ-C30 and EORTC QLQ-OV28 are below and background for each questionnaire, respectively, is available at: http://groups.eortc.be/qol/eortc-qlq-c30 and http://groups.eortc.be/qol/why-do-we-need-modules.

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

EORTC QLQ-C30 Sample Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ-OV28 Sample Questionnaire

ENGLISH

EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have abdominal pain?	1	2	3	4
32. Did you have a bloated feeling in your abdomen / stomach?	1	2	3	4
33. Did you have problems with your clothes feeling too tight?	1	2	3	4
34. Did you experience any change in bowel habit as a result of your disease or treatment?	1	2	3	4
35. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
36. Have you felt full too quickly after beginning to eat?	1	2	3	4
37. Have you had indigestion or heartburn?	1	2	3	4
38. Have you lost any hair?	1	2	3	4
39. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
40. Did food and drink taste different from usual?	1	2	3	4
41. Have you had tingling hands or feet?	1	2	3	4
42. Have you had numbness in your fingers or toes?	1	2	3	4
43. Have you felt weak in your arms or legs?	1	2	3	4
44. Did you have aches or pains in your muscles or joints?	1	2	3	4
45. Did you have problems with hearing?	1	2	3	4
46. Did you urinate frequently?	1	2	3	4
47. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
48. Did you have hot flushes?	1	2	3	4
49. Did you have night sweats?	1	2	3	4

Please go on to next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
50. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
51. Have you been dissatisfied with your body?	1	2	3	4
52. How much has your disease been a burden to you?	1	2	3	4
53. How much has your treatment been a burden to you?	1	2	3	4
54. Were you worried about your future health?	1	2	3	4

During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
55. To what extent were you interested in sex?	1	2	3	4
56. To what extent were you sexually active?	1	2	3	4
Answer the following two questions only if you were sexually active:				
57. To what extent was sex enjoyable for you?	1	2	3	4
58. Did you have a dry vagina during sexual activity?	1	2	3	4

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

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

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

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

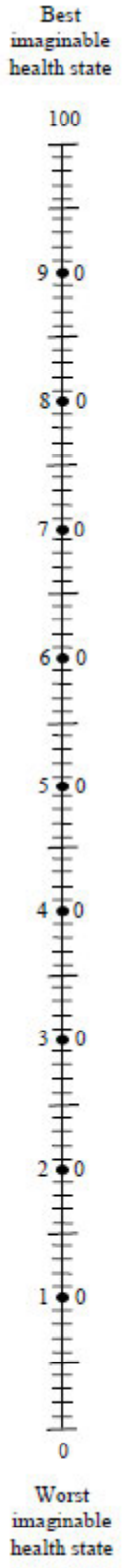
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3