Clinical Study Protocol: CO-338-100

Study Title:	LODESTAR: A Phase 2 Mu**L**ticenter, **O**pen-label Study of Rucaparib as Treatment for Soli**D** Tumors Associated with D**E**leteriou**S** Mu**T**ations in Homologous Recombin**A**tion **R**epair Genes.
Study Number:	CO-338-100
Study Phase:	Phase 2
Product Name:	Rucaparib (CO-338)
IND Number:	120,253
EUDRA CT Number:	2019-002142-20
Indication:	Multiple solid tumor types
Investigators:	Multicenter
Sponsor Name:	Clovis Oncology, Inc.
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Responsible Medical Officer:	Lindsey Rolfe, MBChB

Protocol Version	**Date**
Original Protocol:	09 July 2019
Amendment 1:	25 September 2019
Amendment 2	27 February 2020
Amendment 3	22 October 2020

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Date: 22 October 2020

Version: Amendment 3

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PROTOCOL ACCEPTANCE FORM

Protocol: CO-338-100

Title: LODESTAR: A Phase 2 Mu**L**ticenter, **O**pen-label Study of Rucaparib as Treatment for Soli**D** Tumors Associated with D**E**leteriou**S** Mu**T**ations in Homologous Recombin**A**tion **R**epair Genes.

Date: 22 October 2020

Version: Amendment 3

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

Investigator's Signature	Date (dd MMM yyyy)
Name (printed)	

SPONSOR'S MEDICAL EXPERT FOR THE STUDY

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CLINICAL INVESTIGATORS, STUDY SITES, AND LABORATORIES

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

PROTOCOL SYNOPSIS

Sponsor: Clovis Oncology, Inc.
Name of Finished Product: Rucaparib tablets
Name of Active Ingredient: Rucaparib camsylate (CO-338)
Study Title: LODESTAR: A Phase 2 Mu**L**ticenter, **O**pen-label Study of Rucaparib as Treatment for Soli**D** Tumors Associated with D**E**leterious**S** Mu**T**ations in Homologous Recombin**A**tion **R**epair Genes.
Study Number: CO-338-100
Study Phase: Phase 2
Study Duration: Q4 2019–2022
Background and Study Rationale: Inhibition of deoxyribonucleic acid (DNA) damage repair in cancer cells represents an attractive opportunity for the development of new therapies. In normal cells, single-strand breaks (SSBs) in DNA are repaired through base excision repair (BER) via poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn primarily repaired by homologous recombination repair (HRR) of DNA, a complex process involving multiple proteins. Given the overlap in various DNA repair pathways, inhibition of a single pathway is unlikely to have a significant effect on cancer cell death. However, inhibition of multiple DNA repair pathways may lead to cell death, a concept known as synthetic lethality. For example, normal cells treated with a PARP inhibitor have other intact DNA repair pathways and are thus able to survive, whereas cancer cells with pre-existing homologous recombination deficiency (HRD) that are treated with a PARP inhibitor accumulate DNA damage and enter apoptosis. This concept of synthetic lethality has been demonstrated in key in vitro and in vivo studies, as well as in several clinical studies that evaluated a single-agent PARP inhibitor.[1-3] In addition to breast cancer gene 1 DNA repair associated (BRCA1) and 2 DNA repair associated (BRCA2), multiple other HRR genes have been implicated in the functioning of the HRR pathway and induce HRD when mutated or lost.[4-6] Among these, there is compelling evidence that a deleterious alteration in PALB2, RAD51C and RAD51D may induce HRD, and in turn, sensitivity to a PARP inhibitor

like rucaparib. All 3 genes are essential for DSB repair and germline mutations in these are associated with a higher risk of developing ovarian and breast cancer; additionally, in vitro and in vivo data are supportive of mutations in these genes conferring sensitivity to rucaparib.

Rucaparib is a small molecule inhibitor of PARP-1, PARP-2, and PARP-3 that has demonstrated clinical activity in a number of tumor types, especially those associated with a deleterious mutation in BRCA1/2 or other HRR gene, and/or high level of genomic loss of heterozygosity (LOH). Rucaparib is approved in the United States (US) for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer who have been treated with 2 or more prior chemotherapies, and for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.[7-9] Rucaparib has also been approved in the European Union (EU) as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade EOC, FTC, or PPC who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy, and for maintenance treatment of adult patients with platinum-sensitive recurrent EOC, FTC, or PPC who are in response (complete or partial) to platinum-based chemotherapy.[10]

In October 2018, the US Food and Drug Administration (FDA) granted Clovis Oncology Breakthrough Therapy Designation (BTD) for rucaparib as a monotherapy treatment of adult patients with BRCA1/2-mutated metastatic castration-resistant prostate cancer (mCRPC) who received at least 1 prior androgen receptor (AR)-directed therapy and taxane based chemotherapy. BTD was granted following US FDA review of initial data from 25 patients who had these characteristics, had measurable disease at baseline, and enrolled in Study CO-338-052 (TRITON2).[11] An updated dataset of 45 patients showed a confirmed radiographic response of 44% with a confirmed PSA response of 51.1%. Responses were observed in patients with both germline or somatic BRCA alterations, similar to the observation in ovarian cancer.

Rucaparib has also demonstrated clinical activity in BRCA-mutant breast (1 patient had a complete response [CR] and 3 patients had a partial response [PR] in Part 1 of Study CO-338-010) and pancreatic (1 patient had a PR in Part 1 of Study CO-338-010; 1 patient had a CR and 2 patients had a PR in Study CO-338-023 [RUCAPANC]) cancer. Furthermore, interim analysis of a maintenance study of rucaparib in pancreatic cancer after induction with platinum chemotherapy demonstrated 5 responders (of 19 patients) with a BRCA1/2 mutation.[12] Supportive of these results, a patient with advanced non-small cell lung cancer (NSCLC) bearing a deleterious BRCA mutation, who had failed 2 prior lines of therapy and who received rucaparib under an Individual Treatment IND, had approximately 28 months of disease control before progressing (Clovis Oncology, Inc. [Clovis], correspondence on file).

Rucaparib has also demonstrated clinical activity in tumors associated with a deleterious mutation in genes other than BRCA1/2. In Part 1 of the Phase 2 Study CO-338-017 (ARIEL2), which evaluated rucaparib as treatment of recurrent platinum-sensitive ovarian cancer, 4 patients had a deleterious RAD51C mutation and 1 patient had a deleterious RAD51D mutation. Three of the 4 patients with a deleterious RAD51C

mutation achieved a confirmed PR by Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1. The single patient with a deleterious RAD51D mutation had a best response of stable disease (SD), but experienced a prolonged progression-free survival (PFS) of 11 months, demonstrating benefit from rucaparib. In Part 2 of Study CO-338-017, which enrolled more heavily pre-treated patients with recurrent ovarian cancer and regardless of prior response to platinum therapy, 2 patients had a deleterious RAD51D mutation. Both patients achieved a confirmed PR by RECIST v1.1 with duration of response (DOR) of 5 months and 10 months, respectively. In the Phase 3 Study CO-338-014 (ARIEL3) of rucaparib maintenance in ovarian cancer patients who achieved CR or PR to platinum therapy, that had measurable disease at baseline or study entry, 2 patients had a deleterious RAD51C mutation and 1 patient had a deleterious RAD51D mutation. Of these, 2 patients had a confirmed PR, and 1 had a confirmed CR by RECIST v1.1. All 3 patients were still receiving rucaparib at the time of the treatment blind break (April 2017), with DORs of > 14, > 16, and > 16 months, respectively.[9]

The correlation of PALB2 mutations with sensitivity to PARP inhibitors is supported by data from the interim analysis of a maintenance study of rucaparib in pancreatic cancer, where 2 of 2 patients with a PALB2 mutation showed a response.[13] Additionally, a prostate cancer patient with a deleterious somatic PALB2 mutation remained on treatment with olaparib for 39 weeks.[14]

Lastly, secondary reversion mutations in BRCA1 and BRCA2 that restore protein function, reactivate HRR and lead to therapy resistance have been reported in patients following treatment with DNA damaging chemotherapy or a PARP inhibitor, providing strong evidence that the original mutation sensitized the tumor to these agents.[15, 16] More recently, reversion mutations leading to rucaparib resistance have been identified in RAD51C- and RAD51D-mutated ovarian cancer,[17] and to olaparib resistance in PALB2-mutated prostate cancer,[18] underlining the functional similarities between these 3 genes and BRCA1/2 in determining sensitivity to PARP inhibitors.

Taken together, the evidence described above supports the hypothesis that 1) deleterious mutations in or loss of BRCA1 and BRCA2 induce HRD in cancer cells independent of tissue of origin, leading to rucaparib sensitivity, and 2) RAD51C, RAD51D and PALB2 mutations are additional biomarkers of HRD and predict rucaparib responsiveness in patients with multiple cancer types. Therefore, Clovis (sponsor) anticipates clinical activity of rucaparib in patients harboring a deleterious mutation in one of the genes in this 5-gene panel to be independent of tumor type.

In addition, mutations in other HRR genes, namely BARD1, BRIP1, FANCA, NBN, RAD51 and RAD51B, that are less frequently observed and currently have no or limited clinical evidence of sensitivity to a PARP inhibitor, will also be tested in an exploratory fashion in a smaller cohort of patients.

Primary Objective:

- To determine the objective response rate (ORR), as assessed by the investigator, by RECIST v1.1 (or by RECIST v1.1 and Prostate Cancer Working Group Guidelines Version 3 [PCWG3] criteria in patients with mCRPC).

Secondary Objectives:

- Objective response rate (ORR) as assessed by independent radiology review (IRR) by RECIST v1.1 (or by RECIST v1.1 and PCWG3 in patients with mCRPC);
- DOR;
- Disease Control Rate (DCR), defined as the percentage of CRs, PRs, and SDs greater than 16 weeks;
- PFS;
- Overall survival (OS);
- To evaluate the safety and tolerability of rucaparib;
- To evaluate steady-state pharmacokinetics (PK) of rucaparib.

Exploratory Objectives:

- To assess resistance mutations detected in circulating tumor DNA (ctDNA);
- To evaluate zygosity of deleterious mutations detected in HRR genes within tumor tissue.

Study Design:

This is a Phase 2 multicenter, open-label study evaluating rucaparib as treatment for solid tumors associated with a deleterious mutation in HRR genes. All patients will be required to have received prior treatment with at least 1 line of life-extending therapy (if available) or have a tumor not amenable to treatment with curative intent. Enrollment of at least 30 patients, and up to 220 patients, is planned to allow for the inclusion of multiple rare tumor types that harbor deleterious mutations in various HRR genes. Of these, up to 200 patients will be enrolled in Cohort A, and up to 20 patients will be enrolled in Cohort B.

All patients will be required to provide adequate tumor tissue for analysis. If archival tissue is not available, the patient must undergo a screening biopsy, unless the biopsy procedure is considered unsafe by the investigator or the biopsy site is considered inaccessible. Tumor samples will be analyzed using a central laboratory next-generation sequencing (NGS) test.

Additional screening assessments will include demographics and medical history, prior cancer treatments, prior and current medications and procedures, 12-lead electrocardiogram (ECG), Eastern Cooperative Oncology Group (ECOG) performance status, hematology, chemistry, and tumor marker assessment (as applicable), serum or plasma human chorionic gonadotropin (hCG) pregnancy test (for women of childbearing potential only), urinalysis, physical examination, height, weight, vital signs measurements, adverse events (AEs), and radiologic assessment by computed tomography (CT) or magnetic resonance imaging (MRI).

During the treatment phase (continuous 28-day treatment cycles), patients will receive rucaparib and be monitored for safety and efficacy. Treatment will continue until disease progression by RECIST v1.1 (or modified RECIST v1.1 and PCWG3 for patients with

mCRPC), as assessed by the investigator. Assessments and procedures will include AEs, physical examination, vital signs and weight measurement, local laboratory hematology, clinical chemistry, urinalysis, and tumor marker measurement (as applicable), serum or plasma hCG pregnancy test for women of childbearing potential (WOCBP), concomitant medications, therapies and procedures, disease status assessment, and rucaparib administration and accountability. ECGs will be performed as clinically indicated.

If a patient has radiologic progression, but is still receiving benefit from rucaparib (eg, a patient has mixed radiologic response or is continuing to have symptomatic benefit) according to the investigator, then continuation of treatment will be considered. In such cases, the 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 study treatment. Patients will continue to have all protocol required assessments specified in the Schedule of Assessments.

Assessments will be performed until the discontinuation of treatment and AEs will be collected at 28 days following the last dose of rucaparib. Ongoing serious adverse events (SAEs), adverse events of special interest (AESIs), or treatment-related Grade 3/4 AEs will be followed until either resolution or stabilization, death, or until loss to follow-up. After the 28-day safety follow-up window, 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, are to be reported. Optional post-treatment tumor biopsies will be collected from patients, provided there is appropriate consent.

During long-term follow-up (LTFU), all patients will be followed for survival, subsequent treatments, the AESIs of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), treatment-related SAEs, and monitoring for secondary malignancy every 12 weeks until death, loss to follow-up, withdrawal of consent, or study closure.

The study includes a futility analysis, to enable enrollment discontinuation in tumor subtypes that may not be sensitive to rucaparib. In addition, it incorporates an upper limit of 50 patients with a particular tumor type; however, this limit may be removed if the benefit/risk ratio of the drug is deemed to be favorable for patients.

Interim Safety Monitoring

A safety data review by the Data Monitoring Committee (DMC) will occur after the first 20 patients have been enrolled and completed the first cycle of treatment, and then approximately every 6 months thereafter. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review.

Study Population:

This study will enroll patients with a variety of solid tumor types, including rare ones, that harbor deleterious mutations in certain genes in the HRR pathway, including BRCA1,

BRCA2, PALB2, RAD51C, RAD51D, BARD1, BRIP1, FANCA, NBN, RAD51 and RAD51B.

Number of Patients:

The total number of patients planned for this study is approximately 220 patients, enrolled across 2 cohorts as follows:

- Cohort A will include at least 30, and up to approximately 200 patients with a deleterious mutation in one of the following genes: BRCA1, BRCA2, PALB2, RAD51C and RAD51D.
- Cohort B will include up to 20 patients with a deleterious mutation in one of the following genes: BARD1, BRIP1, FANCA, NBN, RAD51 and RAD51B.

Number of Sites:

This is a multicenter study with patients enrolled across approximately 20 study sites in the US.

Inclusion Criteria:

Eligible patients must meet the following inclusion criteria:

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form prior to any study-specific evaluation.
2. Be ≥ 18 years of age at the time the informed consent is signed.
3. Have an unresectable locally advanced (primary or recurrent) or metastatic solid tumor and have relapsed/ progressive disease as confirmed by radiologic assessment.
4. Have measurable disease as defined by RECIST v1.1 (Appendix 2) or modified RECIST v1.1 and PCWG3 criteria (Appendix 3) for prostate cancer. A measurable tumor lesion in a previously irradiated site is acceptable if subsequent progression has been demonstrated in that lesion.
5. Have a deleterious mutation (germline or somatic) in BRCA1, BRCA2, PALB2, RAD51C or RAD51D (Cohort A) or a deleterious mutation (germline or somatic) in BARD1, BRIP1, FANCA, NBN, RAD51 or RAD51B (Cohort B). Mutations must be identified by either a local or central laboratory that is certified per Clinical Laboratory Improvement Amendments (CLIA) regulations.
   a. Mutations may be identified in a tumor tissue, blood, or saliva sample. For a local laboratory test result, the classification of the mutation as deleterious must be documented in the patient's medical record. Variants of uncertain significance or benign variants will not be eligible for enrollment into the trial.
   b. Patients with EOC, FTC, or PPC must have a deleterious PALB2, RAD51C or RAD51D mutation (or deleterious mutation in another HRR gene, listed in Appendix 1). Patients with a deleterious BRCA1 or BRCA2 mutation are not eligible.
   c. Patients with mCRPC must have a deleterious PALB2, RAD51C or RAD51D mutation (or deleterious mutation in another HRR gene, listed in Appendix 1). Patients with a deleterious BRCA1 or BRCA2 mutation are not eligible.

d. Human epidermal growth factor receptor 2 (HER2) negative breast cancer patients with a deleterious germline BRCA1 or BRCA2 mutation are not eligible, unless the use of both olaparib and talazoparib is contraindicated. Breast cancer patients with a deleterious somatic BRCA mutation are eligible, as are HER2+ patients with a deleterious somatic or germline mutation in any of the 11 genes listed in Appendix 1. HER2 negative patients with a deleterious mutation in any non-BRCA HRR gene listed in Appendix 1 are eligible.

6. Have received at least 1 line of available therapy(ies) with treatment demonstrated to have a survival benefit in the relevant tumor type or, in the absence of any OS-extending treatment, have received at least 1 standard-of-care treatment regimen.
   a. A treatment regimen that is held for reasons other than disease progression, and subsequently resumed at a later date with no other intervening systemic anti-cancer therapy, is considered 1 treatment regimen.
   b. Patients with EOC, FTC, or PPC must have received 2 prior lines of platinum-based chemotherapy and:
      i. Had documented treatment-free interval of ≥ 6 months following the first platinum-based chemotherapy regimen received; and
      ii. Had either platinum-sensitive or platinum-resistant disease (progression-free interval [PFI] ≥ 1 month) after last dose of platinum. Patients with platinum-refractory disease (ie, whose disease progressed during or within 1 month of completing treatment with their most recent platinum-based therapy) are excluded.
   c. Patients with locally advanced or metastatic endometrial cancer, excluding uterine carcinosarcoma, must have received at least 1 line of platinum-containing therapy, but no more than 2 prior chemotherapy-based regimens (eg, carboplatin/cisplatin, taxanes, doxorubicin, ifosfamide, topotecan or other chemotherapy regimens recommended by regional guidelines). Hormonal therapy, immunotherapy, mechanistic target of rapamycin [mTOR] inhibitors, anti-vascular endothelial growth factor [VEGF] or anti-HER2 therapy are not counted towards lines of therapy. Patients must not have had radiologic disease progression within 3 months of initiating platinum-containing chemotherapy, with a best response of SD or better.
   d. Patients with locally advanced or metastatic cervical cancer must have received at least 1 line of platinum-containing therapy, but no more than 2 prior chemotherapy-based regimens (including carboplatin/cisplatin, taxanes, topotecan, other chemotherapy regimens recommended by regional guidelines). Immunotherapy or anti-VEGF therapy are not counted towards the prior treatment lines Patients must not have had radiologic disease progression within 3 months of initiating platinum-containing chemotherapy, with a best response of SD or better.
   e. Patients with either ovarian or uterine carcinosarcoma are restricted to 1 line of platinum-containing therapy and must not have had radiologic disease progression within 3 months of initiating platinum-containing chemotherapy, with a best response of SD or better.

f. Patients with breast cancer:
   i. Triple-negative breast cancer (TNBC) patients must have received no more than 2 prior lines of chemotherapy for metastatic disease. Patients may have previously received radiation therapy and 1 line of immunotherapy. Prior platinum as potentially curative treatment for prior cancer (eg, ovarian) or as adjuvant or neoadjuvant treatment for breast cancer is allowed; however, patients must not have progressed during treatment.
   ii. All breast cancer patients with tumors other than TNBC must have received no more than 2 prior chemotherapy regimens for locally advanced and/or metastatic disease with no limit on prior hormonal therapies or targeted anticancer therapies such as mTOR inhibitors or cyclin-dependent kinase (CDK) 4/6 inhibitors (other than PARP inhibitors). Patients who have received platinum in the adjuvant or neoadjuvant setting are eligible; however, subjects must not have progressed during treatment.

g. Patients with mCRPC must have received prior androgen-receptor (AR)-targeted therapies (such as abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent; 1 to 2 AR-directed agents allowed) and may not have received more than 2 lines of taxane for mCRPC.

h. Patients with pancreatic cancer must have received no more than 2 prior chemotherapy-based regimens for locally advanced or metastatic disease and are eligible as long as they did not have radiologic disease progression during treatment with or within 3 months of receiving platinum-containing chemotherapy and have a best response of SD or better.
   i. Neoadjuvant/adjuvant chemotherapy will not be counted as a treatment regimen if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the regimen will be counted.

i. Patients with gastric or esophageal cancer must have received no more than 2 prior chemotherapy-based regimens for locally advanced or metastatic disease and are eligible as long as they did not have radiologic disease progression during treatment with or within 3 months of receiving platinum-containing chemotherapy and have a best response of SD or better.
   i. Neoadjuvant/adjuvant chemotherapy will not be counted as a treatment regimen if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the regimen will be counted.

j. Patients with colorectal cancer must have received no more than 2 prior chemotherapy-based regimens for locally advanced or metastatic disease and are eligible as long as they did not have radiologic disease progression during treatment with or within 3 months of receiving platinum-containing chemotherapy and have a best response of SD or better.
   i. Neoadjuvant/adjuvant chemotherapy will not be counted as a treatment regimen if disease progression occurred ≥ 6 months following completion of

chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the regimen will be counted.

k. Patients with locally advanced or metastatic bladder cancer must have received 1 or 2 prior treatment lines (eg, cisplatin- or carboplatin-containing therapy, immune checkpoint inhibitor) for locally advanced unresectable or metastatic disease. Patients who receive platinum-containing chemotherapy should not have radiologic disease progression within 3 months of initiation of platinum-containing chemotherapy and must have best response of SD or better.
   i. Neoadjuvant and/or adjuvant treatment for muscle invasive disease will be considered a treatment regimen if radiologic disease progression occurred within 12 months from the completion of treatment.
   ii. No more than 1 prior platinum-containing chemotherapy regimen for advanced disease is permitted. A change of platinum chemotherapy within the same treatment regimen will be considered 1 prior platinum-containing chemotherapy. Platinum-containing chemotherapy given as radio-sensitization combined with radiation therapy to control locally advanced disease will not be considered as a prior regimen of systemic therapy.
   iii. For patients who have never received platinum, the patient must currently be ineligible for cisplatin treatment.

l. Patients with metastatic NSCLC must have received no more than 2 prior lines of chemotherapy, including one line of platinum-containing therapy. Immunotherapy or targeted therapy (such as epidermal growth factor receptor [EGFR] inhibitor, c-ros oncogene [ROS] inhibitor, anaplastic lymphoma kinase [ALK] inhibitor or B-rapidly accelerated fibrosarcoma gene [BRAF]) inhibitor) are permitted and do not count towards these prior lines.
   i. Neoadjuvant/adjuvant chemotherapy after primary resection will not be counted as a treatment line if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the line of therapy will be counted.
   ii. No more than 1 prior platinum-containing chemotherapy line for advanced disease is permitted. A change of platinum chemotherapy within the same treatment regimen will be considered 1 prior platinum-containing chemotherapy. Patients must not have radiologic disease progression within 3 months of initiating platinum-containing chemotherapy and must have best response of SD or better.
   iii. Platinum-containing chemotherapy given as radio-sensitization combined with radiation therapy to control locally advanced disease will not be considered as a prior regimen of systemic therapy.
   iv. Prior combined chemotherapy and radiotherapy is permitted provided the patient has measurable disease outside the radiation field or disease in the irradiated field has progressed.

m. Patients with all other tumor types not mentioned above must have received 1, but no more than 3, lines of chemotherapy. In the rare circumstance where chemotherapy is not indicated / considered to be a preferred / recommended

standard-of-care treatment for a given tumor type, an alternative therapy (eg, targeted therapy or immunotherapy) may meet the requirement for prior treatment provided it is clearly documented to be the appropriate standard-of-care treatment for that tumor type (eg, if listed in NCCN Guidelines).

i. Neoadjuvant or adjuvant chemotherapy after primary resection will not be counted as a treatment line if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the line of therapy will be counted.

ii. No more than 1 prior platinum-containing chemotherapy line for advanced disease is permitted. A change of platinum chemotherapy within the same treatment regimen will be considered 1 prior platinum-containing chemotherapy. Patients must not have radiologic disease progression within 3 months of initiating platinum-containing chemotherapy and must have best response of SD or better.

iii. Platinum-containing chemotherapy given as radio-sensitization combined with radiation therapy to control locally advanced disease will not be considered as a prior regimen of systemic therapy.

iv. Prior combined chemotherapy and radiotherapy is permitted provided the patient has measurable disease outside the radiation field or disease in the irradiated field has progressed.

7. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue for planned analyses. In the event archival tumor tissue is not available, a screening biopsy sample must be collected and provided to the central laboratory, unless the biopsy procedure is considered unsafe or the biopsy site is considered inaccessible by the investigator. Cytospin blocks from ascites are not acceptable.
8. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to randomization:
   a. Bone Marrow Function
      i. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L;
      ii. Platelets ≥ 100×10^9/L; and
      iii. Hemoglobin ≥ 9 g/dL independent of transfusion ≤ 14 days prior to screening hemoglobin assessment.
   b. Hepatic Function
      i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN). If liver metastases are present, then ≤ 5 × ULN;
      ii. Total bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome; and
      iii. Serum albumin ≥ 30 g/L (3.0 g/dL).
   c. Renal Function
      i. Serum creatinine ≤ 1.5 x ULN; or

ii. Estimated glomerular filtration rate (GFR ≥ 45 mL/min using the Cockcroft-Gault formula; or

iii. Measured creatinine clearance (CL_{cr}) ≥ 30 mL/min.

9. Have an ECOG performance status of 0 to 1.
10. Have a life expectancy of at least 4 months.
11. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of the initiation of antiviral therapy are eligible for this trial, unless the anti-retroviral therapy interferes with rucaparib (see Concomitant Medications section).
12. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable within 6 months of the initiation of antiviral therapy on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load within 6 months of the initiation of antiviral therapy. Concurrent anti-HBV or anti-HCV treatment should not interfere with rucaparib treatment (see Concomitant Medications section).

Exclusion Criteria:

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

1. Symptomatic and/or untreated central nervous system (CNS) metastases or leptomeningeal disease or with primary tumor of CNS origin. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
2. Presence of active second malignancy in addition to the tumor type to be treated with rucaparib. Patients with any of the following are allowed to enroll:
   a. History of malignancy that has been successfully treated, with no evidence of active cancer for 1 year prior to enrollment;
   b. Surgically cured and/or low-risk tumors, such as early stage cervical or endometrial cancer, any cancer in situ, or non-melanoma skin cancers; or
   c. Patients receiving ongoing anticancer hormonal therapy for a previously treated cancer.
3. Received > 3 prior lines of chemotherapy in the locally advanced/metastatic setting.
4. Received prior treatment with a PARP inhibitor.
5. History of MDS or AML or features suggestive of MDS/AML such as aberrant blood cell profiles requiring transfusion, growth factor treatment or other supportive therapy.
6. Pre-existing gastrointestinal disorders or conditions that would, in the opinion of the investigator, interfere with ingestion or absorption of rucaparib.
7. Received anti-cancer treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior (≤ 28 days prior in case of checkpoint inhibitor therapy) to first dose of study drug and/or ongoing adverse effects from such treatment

> National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (v5.0) Grade 1, with the exception for alopecia and Grade 2 peripheral neuropathy.

8. 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.
9. Drainage of ascitic fluid 2 or more times in the 4 weeks prior to the first dose of study drug or permanent drain in place (eg, PleurX®) for ascites or pleural effusion.
10. Hospitalization for bowel obstruction within 3 months prior to enrollment.
11. For female patients of childbearing potential and all male patients, the following are exclusion criteria, as applicable:
    a. Female patients who refuse to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib.
    b. Women of childbearing potential (WOCBP) who are pregnant or breast-feeding or who have a positive serum/plasma hCG pregnancy test ≤ 3 days prior to the first dose of rucaparib. WOCBP must not be considering getting pregnant during the study and for 6 months following the last dose of rucaparib.
    c. Male patients who refuse to use highly effective method of contraception or to practice true abstinence during treatment and for 3 months after the last dose of rucaparib. Male patients must not make semen donations during treatment and for 3 months following the last dose of rucaparib.
12. 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.

Randomization:

No randomization or blinding will be performed in this study.

Study Treatment:

Patients will take 600 mg rucaparib orally twice a day (BID), as close as possible to 12 hours apart and preferably at the same times every day, with water starting on Day 1. Rucaparib tablets must be swallowed whole and may be taken with or without food. Rucaparib may be provided as 200 mg, 250 mg, and/or 300 mg dose strength tablets.

Patients will take rucaparib BID for continuous 28-day cycles until disease progression as assessed by the investigator, or other reason for discontinuation.

Dose reductions and dose holds are permitted in the event of unacceptable toxicity.

Concomitant Medications:

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.

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

accordance with institutional guidelines.

Palliative radiotherapy for the treatment of lesions not considered target lesions for tumor assessments is permitted during the study.

No other anticancer therapies (including chemotherapy, radiation, antibody, immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is receiving rucaparib.

Caution should be used in patients on rucaparib taking concomitant medications that are sensitive clinical substrates of cytochrome P450 (CYP) CYP1A2, CYP2C19, CYP2C9, and/or CYP3A.

Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice.

Caution is advised when metformin or a medicine that is a breast cancer resistance protein (BCRP) substrate (eg, rosuvastatin) 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.

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 (unless treatment post-progression is agreed upon by the investigator and 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;
- Noncompliance by the patient with protocol mandated procedures;
- The study is terminated; or
- A positive pregnancy test at any time during the study.

Efficacy Assessments:

Efficacy measures will include tumor assessments using CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1, tumor marker(s) (as appropriate), and clinical examination; other assessments (MRI, X-ray, positron emission tomography [PET], bone scan, and ultrasound) may be performed if clinically indicated.

Disease assessments will be performed during screening, at the end of every 8 calendar weeks (± 7 days is permitted) relative to Cycle 1 Day 1, until radiologically confirmed disease progression by RECIST v1.1, as assessed by the investigator, loss to follow-up, withdrawal from study, death, or study closure. Tumor assessments should be performed at the time of treatment discontinuation if the reason was other than death or

radiologically confirmed disease progression or it has been ≥ 8 weeks since the last assessment, and every 8 weeks thereafter until initiation of another therapy, disease progression or death. Patients who have been on study at least 18 months may decrease the frequency of tumor assessments to every 16 weeks (± 7 days is permitted). If a CR or PR is noted, confirmatory scans should be performed at least 4 weeks after a response was first documented. Copies of CT scans will be collected from all patients for IRR.

For mCRPC patients, disease assessment by CT/MRI/PET/bone scans will be performed and modified RECIST v1.1/PCWG3 criteria will be used to evaluate efficacy; up to 10 lesions in any metastatic site shall be recorded for extra-skeletal disease according to PCWG3. For all other tumor types, up to 5 tumor lesions are allowed.

Safety Assessments:

Adverse event assessment and safety laboratory assessments will be performed as described in the Schedule of Assessments. Safety and tolerability will be assessed based on the following:

- Incidence, type, seriousness, severity and causality of AEs reported
- Clinical laboratory investigations
- Physical examinations, body weight, and height
- Vital signs
- 12-lead ECGs
- ECOG performance status

Pharmacokinetic Assessments:

Trough PK will be evaluated prior to rucaparib dosing on Day 1 of Cycles 2 through 6.

Statistical Methods:

Sample Size Justification

Estimated enrollment is from 30 to 220 patients.

Evaluation of efficacy, safety, and tolerability of rucaparib will be focused on patients in Cohort A (patients harboring mutations in certain HRR genes with tumor types that have not been sufficiently evaluated previously in a Clovis-sponsored study of rucaparib monotherapy). The minimum expectation is to enroll 10 or more patients in at least 1 additional tumor type with multiple other tumor types represented with only a few patients each. These additional data could be collected in as few as 30 patients if many of the early enrolled patients are in a single tumor type. Conversely, if the study enrolls patients in a wide variety of tumor types, it may take more than 30 patients to collect data on at least 10 patients in a single tumor type. If enrollment to a given tumor type reaches 11 patients, a futility analysis is planned to gate further enrollment within that tumor type.

The total study sample size is dependent on enrollment of the various tumor types, risk:benefit assessments throughout the study, and potential regulatory considerations. If the risk:benefit is favorable, enrollment may reach up to 200 patients in Cohort A. Combined with the up to 20 patients to be enrolled in Cohort B, the total enrollment could reach a maximum of approximately 220 patients.

Data Monitoring Committee: The DMC will comprise of key investigators and personnel from the sponsor (or their designees) and will review both safety and efficacy data after the first 20 patients have been enrolled and completed the first cycle of treatment, and then approximately every 6 months, or earlier as needed, throughout the study.
Date of Protocol Approval: Original: 09 July 2019 Amendment 1: 25 September 2019 Amendment 2: 27 February 2020 Amendment 3: 22 October 2020

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	
[^{14}C]	carbon-14
ADP	adenosine diphosphate
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALCOA+	A framework for ensuring data integrity and good documentation practices defined as Attributable, Legible, Contemporaneous, Original or Certified Copy, Accurate, and 'Plus' (+) Complete, Consistent, Enduring, and Available.
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
BARD1	BRCA-associated RING domain 1
BCRP	breast cancer resistance protein
BER	base excision repair
BID	twice a day
BRAF	B-rapidly accelerated fibrosarcoma gene
BRCA	breast cancer gene
BRCA1	BRCA1 DNA repair associated
BRCA2	BRCA2 DNA repair associated
BRCA1/2m	BRCA1 or BRCA2 mutated
BRIP1	BRCA1 interacting protein C-terminal helicase 1
BTD	Breakthrough Therapy Designation
BUN	blood urea nitrogen
CA-125	cancer antigen-125
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval

Abbreviations	
CL_{cr}	creatinine clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma concentration
C_{min}	Steady-state minimum concentration
CNS	central nervous system
CO_2/HCO_3	bicarbonate
CR	complete response
CRO	Contract Research Organization
CRPC	castration-resistant prostate cancer
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double-strand break
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EOT	end of treatment
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials database
FANCA	Fanconi anemia complementation group A
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
FTC	fallopian tube cancer

Abbreviations	
gBRCA	germline BRCA
GCP	good clinical practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
HBV	hepatitis B Virus
hCG	human chorionic gonadotropin
HCV	hepatitis C Virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRD	homologous recombination deficiency
HRR	homologous recombination repair
HUGO	Human Genome Organization
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	Institutional Review Board
IRR	independent radiology review
irrORR	objective response rate as assessed by independent radiology review
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IWRS	Interactive Web Response System
LA	locally advanced
LD	longest diameter
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone

Abbreviations	
LOH	loss of heterozygosity
LTFU	long-term follow-up
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mCRPC	metastatic castration-resistant prostate cancer
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mTOR	mechanistic target of rapamycin
NBN	nibrin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluated
NGS	next-generation sequencing
NR	not reported
NS	not seen
NSCLC	non-small cell lung cancer
OC	ovarian cancer
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PALB2	partner and localizer of BRCA2
PARP	poly(ADP-ribose) polymerase
PARPi	poly(ADP-ribose) polymerase inhibitor
PCWG3	Prostate Cancer Working Group Guidelines Version 3
PD	progressive disease
PET	positron emission tomography
PFI	progression-free interval
PFS	progression-free survival
PIS	patient information sheet
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPC	primary peritoneal cancer
PPI	proton pump inhibitor

Abbreviations	
PPK	population pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
PV	pharmacovigilance
QD	once a day
QT	interval from Q wave to T wave
QT_CF	QT interval corrected for heart rate, Fridericia's formula
RAD51	RAD51 recombinase
RAD51B	RAD51 paralog B
RAD51C	RAD51 paralog C
RAD51D	RAD51 paralog D
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROS	c-ros oncogene
SAE	serious adverse event
SAP	statistical analysis plan
sBRCA	somatic BRCA
SD	stable disease
SI	International System of Units
SmPC	Summary of Product Characteristics
StD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TNBC	triple-negative breast cancer
UGT	uridine diphosphate-glucuronosyl transferase
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
VEGF	vascular endothelial growth factor
WBC	white blood cell
WOCBP	women of childbearing potential

1 INTRODUCTION

1.1 Background

1.1.1 Type of Cancers Being Studied – All Non-Central Nervous System Solid Tumors

This study is a tumor-agnostic study and will be conducted in all solid tumors barring those of central nervous system (CNS) origin. The study is expected to enroll a greater number of patients with tumor types that are more prevalent in the general population, or that harbor a higher mutational frequency in homologous recombination repair (HRR) genes, such as in breast, ovarian, pancreatic and prostate cancer). Tumor types that are expected to be lower in prevalence include gastric, bladder, endometrial and cervical cancer. In particular, it is anticipated that rare tumor types harboring deleterious mutations in the specified HRR genes will also be represented in this study, such as in uterine/ovarian carcinosarcoma, leiomyosarcoma and others.

1.1.2 Investigational Product Under Study - Rucaparib

Rucaparib is a potent, oral small molecule inhibitor of poly(adenosine diphosphate [ADP] ribose polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, that play a critical role in base excision repair (BER).[19] When PARP function is impaired, double stranded deoxyribonucleic acid (DNA) breaks accumulate in the absence of effective BER; in cells that are homologous recombination deficient (HRD), these breaks cannot be accurately repaired, resulting in synthetic lethality.[20]

While mutations in breast cancer gene (BRCA)1 and BRCA2[1] are gene mutations most commonly associated with HRD, other essential HRR proteins can also be mutated or functionally deficient. Among these, there is compelling evidence that a deleterious alteration in PALB2, RAD51C, and RAD51D may also predict responsiveness to rucaparib. All 3 genes are essential for double-stranded DNA damage repair: PALB2 interacts with BRCA2 and helps localize it to sites of DNA damage,[21] while RAD51C and RAD51D act in the early steps of HRR to promote the formation of DNA repair foci.[22] Germline mutations in these three genes are associated with increased risk of developing ovarian, breast, pancreatic, and prostate cancers.[23-27] Somatic mutations in these genes also occur and may be involved in tumorigenesis.

1.1.3 Non-Clinical Experience

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

[1] Gene and protein names should typically be in italics and plain text, respectively, based on HUGO Gene Nomenclature Committee guidelines. However, in this document mutations which occur at both the gene and protein level are often discussed. Therefore, for enhanced readability, gene and protein names are written in plain text.

multiple cell lines and patient-derived xenograft models with mutations in BRCA1, BRCA2, PALB2, RAD51C, and RAD51D. 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 resistance protein (BCRP) substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. In vitro data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and dogs. Rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and uridine diphosphate-glucuronosyl transferase (UGT)1A1. Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1) and may inhibit P-gp and BCRP in the gut.

Oral dosing of rucaparib in single- and repeat-dose toxicity studies in rats and dogs resulted in toxicity to the hematopoietic, lymphopoietic, and gastrointestinal systems. These toxicities were generally both reversible upon recovery and predictive of toxicities observed in patients. Rucaparib was shown to be clastogenic in an in vitro chromosomal aberration assay suggesting potential genotoxicity in humans. Reproductive and development toxicity studies in rat showed that rucaparib caused maternal toxicity and was embryo-toxic. Although no rucaparib-related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors (PARPi) have the potential to impair spermatogenesis and reduce fertility.[28-31]

1.1.4 Clinical Experience

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

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

Clinical pharmacology studies are ongoing in patients with advanced solid tumors to more fully characterize rucaparib drug-drug interactions (DDI), mass balance and drug metabolism, as well as PK and safety in patients with moderate hepatic impairment.

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

1.1.5 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 (70%). The steady-state was achieved following 1 week of dosing with rucaparib BID, with approximately 4-fold accumulation.

A high-fat meal increased the C_{max} and area under the concentration-time curve from 0 to 24 hours $(AUC)_{0\text{-}24h}$ of rucaparib by 20% and 38%, respectively, as compared with that under fasted conditions. The food effect is not considered clinically significant, thus rucaparib can be taken with or without food.[32]

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

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

Results from Study CO-338-044 evaluating potential DDI with rucaparib, indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on P-gp.[33] Caution should be exercised in the concomitant use of drugs that are substrates of the above CYP enzymes (Appendix 5).

In another DDI study (Study CO-338-095) in cancer patients, effects of rucaparib on oral rosuvastatin as BCRP substrate and on 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 approximately 46% increase in area under the concentration-time curve from 0 to infinity ($AUC_{0\text{-}inf}$) without apparent change in C_{max}.

Results from the mass balance and metabolite profiling portion (Part 1) of Study CO-338-045 following a single oral dose of carbon-14 [^{14}C] rucaparib showed 71.9% and 17.4% recovery

of the [^{14}C] radioactive dose in feces and urine, respectively. Oxidation, N-demethylation, N-methylation, and glucuronidation were the major metabolic pathways for rucaparib, with M324, derived from oxidation of rucaparib, identified as the most abundant metabolite.

Refer to rucaparib Investigator's Brochure (IB) for details.

1.1.6 Overview of Efficacy

Rucaparib has demonstrated clinical benefit in the treatment and maintenance settings in ovarian cancer patients.[34, 35] Based on these results, rucaparib was approved in the US for the treatment of patients with a deleterious BRCA mutation (germline and/or somatic) associated epithelial ovarian cancer (EOC), FTC, or PPC who have been treated with 2 or more chemotherapies, and for the maintenance treatment of adult patients with EOC, FTC or PPC (regardless of BRCA status) who are in a complete or partial response to platinum-based chemotherapy.[7] Rucaparib has also been approved in the European Union (EU) as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade advanced ovarian cancer who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy, and for maintenance treatment of adult patients with platinum-sensitive recurrent EOC, FTC, or PPC who are in response (complete or partial) to platinum-based chemotherapy.[10]

In addition to BRCA1 and BRCA2, ovarian cancer patients with a deleterious RAD51C or RAD51D mutation also derived clinical benefit from rucaparib in the treatment (Study CO-338-017; ARIEL2) and maintenance (Study CO-338-014; ARIEL3) settings.[36, 37]

While rucaparib has demonstrated significant clinical benefit in ovarian cancer in the treatment and maintenance settings, rucaparib clinical activity is not limited to ovarian cancer. Rucaparib recently received a Food and Drug Administration (FDA) Breakthrough Therapy Designation (BTD) based on preliminary clinical activity in 25 patients with mCRPC harboring a deleterious BRCA mutation and measurable disease at baseline enrolled in Study CO-338-052 (TRITON2).[11] Clinical benefit from rucaparib treatment has also been observed in mCRPC patients with a deleterious PALB2 mutation.[11]

Rucaparib clinical data further supports the hypothesis that patients with BRCA-mutated solid tumors from indications beyond ovarian and prostate cancers may likely benefit from rucaparib treatment. In a Phase 1 dose-escalation study (CO-338-010) of rucaparib in patients with an advanced solid tumor, 4 breast cancer patients and 1 pancreatic cancer patient, all harboring a deleterious BRCA mutation, achieved a Response Evaluation Criteria in Solid Tumors (RECIST)-confirmed partial response (PR).[38] In RUCAPANC (CO-338-023), a Phase 2 study assessing the efficacy of rucaparib in BRCA-mutated pancreatic cancer, clinical benefit was observed (objective response rate [ORR] of 33.3% and disease control rate [DCR] of 44.4%) in the subgroup of patients who had received only 1 prior chemotherapy regimen for locally advanced/metastatic disease.[39] Similarly, clinical benefit (ORR of 36.8% and median progression-free survival [PFS] of 9.1 months) was also observed with maintenance treatment of rucaparib in patients with platinum-sensitive BRCA mutated pancreatic cancer.[13]

1.1.7 Overview of Safety

Results of a recent integrated safety analysis in over 1,000 patients with ovarian or prostate cancer who received 600 mg BID rucaparib in the treatment or maintenance setting showed that the most common treatment-emergent adverse events (TEAEs) reported were primarily mild to moderate (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1-2) in severity and included gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, anemia/decreased hemoglobin, alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) increased, decreased appetite, and dysgeusia. The most common TEAE ≥ Grade 3 include anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue. Section 6.6 of the rucaparib IB serves as guidance to the investigator on adverse drug reactions (ADRs) for rucaparib, based on incidence of TEAEs by all CTCAE grades and by CTCAE ≥ Grade 3.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin (and associated increase in mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]), increased ALT, increased AST, and increased serum creatinine, most commonly occurring. Decreased platelets, neutrophils, leukocytes, lymphocytes and increased cholesterol were observed to a lesser extent. The transient elevations in ALT/AST with rucaparib treatment were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity and generally resolved over time. Furthermore, no cases met Hy's law criteria for drug-induced liver injury (DILI),[40, 41] and few patients discontinued rucaparib due to ALT/AST elevations.[8, 9] Similarly, elevations in creatinine were self-limiting and generally stabilized over time. The majority of creatinine elevations were Grade 1 or Grade 2. Elevated serum creatinine levels resolved upon interruption or discontinuation of rucaparib, were not accompanied by changes in blood urea nitrogen (BUN) and did not lead to discontinuation of rucaparib treatment. Increased creatinine with rucaparib treatment is likely due to the potent inhibition by rucaparib of MATE1 and MATE2-K renal transporters (Section 1.1.3).

An updated analysis of safety presented in the United States (US) prescribing information (USPI)[7] and the EU Summary of Product Characteristics (SmPC)[10] demonstrate that safety results in ovarian cancer patients treated with rucaparib have remained consistent with those previously reported, and that the safety profile across both the treatment and maintenance indications is consistent. The safety profile in mCRPC is similar to that in ovarian cancer patients.

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

1.1.7.1 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 PARPi, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, and in some cases a deleterious BRCA mutation, which increases the risk of developing cancer(s). Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib. More information on AESIs of MDS and AML experienced by patients in rucaparib clinical studies is provided in the rucaparib IB.

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 8.7. Refer to the rucaparib IB for information regarding the AESI of pneumonitis.

1.2 Study Rationale

1.2.1 Known and Potential Risks and Benefits to Subjects/Patients

Rucaparib has demonstrated clinical benefit in patients with deleterious mutations in HRR genes in a variety of tumor types as described previously (Section 1.1.4) and is approved for EOC, FTC and PPC, and mCRPC (Section 1.1.6).

The benefit:risk ratio of rucaparib is described in detail in the IB.

1.2.2 Rationale for the Study Design

This study is designed to test the effectiveness of rucaparib across a range of solid tumor types, including more prevalent types (eg, breast cancer) as well as rarer tumor types (eg, sarcoma). Patients will be required to have deleterious mutations in certain HRR genes hypothesized to drive responsiveness to rucaparib. The drug is intended to be tested in second-line onwards, while restricting pretreatment to 3 chemotherapy treatment lines in most instances. A futility analysis is planned for each tumor type, to identify tumor types that may be inherently non-responsive to rucaparib, (perhaps due to deleterious mutations in HRR genes not being driver mutations in those tumors, or a high rate of reversion mutations). There is no comparator arm in this study, as the study incorporates a variety of tumor types with vastly different treatment paradigms. The study is expected to enroll a wide variety of tumor types, thereby providing support for a tumor-agnostic indication for rucaparib.

1.2.3 Dose Rationale

Rucaparib will be dosed at 600 mg BID as the starting dose, the approved dose for ovarian cancer indications and also the dose used in a variety of ongoing trials. More supportive evidence for this dose is found in the IB.

1.2.4 Rationale for Duration of Treatment

Patients will be treated as long as they tolerate the drug well, do not progress and do not withdraw consent to be in the trial, since the goal of the trial is to assess rucaparib safety and efficacy in various tumor types.

2 STUDY OBJECTIVES AND ENDPOINTS

Primary, secondary, and exploratory objectives and endpoints are shown in Table 1.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints	Justifications
Primary Objective	**Primary Endpoint**	**Justification for Primary Endpoint**
To determine the ORR by tumor type, as assessed by the investigator, to be evaluated by RECIST v1.1 (or by RECIST v1.1 and Prostate Cancer Working Group Guidelines Version 3 [PCWG3] in patients with mCRPC).	Best overall response as assessed by the investigator by RECIST v1.1 (or by RECIST v1.1 and PCWG3 in patients with mCRPC).	Best overall response is summarized across patients as ORR, which is the proportion of complete responses and partial responses confirmed in patients with measurable disease and is a direct measure of the drug's anti-tumor activity. It is commonly used in Phase 2 trials. It excludes stable disease, which may be more reflective of the natural history of the disease rather than response to the investigational drug.
Secondary Objectives	**Secondary Endpoints**	**Justifications for Secondary Endpoints**
1. To assess ORR by independent radiology review (IRR).	1. ORR as assessed by IRR (irrORR) by RECIST v1.1 (or by RECIST v1.1 and PCWG3 in patients with mCRPC).	1. Best overall response as assessed by IRR is summarized across patients as irrORR, which provides a measure of ORR that is devoid of the heterogeneity arising from radiology data being evaluated at various investigational sites and serves as a more independent evaluation of ORR.
2. To assess the duration of response (DOR).	2. DOR	2. DOR, defined as the time from initial tumor response to documented tumor progression, provides additional information on the longevity of tumor response.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints	Justifications
3. To evaluate DCR.	3. DCR	3. DCR, defined as the percentage of complete response (CR), PR, and stable disease (SD) beyond 16 weeks, is another measure of clinical benefit to the investigational drug, being a composite of SD and ORR.
4. To estimate progression-free survival (PFS).	4. PFS	4. Defined as the duration from entry into study to objective tumor progression or death of a patient, PFS is a measure of clinical benefit.
5. To estimate OS.	5. OS	5. Defined as the duration from entry into study to death, OS is the gold standard for oncology clinical trials.
6. To evaluate the safety and tolerability of rucaparib.	6. Incidence of adverse events, clinical laboratory abnormalities and dose modifications.	6. In accordance with International Council for Harmonisation (ICH) E9 principles, acute and long-term evaluation of medical risks including adverse events (AEs), laboratory tests, vital signs and other special safety tests (eg, ECGs) will be assessed.
7. To evaluate steady-state PK of rucaparib.	7. Steady-state minimum concentration (C_{min}).	7. Sparse PK allows for monitoring of rucaparib exposure in various cancer types and exploratory exposure response analysis.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints	Justifications
Exploratory Objectives	**Exploratory Endpoints**	**Justification for Exploratory Endpoints**
1. To assess resistance mutations detected in circulating tumor DNA (ctDNA).	1. Best overall response, DOR and PFS summarized in patients with and without resistance mutations in ctDNA.	1. Primary and acquired resistance mutations to rucaparib have been identified in ctDNA from ovarian and prostate cancer patients. This objective will evaluate if these resistance mutations have an impact on rucaparib clinical efficacy across tumor types.
2. To evaluate zygosity of deleterious mutations detected in HRR genes within tumor tissue.	2. Best overall response, DOR and PFS summarized in patients with homozygous vs heterozygous mutations in HRR genes.	2. HRD typically results from biallelic inactivation of an HRR gene. This exploratory objective will evaluate if patients with homozygous mutations in HRR genes derive greater rucaparib clinical efficacy.

Abbreviations: AE = adverse event; C_{min} = steady-state minimum concentration; CR = complete response; ctDNA = circulating tumor DNA; DCR = disease control rate; DNA = deoxyribonucleic acid; DOR = duration of response; ECG = electrocardiogram; HRD = homologous recombination deficiency; HRR = homologous recombination repair; ICH = International Council for Harmonisation; IRR = independent radiology review; irrORR = objective response rate as assessed by independent radiology review; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; OS = overall survival; PCWG3 = Prostate Cancer Working Group Guidelines Version 3; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SD = stable disease.

3 STUDY DESIGN

3.1 Overall Study Design

This study is a Phase 2, open-label, single arm trial designed to evaluate the response to rucaparib of patients with various solid tumors and with deleterious mutations in HRR genes, including the following: BRCA1, BRCA2, PALB2, RAD51C or RAD51D (comprising Cohort A). Patients with deleterious mutations in BARD1, BRIP1, FANCA, NBN, RAD51 and RAD51B may also enroll into an exploratory cohort (Cohort B). Since the trial is designed to test rucaparib responsiveness across a range of tumor types (tumor-agnostic indication), patients with rare tumor types with these mutations, eg, leiomyosarcoma or uterine carcinosarcoma, are equally eligible, in addition to the high prevalence tumor types such as breast, prostate and lung cancer. Patients may be grouped by tumor types, that may range in size from as few as a single patient (for rare tumor types) to an upper limit described below.

The study incorporates a futility analysis; if there are at least 11 patients of a particular tumor type enrolled into the study without a response, enrollment of additional patients with that tumor may be discontinued. In addition, the study incorporates an upper limit of 50 patients of a particular tumor type; however, this limit may be removed if the benefit-risk ratio of the drug is deemed to be favorable for patients.

3.1.1 Screening Period

All patients will undergo screening assessments up to 4 weeks prior to enrollment.

Screening assessments will include, but may not be limited to, demographics and medical history, prior cancer treatments, prior and current medications and procedures, 12-lead ECG, Eastern Cooperative Oncology Group (ECOG) performance status, hematology and serum/plasma chemistry, urinalysis, physical examination, vital signs measurements, radiologic assessment by computed tomography (CT) or magnetic resonance imaging (MRI). Patients will be required to provide a sample of the most recent archival tumor tissue. If an archival sample is not available, a screening biopsy must be obtained, unless the biopsy location is inaccessible, or the procedure is deemed unsafe by the investigator. The sample will be used for central laboratory confirmation of the mutations; however, receipt of archival tissue or central laboratory results are not required prior to patient starting on study. Data from procedures that are considered standard of care and performed before obtaining patient informed consent for the study may be collected and entered into the electronic case report form (eCRF).

3.1.2 Enrollment

Eligible patients will be enrolled in parallel in either Cohort A or Cohort B at all sites.

3.1.3 Treatment Period

Treatment cycles will be 28 days in length. All patients will be monitored for efficacy as well as safety throughout the treatment phase. Assessments will include, but may not be limited

to, physical examination, vital signs and weight measurement, hematology, serum chemistry, urinalysis, concomitant medications, ECOG performance status, disease status assessment, 12-lead ECG, AEs with any associated therapies and procedures, study drug administration and accountability. Blood samples will also be collected for PK and biomarker analyses.

Disease response to drug will be evaluated by physical examination and imaging methods, with tumor scans being done every 8 weeks of treatment (2 treatment cycles, ± 7 days permitted). All responses (CR or PR) must be confirmed with a scan no less than 4 weeks after the initial response.

Disease progression will be determined by RECIST v1.1 (Appendix 2), or in the case of prostate cancer, by modified RECIST v1.1/PCWG3 guidelines (Appendix 3). If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST v1.1 per the Schedule of Assessments. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, will be discontinued from study treatment and enter follow-up. However, if the patient has met criteria for radiologic progression by RECIST, but the patient is still receiving benefit from the study drug(s) (eg, patient has mixed radiologic response or is continuing to have symptomatic benefit), according to the investigator, the decision to continue will be made jointly between the investigator and the sponsor (or designee), and the patient must consent prior to continuing treatment with rucaparib.

3.1.4 Post-treatment Period

Upon treatment discontinuation, regardless of reason (with the exception of withdrawal of consent or death), patients will have an End-of-Treatment (EOT) Visit with assessments as detailed in Section 7.

All patients will be followed for at least 28 days after the last dose of study drug and will then proceed to long-term follow-up (LTFU).

Patients who discontinue treatment for a reason other than disease progression or death should continue to have tumor scans performed at the interval specified until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination, or initiation of subsequent anticancer treatments.

Ongoing serious adverse events (SAEs), AESIs and treatment-related CTCAE Grade 3/4 AEs will be followed until resolution or stabilization has been determined, death, or loss to follow-up. After the 28-Day Follow-Up Visit, only SAEs considered as potentially related to study drug should be reported per Clovis PV requirements and captured in the Clovis Pharmacovigilance (PV) database. This includes serious reports of pneumonitis or similar events, if considered to be related to study drug.

After the 28-day Safety 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 Safety Follow-up Visit.

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

An optional tumor biopsy will be collected from patients who experience disease progression and provide additional consent.

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

3.2 Data Monitoring Committee

The study will have a Data Monitoring Committee (DMC) that will include key investigators and sponsor personnel. The DMC will review both safety and efficacy data after the first 20 patients have been enrolled and completed the first cycle of treatment, and then approximately every 6 months, or earlier as needed, throughout the study.

3.3 Removal of Patients from Therapy or Assessment

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 (where acceptable according to national law and/or local regulations);
- Progression of patient's underlying cancer per RECIST v1.1, or modified RECIST v1.1/PCWG3 guidelines for prostate cancer, as assessed by the investigator, unless the patient continues to derive clinical benefit from the study drug(s) according to the investigator, the investigator has consulted with the sponsor's medical officer or designee, and the patient has provided additional consent for treatment beyond progression at the next study visit;
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient;
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy;
- Noncompliance by the patient with protocol-mandated procedures;
- Study termination; 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. Information that is collected while the patient has consented to be in the study cannot be withdrawn. Details are provided in the Informed Consent Form (ICF).

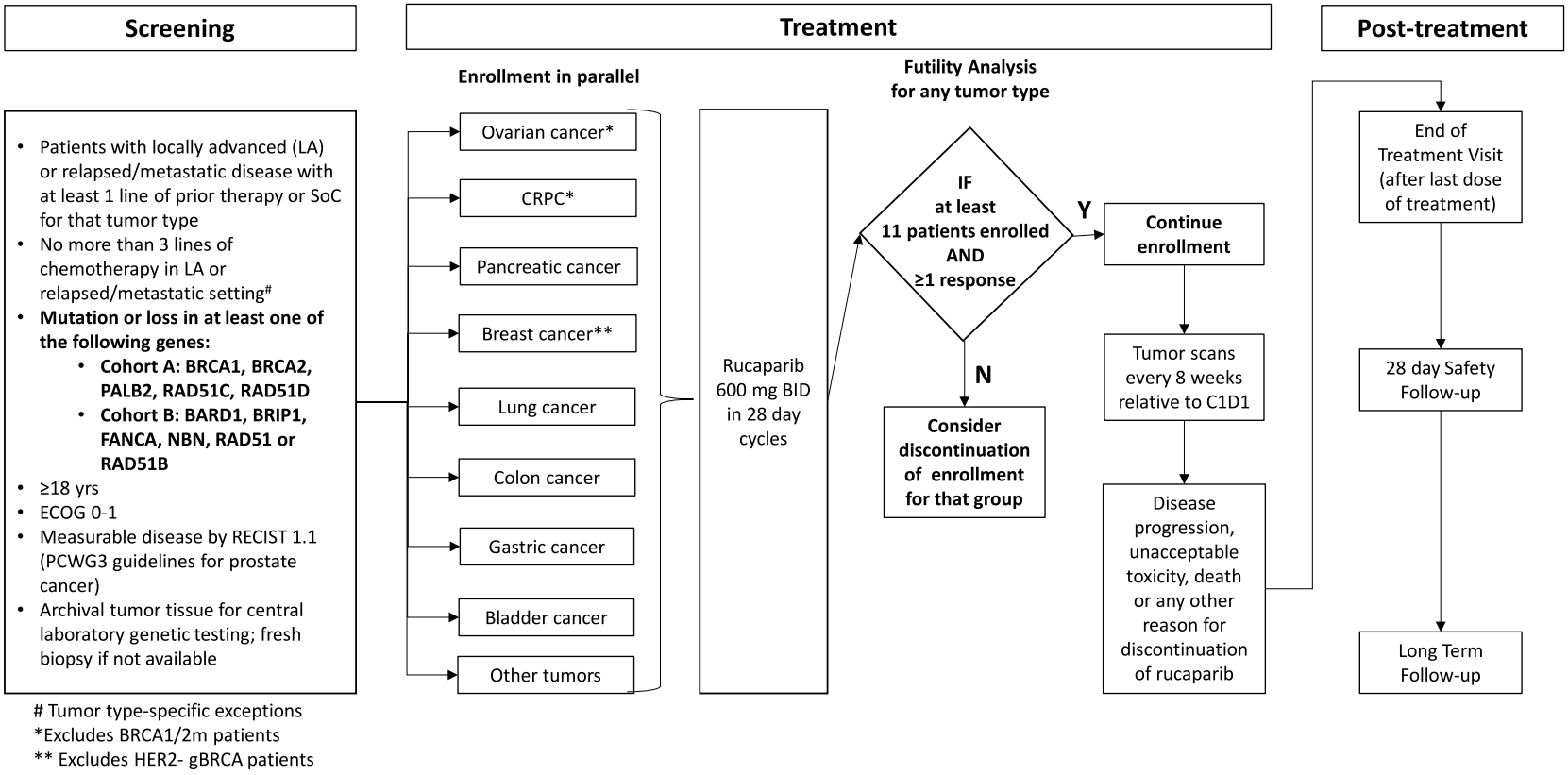
If the patient withdraws consent to continue in the study or discontinues the study for another reason it will be documented on the appropriate eCRF. A patient may withdraw consent to participate in an additional or optional part of a study that has a corresponding consent (ie, optional tumor biopsy) 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 10.6.

3.4 Study Schema

The study schema in Figure 1 summarizes the treatment design of the study.

Figure 1. Study Schema



Abbreviations: BID = twice a day; BRCA1/2m = BRCA1 or BRCA2 mutated; C1D1 = Cycle 1, Day 1; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group performance status; gBRCA = germline BRCA; HER2 = human epidermal growth factor receptor 2; LA = locally advanced; PCWG3 = Prostate Cancer Working Group Guidelines Version 3; RECIST = Response Evaluation Criteria in Solid Tumors; SoC = standard of care.

3.5 End of Study

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 LTFU may transition to have their LTFU and scans, if applicable, captured via another mechanism.

4 STUDY POPULATION

4.1 Number of Patients and Sites

The total enrollment planned for this study is approximately 220 patients. There will be approximately 20 study sites in the US.

4.2 Inclusion Criteria

Eligible patients must meet the following inclusion criteria:

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form prior to any study-specific evaluation.
2. Be ≥ 18 years of age at the time the informed consent is signed.
3. Have an unresectable, locally advanced (primary or recurrent) or metastatic solid tumor and have relapsed/ progressive disease as confirmed by radiologic assessment.
4. Have measurable disease as defined by RECIST v1.1 (Appendix 2) or modified RECIST v1.1 and PCWG3 criteria (Appendix 3) for prostate cancer. A measurable tumor lesion in a previously irradiated site is acceptable if subsequent progression has been demonstrated in that lesion.
5. Have a deleterious mutation (germline or somatic) in BRCA1, BRCA2, PALB2, RAD51C or RAD51D (Cohort A) or a deleterious mutation (germline or somatic) in BARD1, BRIP1, FANCA, NBN, RAD51 or RAD51B (Cohort B). Mutations must be identified by either a local or central laboratory that is certified per Clinical Laboratory Improvement Amendments (CLIA) regulations.
    a. Mutations may be identified in a tumor tissue, blood, or saliva sample. For a local laboratory test result, the classification of the mutation as deleterious must be documented in the patient's medical record. Variants of uncertain significance or benign variants will not be eligible for enrollment into the trial.
    b. Patients with EOC, FTC, or PPC must have a deleterious PALB2, RAD51C or RAD51D mutation (or deleterious mutation in another HRR gene, listed in Appendix 1). Patients with a deleterious BRCA1 or BRCA2 mutation are not eligible.
    c. Patients with mCRPC must have a deleterious PALB2, RAD51C or RAD51D mutation (or deleterious mutation in another HRR gene, listed in Appendix 1). Patients with a deleterious BRCA1 or BRCA2 mutation are not eligible.
    d. Human epidermal growth factor receptor (HER2) negative breast cancer patients with a deleterious germline BRCA1 or BRCA2 mutation are not eligible, unless the use of both olaparib and talazoparib is contraindicated. Breast cancer patients with somatic BRCA mutations are eligible, as are HER2+ patients with deleterious somatic or germline mutations in any of the 11 genes listed in Appendix 1. HER2 negative patients with a deleterious mutation in any non-BRCA HRR gene listed in Appendix 1 are eligible.
6. Have received at least 1 line of available therapy(ies) with treatment demonstrated to have a survival benefit in the relevant tumor type or, in the absence of any OS-extending treatment, have received at least 1 standard-of-care treatment regimen.

a. A treatment regimen that is held for reasons other than disease progression and subsequently resumed at a later date with no other intervening systemic anti-cancer therapy is considered 1 treatment regimen.
b. Patients with EOC, FTC, or PPC must have received 2 prior lines of platinum-based chemotherapy and:
   i. Had documented treatment-free interval of ≥ 6 months following the first platinum-based chemotherapy regimen received; and
   ii. Had either platinum-sensitive or platinum-resistant disease (progression-free interval [PFI] ≥ 1 month after last dose of platinum). Patients with platinum-refractory disease (ie, whose disease progressed during or within 1 month of completing treatment with their most recent platinum-based therapy) are excluded.
c. Patients with locally advanced or metastatic endometrial cancer, excluding uterine carcinosarcoma, must have received at least 1 line of platinum-containing therapy but no more than 2 prior chemotherapy-based regimens (eg, carboplatin/cisplatin, taxanes, doxorubicin, ifosfamide, topotecan or other chemotherapy regimens recommended by regional guidelines). Hormonal therapy, immunotherapy, mechanistic target of rapamycin [mTOR] inhibitors, anti-vascular endothelial growth factor [VEGF] or anti-HER2 therapy are not counted towards lines of therapy. Patients must not have had radiologic disease progression within 3 months of initiating platinum-containing chemotherapy, with a best response of SD or better.
d. Patients with locally advanced or metastatic cervical cancer must have received at least 1 line of platinum-containing therapy, but no more than 2 prior chemotherapy-based regimens (including carboplatin/cisplatin, taxanes, topotecan, other chemotherapy regimens recommended by regional guidelines). Immunotherapy or anti-VEGF therapy are not counted towards the prior treatment lines. Patients must not have had radiologic disease progression within 3 months of initiating platinum-containing chemotherapy, with a best response of SD or better.
e. Patients with either ovarian or uterine carcinosarcoma are restricted to 1 line of platinum-containing therapy and must not have had radiologic disease progression within 3 months of initiating platinum-containing chemotherapy, with a best response of SD or better.
f. Patients with breast cancer:
   i. Triple-negative breast cancer (TNBC) patients must have received no more than 2 prior lines of chemotherapy for metastatic disease. Patients may have previously received radiation therapy and 1 line of immunotherapy. Prior platinum as potentially curative treatment for prior cancer (eg, ovarian) or as adjuvant or neoadjuvant treatment for breast cancer is allowed; however, patients must not have progressed during treatment.
   ii. All other breast cancer patients with tumors other than TNBC must have received no more than 2 prior chemotherapy regimens for locally advanced and/or metastatic disease, with no limit on prior hormonal therapies or targeted anticancer therapies such as mTOR inhibitors or cyclin-dependent kinase (CDK) 4/6 inhibitors (other than PARP inhibitors). Patients who have received

platinum in the adjuvant or neoadjuvant setting are eligible; however, subjects must not have progressed during treatment.

g. Patients with mCRPC must have received prior androgen-receptor (AR)-targeted therapies (such as abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent; 1 to 2 AR-directed agents allowed) and may not have received more than 2 lines of taxane for mCRPC.

h. Patients with pancreatic cancer must have received no more than 2 prior chemotherapy-based regimens for locally advanced or metastatic disease and are eligible as long as they did not have radiologic disease progression during treatment with or within 3 months of receiving platinum-containing chemotherapy and have a best response of SD or better.

   i. Neoadjuvant/adjuvant chemotherapy will not be counted as a treatment regimen if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the regimen will be counted.

i. Patients with gastric or esophageal cancer must have received no more than 2 prior chemotherapy-based regimens for locally advanced or metastatic disease and are eligible as long as they did not have radiologic disease progression during treatment with or within 3 months of receiving initiation of platinum-containing chemotherapy and have a best response of SD or better.

   i. Neoadjuvant/adjuvant chemotherapy will not be counted as a treatment regimen if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the regimen will be counted.

j. Patients with colorectal cancer must have received no more than 2 prior chemotherapy-based regimens for locally advanced or metastatic disease and are eligible as long as they did not have radiologic disease progression during treatment with or within 3 months of initiation of platinum-containing chemotherapy and have a best response of SD or better.

   i. Neoadjuvant/adjuvant chemotherapy will not be counted as a treatment regimen if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the regimen will be counted.

k. Patients with locally advanced or metastatic bladder cancer must have received 1 or 2 prior treatment lines (eg, cisplatin- or carboplatin-containing therapy, immune checkpoint inhibitor) for locally advanced resectable or metastatic disease. Patients who have received platinum-containing chemotherapy should not have radiologic disease progression within 3 months of initiation of platinum-containing chemotherapy and must have a best response of SD or better.

   i. Neoadjuvant and/or adjuvant treatment for muscle invasive disease will be considered a treatment regimen if radiologic disease progression occurred within 12 months from the completion of treatment.

   ii. No more than 1 prior platinum-containing chemotherapy regimen for advanced disease is permitted. A change of platinum chemotherapy within the same

treatment regimen will be considered 1 prior platinum-containing chemotherapy. Platinum-containing chemotherapy given as radio-sensitization combined with radiation therapy to control locally advanced disease will not be considered as a prior regimen of systemic therapy.

iii. For patients who have never received platinum, the patient must currently be ineligible for cisplatin treatment.

l. Patients with metastatic non-small cell lung cancer (NSCLC) must have received no more than 2 prior lines of chemotherapy, including one line of platinum-containing therapy. Immunotherapy or targeted therapy (such as epidermal growth factor receptor [EGFR] inhibitor, c-ros oncogene [ROS] inhibitor, anaplastic lymphoma kinase [ALK] inhibitor or B-rapidly accelerated fibrosarcoma gene [BRAF] inhibitor) are permitted and do not count towards these prior lines.

i. Neoadjuvant/adjuvant chemotherapy after primary resection will not be counted as a treatment line if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the line of therapy will be counted.

ii. No more than 1 prior platinum-containing chemotherapy line for advanced disease is permitted. A change of platinum chemotherapy within the same treatment regimen will be considered 1 prior platinum-containing chemotherapy. Patients must not have had radiologic disease progression within 3 months of initiating platinum-containing chemotherapy and must have best response of SD or better.

iii. Platinum-containing chemotherapy given as radio-sensitization combined with radiation therapy to control locally advanced disease will not be considered as a prior regimen of systemic therapy.

iv. Prior combined chemotherapy and radiotherapy is permitted provided the patient has measurable disease outside the radiation field or disease in the irradiated field has progressed.

m. Patients with all other tumor types not mentioned above must have received 1, but no more than 3, lines of chemotherapy. In the rare circumstance where chemotherapy is not indicated / considered to be a preferred / recommended standard-of-care treatment for a given tumor type, an alternative therapy (eg, targeted therapy or immunotherapy) may meet the requirement for prior treatment provided it is clearly documented to be the appropriate standard-of-care treatment for that tumor type (eg, if listed in NCCN Guidelines).

i. Neoadjuvant or adjuvant chemotherapy after primary resection will not be counted as a treatment line if disease progression occurred ≥ 6 months following completion of chemotherapy. If disease progression occurred < 6 months following completion of chemotherapy, the line of therapy will be counted.

ii. No more than 1 prior platinum-containing chemotherapy line for advanced disease is permitted. A change of platinum chemotherapy within the same treatment regimen will be considered 1 prior platinum-containing chemotherapy. Patients must not have had radiologic disease progression within 3 months of initiating platinum-containing chemotherapy and must have best response of SD or better.

iii. Platinum-containing chemotherapy given as radio-sensitization combined with radiation therapy to control locally advanced disease will not be considered as a prior regimen of systemic therapy.

iv. Prior combined chemotherapy and radiotherapy is permitted provided the patient has measurable disease outside the radiation field or disease in the irradiated field has progressed.

7. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue for planned analyses. In the event archival tumor tissue is not available, a screening biopsy sample must be collected and provided to the central laboratory, unless the biopsy procedure is considered unsafe or the biopsy site is considered inaccessible by the investigator. Cytospin blocks from ascites are not acceptable.
8. 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) $\geq 1.5 \times 10^9$/L;
      ii. Platelets $\geq 100 \times 10^9$/L; and
      iii. Hemoglobin ≥ 9 g/dL independent of transfusion ≤ 14 days prior to screening hemoglobin assessment.
   b. Hepatic Function
      i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ upper limit of normal (ULN). If liver metastases are present, then $\leq 5 \times$ ULN;
      ii. Total bilirubin $\leq 1.5 \times$ ULN; $< 2 \times$ ULN if hyperbilirubinemia is due to Gilbert's syndrome; and
      iii. Serum albumin≥ 30 g/L (3.0 g/dL).
   c. Renal Function
      i. Serum creatinine ≤ 1.5 x ULN; or
      ii. Estimated glomerular filtration rate (GFR ≥ 45 mL/min using the Cockcroft Gault formula; or
      iii. Measured creatinine clearance (CL_{cr}) ≥ 30 mL/min.
9. Have an ECOG performance status of 0 to 1.
10. Have a life expectancy of at least 4 months.
11. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of the initiation of antiviral therapy are eligible for this trial, unless the anti-retroviral therapy interferes with rucaparib (see Concomitant Medications section).
12. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable within 6 months of the initiation of antiviral therapy on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load within 6 months of the initiation of antiviral therapy. Concurrent anti-HBV or anti-HCV

treatment should not interfere with rucaparib treatment (see Concomitant Medications section).

4.3 Exclusion Criteria

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

1. Symptomatic and/or untreated central nervous system (CNS) metastases or leptomeningeal disease or with a primary tumor of CNS origin. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
2. Presence of active second malignancy in addition to the tumor type to be treated with rucaparib. Patients with any of the following will be allowed to enroll under the following circumstances:
   a. History of malignancy that has been successfully treated, with no evidence of active cancer for 1 year prior to enrollment;
   b. Surgically cured and/or low risk tumors, such as early stage cervical or endometrial cancer, any cancer in situ or non-melanoma skin cancers; or
   c. Patients receiving ongoing anticancer hormonal therapy for a previously treated cancer.
3. Received > 3 prior lines of chemotherapy in the locally advanced/metastatic setting.
4. Received prior treatment with a PARP inhibitor.
5. History of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) or features suggestive of MDS/AML such as aberrant blood cell profiles requiring transfusion, growth factor treatment or other supportive therapy.
6. Pre-existing gastrointestinal disorders or conditions that would, in the opinion of the investigator, interfere with ingestion or absorption of rucaparib.
7. Received anti-cancer treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior (≤ 28 days prior in case of checkpoint inhibitor therapy) to first dose of study drug and/or ongoing adverse effects from such treatment > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (v5.0) Grade 1, with the exception for alopecia and Grade 2 peripheral neuropathy.
8. 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.
9. Drainage of ascitic fluid 2 or more times in the 4 weeks prior to the first dose of study drug or permanent drain in place (eg, PleurX®) for ascites or pleural effusion.
10. Hospitalization for bowel obstruction within 3 months prior to enrollment.
11. For female patients of childbearing potential and all male patients, the following are exclusion criteria, as applicable:

a. Female patients who refuse to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib.
b. Women of childbearing potential (WOCBP) who are pregnant or breastfeeding or who have a positive serum/plasma hCG pregnancy test ≤ 3 days prior to the first dose of rucaparib. WOCBP must not be considering getting pregnant during the study and for 6 months following the last dose of rucaparib.
c. Male patients who refuse to use highly effective method of contraception or to practice true abstinence during treatment and for 3 months after the last dose of rucaparib. Male patients must not make semen donations during treatment and for 3 months following the last dose of rucaparib.

12. 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.

4.4 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion. WOCBP or male patients of reproductive potential with female partners of childbearing potential must not be considering getting pregnant and must avoid pregnancy during the study and for at least 6 months (female patients) or 3 months (partners of male patients of reproductive potential) after the last dose of rucaparib or longer if requested by local authorities.

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

Male patients are required to use a condom during sex with a partner to avoid the possibility of exposure of the partner to rucaparib, regardless of whether the partner is a WOCBP or not. Male patients must not make semen donations during treatment and for 3 months following the last dose of rucaparib.

Male patients are considered to be of reproductive potential unless permanently sterile by bilateral orchiectomy or vasectomized with appropriate post-vasectomy documentation of absence of sperm in ejaculate.

Female patients or partners of male patients are considered to be of childbearing potential unless one of the following applies:

- Considered to be permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy; or
- Is postmenopausal, defined as no menses for at least 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the

postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.

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

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

Female patients will be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with rucaparib, and male patients will be instructed to notify the investigator if pregnancy is discovered in their female partner either during or within 3 months of completing treatment with rucaparib (refer to Section 8.6).

4.5 Compliance with Inclusion/Exclusion Criteria

All inclusion/exclusion criteria must be met for the prospective participant to enroll. Neither the investigator, nor the sponsor/designee, may allow a prospective participant who has not met the inclusion/exclusion criteria to enter the study.

5 STUDY TREATMENT(S)

5.1 Description of Investigational Product(s) and Storage

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

Table 2. Description of Rucaparib Tablets

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

Abbreviations: INN = International Nonproprietary Name.

5.2 Packaging and Labeling

Rucaparib tablets are provided in 60-count high-density polyethylene (HDPE) bottles with child resistant caps and should be stored in the provided containers between 15°C and 30°C (59°F 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.

Details with respect to packaging and labeling of rucaparib tablets are described in the Pharmacy Manual.

Study drug containers containing rucaparib tablets will be labeled according to national regulations for investigational products. Where accepted, the expiry date will not appear on the labels, but will be controlled by the use of an Interactive Web Response System (IWRS).

5.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; the investigational product will not be blinded or masked. All patients enrolled will receive rucaparib.

5.4 Method of Assigning Patients to Treatment Groups

Enrollment in the study for all tumor types will be competitive. Sites may be actively enrolling in more than 1 tumor type simultaneously.

5.5 Preparation and Administration of Rucaparib

The investigator or designee will be responsible for distributing rucaparib tablets to all patients. Study sites should follow local guidelines for the handling of oral cytotoxic drugs.

The starting dose of rucaparib is 600 mg BID. Patients may take rucaparib with or without food. Each dose should be taken with water. Tablets should be swallowed whole without crushing or chewing. Tablet strength combinations shall be determined by the IWRS.

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), he/she should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up.

Patients will be provided a sufficient quantity of rucaparib for 28 days, with a small overage, until the next rucaparib dispensation visit. 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.

5.6 Dose Modifications of Protocol-specified Treatment

Doses of rucaparib may be interrupted or delayed for toxicity and other protocol-specified criteria. Dose reductions are permitted for rucaparib. Treatment may be discontinued due to withdrawal of consent, unacceptable toxicity, disease progression, completion of treatment cycles, or termination of the study, whichever occurs first.

Dose modification and re-treatment of rucaparib are to be based on the criteria presented in Table 3.

Table 3. Dose Modification and Re-Treatment Criteria for Study Drug

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib		
		Treatment Interruption	Re-treatment	Dose Modification
Adverse event or laboratory abnormality	1 or 2	None[a]	N/A	None
Adverse event[b]	3 or 4	Hold dose	≤ Grade 2	**1st occurrence:** Same dose **2nd or 3rd occurrence of same AE:** Reduce dose[c]
ALT/AST elevation (in the absence of other signs of liver dysfunction)	3	Continuation of dosing permitted provided total bilirubin is < ULN and ALP is < 3 x ULN; monitor LFTs weekly; Hold if levels do not decline within 2 weeks or if levels increase	≤ Grade 2	**1st occurrence:** Same dose **2nd occurrence or more of same AE:** Reduce dose[c]
ALT/AST elevation	4	Hold	≤ Grade 2	Reduce dose; monitor LFTs weekly for 3 weeks (Section 5.6.1)
ALT or AST elevations (> 3 × ULN) AND Total bilirubin (> 2 × ULN) - Suspected DILI [Section 8.9]	NA	Hold[d]; Monitor LFTs weekly	≤ Grade 1 (or baseline)	Subject to investigation: reduce dose[c] If DILI is confirmed, treatment should be permanently discontinued

Table 3. Dose Modification and Re-Treatment Criteria for Study Drug

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib		
		Treatment Interruption	Re-treatment	Dose Modification
Anemia	≥ 3	Hold dose[e]	≤ Grade 2	Same or reduced dose[a, c]

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DILI = drug-induced liver injury; INR = international normalized ratio; LFT = liver functions test; N/A = not applicable; ULN = upper limit of normal.

[a] At the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity that is attributed to rucaparib and not adequately controlled by concomitant medications and/or supportive care.

[b] Exceptions include Grade 3 or 4 nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to institutional guidelines

[c] For dose reductions, see Section 5.6.1

[d] Evaluate patient 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 INR should be implemented as indicated. If no alternative cause is identified, study drugs must be permanently discontinued. Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin.

[e] If anemia CTCAE Grade ≥ 3 persists for > 14 consecutive days, or a dependence upon blood transfusions occurs, then weekly complete blood counts should be performed until resolution of the event. If after 42 days of interruption and anemia has not improved to CTCAE Grade ≤ 1, the patient should be referred to hematologist and analysis of the bone marrow with cytogenetic studies and recommended according to standard practice. Bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

5.6.1 Dose Modification Criteria

Dose reduction steps for rucaparib are presented in Table 4.

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

Dose modifications (ie, interruption, reduction, and/or re-escalation) must be recorded for each patient in the appropriate section of the eCRF.

Table 4. 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

Abbreviations: BID = twice a day.

[a] Further dose reduction is possible but requires consultation with the sponsor's medical monitor.

5.6.2 Management of Anemia

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

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

5.6.3 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 computed tomography [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 study medical monitor. Retreatment with rucaparib may be resumed at the current or a reduced

dose, if appropriate.

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

5.6.4 Rucaparib Discontinuation

Rucaparib should be permanently discontinued for any of the following:

- If a patient continues to experience toxicity despite dose reduction steps to the lowest permissible dose or if dosing is interrupted for > 21 consecutive days due to toxicity, treatment with rucaparib should be discontinued, with the following exceptions:
  - Treatment interruption > 21 days may be allowed if approved by the sponsor. Prior to re-initiating treatment for a patient with a treatment interruption lasting > 21 days, the study medical monitor/designee must be consulted. Tumor assessments should continue as per protocol even if treatment is interrupted.
- Confirmed diagnosis of MDS or AML;
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued oral study treatment dosing; or
- Patient with progressive disease. If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria (or modified RECIST v1.1 criteria for mCRPC patients), but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the sponsor.

5.7 Treatment Compliance

Study site personnel will review dosing information with the patient (or legally authorized representative, where acceptable according to national law and/or local regulations) 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, where acceptable according to national law and/or local regulations) will be instructed to keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at scheduled clinic visits. A compliance check and tablet count will be performed by study site personnel during clinic visits. Study site personnel will record compliance information on the eCRF. Additional details regarding study drug dispensation and return can be found in the Pharmacy Manual.

Documentation of dosing will be recorded in a study-specific dosing diary provided by the sponsor (or designee). Dosing noncompliance is defined as a patient missing > 14 days of study drug within a cycle for 2 consecutive cycles for reasons other than toxicity. The sponsor may require patients meeting noncompliance criteria to discontinue study treatment.

Every effort should be made to ensure patients return rucaparib containers/unused rucaparib 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 documentation may serve as source documentation for entering dosing data on the appropriate eCRF.

5.8 Accountability of Protocol-specified Treatment

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

The site is responsible for the return or destruction of study drug supplied by the sponsor, as required. Authorization for on-site destruction of study drug that has not been dispensed to a patient (eg, expired study drug), must be requested from the sponsor prior to destruction. All study drug containers must be accounted for prior to their destruction at the study site, according to institutional procedures for disposal of hazardous materials. Unused and returned study drug product and containers should be destroyed on-site if possible. If on-site destruction is not possible, supply should be returned to the drug depot, following the sponsor's instructions.

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

6 PRIOR AND CONCOMITANT THERAPY

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

6.1 Supportive Care

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

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

6.2 Anticancer or Experimental Therapy

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

Any botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care are strongly discouraged (see Section 6.9).

6.3 Radiotherapy

Palliative radiotherapy on lesions not considered target lesions for tumor evaluation per RECIST v1.1 is permitted during the study. Treatment with rucaparib should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation-related toxicity.

6.4 Cytochrome P450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo CYP interaction study (CO-338-044), rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used in patients on rucaparib taking concomitant medicines that are sensitive clinical substrates of CYP1A2, CYP2C9, CYP2C19, and/or CYP3A (Appendix 5).

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

6.5 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).

6.6 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 international normalized ratio (INR) monitored regularly per standard clinical practice.

6.7 Luteinizing Hormone-releasing Hormone Analogs

For prostate cancer patients who have not undergone an orchiectomy and are currently being treated with luteinizing hormone-releasing hormone (LHRH) analogs at the time of consent, therapy must be continued throughout the study.

6.8 Bisphosphonates or other Bone Targeting Agents

Patients cannot have initiated denosumab or bisphosphonate therapy or adjusted bisphosphonate or denosumab dose/regimen within 4 weeks prior to first dose of rucaparib. Patients on a stable denosumab or bisphosphonate regimen are eligible and may continue treatment. Initiation of bisphosphonates or other approved bone targeting agents, if clinically indicated, is allowed, and should not result in study treatment discontinuation unless patient has radiographic evidence of disease progression.

6.9 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 are discouraged 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 area under the concentration-time curve (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 MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could decrease metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib.

6.10 General Restrictions

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

7 STUDY PROCEDURES AND METHODS

7.1 Schedule of Assessments

Table 5 summarizes the procedures and assessments to be performed for all patients.

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

Table 5. Schedule of Assessments for All Patients

Procedure[a]	Screening Phase	Treatment Phase (28-day cycles ± 3 days)			Post-treatment Phase		
		Cycles 1 and 2		Cycles 3+			
	Day -28 to Day -1	Day 1	Day 15	Day 1	End of Treatment	28-day Safety Follow-up[b]	Long-Term Follow-up
Informed Consent (Section 7.2)[c]	X						
Medical/Oncology History (Section 7.3.1)	X						
Archival Tumor Tissue Sample or Fresh Biopsy[d]	X						
Physical Examination (Section 7.3.4.5)[e]	X	X		X	X	X	
Vital Signs (Section 7.3.4.3)	X	X	X	X	X	X	
12-lead ECG (Section 7.3.4.4)[f]	X				X		
Prior/Concomitant Medications/Procedures (Section 7.3.2)	X	X	X	X	X	X	
Disease Assessment/Tumor Scans[g] (Section 7.3.3.1)	X			X	X	X	X
ECOG Performance Status (Section 7.3.4.6)	X	X		X	X	X	
Hematology (local lab) (Section 7.3.4.2)	X	X	X	X	X	X	
Serum/Plasma Chemistry (local lab) (Section 7.3.4.2)	X	X	X	X	X	X	
Urinalysis (local lab) (Section 7.3.4.2)	X	X	X	X	X	X	
Pregnancy test (WOCBP only; local lab) (Section 7.3.4.2)[h]	X	X		X	X		
Tumor marker measurement (local lab)[i] or PSA measurement (local lab)[j] (Section 7.3.3.2)	X	X		X	X	X	
Blood Sample for g/s mutation status (central lab)[k] (Section 7.3.6.3)		X					

Table 5. Schedule of Assessments for All Patients

Procedure[a]	Screening Phase	Treatment Phase (28-day cycles ± 3 days)			Post-treatment Phase		
		Cycles 1 and 2		Cycles 3+			
	Day -28 to Day -1	Day 1	Day 15	Day 1	End of Treatment	28-day Safety Follow-up[b]	Long-Term Follow-up
Blood Sample for ctDNA analysis (central lab)[l] (Section 7.3.6.2)	X	X		X	X	X	
Rucaparib Administration[m]		X		X			
Adverse Events[n] (Sections 8.7 and 8.8)	(X)	X	X	X	X	X	
Plasma sample for PK[o] (Section 7.3.5)		X		X			
Tumor Tissue Biopsy (OPTIONAL; additional consent required)[p]					X		
Subsequent Treatments, treatment-related SAEs, AESIs, & Survival[q]							X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BRCA = breast cancer gene; ctDNA = circulating tumor deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; gBRCA = germline BRCA; HRD = homologous recombination deficiency; PK = pharmacokinetics; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; sBRCA = somatic BRCA; WOCBP = women of child-bearing potential.

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

[b] Follow-up visit should occur 28 days (±7) from the last dose of study drug, or can be performed on the date of discontinuation if that date is at least 28 days from last dose. Chemistry and hematology are only necessary at follow-up visit if toxicities are present. The follow-up visit should be conducted in person.

[c] Informed consent may be completed outside the screening window of 28 days prior to study start, as informed consent does not expire, except as required by applicable regulatory requirements or if informed consent is withdrawn by patient.

[d] All patients will be required to provide adequate tumor tissue (tumor content > 30% is strongly preferred) for analysis. In the event archival tumor tissue is not available, a screening biopsy sample must be collected and provided to the central laboratory, unless the biopsy procedure is considered unsafe by the investigator or the biopsy site is considered inaccessible. Availability of adequate tumor tissue samples must be confirmed prior to enrollment, but tissue sample may be sent after the patient is enrolled. Submission of a tumor block is strongly preferred. Refer to the Laboratory Manual for detailed sample collection and handling instructions.

[e] Height measured at screening and at the EOT visit only.

[f] 12-lead ECGs may be repeated at other times as clinically indicated.

[g] Disease assessments to consist of clinical examination and appropriate imaging techniques per RECIST v1.1 or modified RECIST (for mCRPC) every 8 weeks (± 7 days). Other complementary assessments may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions (including in the CNS), throughout the clinical study. Confirmatory scans should follow at least 4 weeks after the scan at which a response was first documented. For patients who discontinue from study treatment for a reason other than disease progression or death, scans should occur at treatment discontinuation or the 28-day Safety Follow-up Visit if it has been ≥ 8 weeks since the last scan or if disease progression was noted on the last scan, and every 8 weeks (± 7 days) thereafter, until disease progression, death, loss to follow-up, withdrawal from study, study termination, or initiation of subsequent anticancer treatment. Patients who have been on study at least 18 months will decrease the frequency of tumor assessments to every 16 weeks (± 7 days is permitted).

[h] Female patients of childbearing potential must have a negative serum or plasma hCG pregnancy test result ≤ 3 days prior to administration of the first dose of rucaparib. In addition, a serum or plasma hCG 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.

[i] Tumor marker measurements per standard of care for a particular tumor type should be performed for patients at screening and on Day 1 of every subsequent cycle, at treatment discontinuation, the 28-day safety follow-up, and as clinically indicated. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging and ctDNA sampling.

[j] All PSA measurements should be performed for patients with prostate cancer by the local laboratory. Serial PSA measurements that show progression at study entry must follow the protocol specification.

[k] If sample is not collected on Day 1 of Cycle 1, it should be collected at the next clinic visit.

[l] Screening, Day 1 of Cycle 1 through Cycle 6, every other cycle after Cycle 6, and at the End-of-Treatment and 28-day Follow-Up. Refer to the Laboratory Manual for detailed sample collection and handling instructions.

[m] First dose of study drug in Cycle 1 should be administered within 3 days of enrollment. Study treatment continues in 28-day cycles until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, initiation of any other cancer therapy, positive pregnancy test, or termination of the study. Study visit should take into account the patient's rucaparib supply. A quantity of rucaparib sufficient to complete 1 cycle (28 days) should be dispensed to the subject/patient on Day 1 of each cycle.

[n] AEs, SAEs, and AESIs that occur after first administration of study drug through to 28 days after last dose of study drug(s). In addition, SAEs that were related to a screening procedure will also be recorded. Ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed to resolution or stabilization. After the Safety Follow-up 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 the AESIs of MDS and AML regardless of causality, will be recorded in the eCRF. If a patient discontinues from treatment in the rollover study and begins a subsequent anticancer therapy, the sponsor will terminate collection of SAEs.

[o] Cycles 2 through 6 only. PK samples should be collected prior to the morning dose on the visit days, and as close as possible to 12 hours after the last dose (even if the morning dose on the specified visit days is not administered). If a new treatment cycle is delayed, the predose PK sample closest to 12 hours after the last dose should still be collected on that visit and should not be collected on Day 1 of the delayed treatment cycle. Refer to the Laboratory Manual for detailed sample collection and handling instructions.

[p] An optional tumor biopsy may be collected from patients within 30 days after the time of disease progression or treatment discontinuation. Additional consent is required. Refer to the Laboratory Manual for detailed sample collection and handling instructions.

[q] All patients discontinued from treatment, regardless of reason, should be followed for subsequent treatments, secondary malignancy, and survival every 12 weeks relative to the last dose of study drug until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone and can be completed to coincide with scheduled tumor assessments during this period. Diagnosis of any secondary malignancy requires appropriate documentation (ie, laboratory and/or pathology reports).

7.2 Informed Consent Process

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

The first study-specific, screening activity performed after signature of the Informed Consent Form begins the Screening Phase. Informed consent (IC) may be completed outside the screening window of 28 days prior to study start, as IC does not expire, except as required by applicable regulatory requirements or if IC is withdrawn by patient.

Patients with radiologic disease progression who are still receiving benefit and are permitted to continue rucaparib treatment following disease progression must provide consent for continued treatment. Patients participating in the optional tumor tissue biopsy at the time of radiographic disease progression must provide additional consent for this procedure.

7.3 Methods of Data Collection

7.3.1 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 rucaparib, 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 the tumor type they are being treated for in this study, prior surgeries/treatments received for cancer, dates of treatment administration, best response achieved, date of progression and how assessed, PFI after last platinum regimen (if applicable), radiology reports, and status (germline or somatic – if known) of deleterious mutation in BRCA1/2 or other HRR gene.

7.3.2 Prior and Concomitant Medication Assessments

Medications being used by the patient will be recorded as prior/concomitant 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 discontinuation treatment. Medication information will be entered in the appropriate eCRF after it is obtained at each study visit.

7.3.3 Efficacy Evaluations

7.3.3.1 Disease/Tumor Assessments

Target and non-target lesions will be evaluated for evidence of radiographic response based on RECIST v1.1 criteria (Appendix 2) or, in the case of prostate cancer, on modified RECIST v1.1 and/or PCWG3 (for bone lesions only) criteria (Appendix 3).

Tumor assessment measurements will be performed at screening, at the end of every 8 calendar weeks (± 7 days) relative to Cycle 1 Day 1 until radiologically confirmed disease progression by RECIST v1.1, as assessed by the investigator, loss to follow-up, withdrawal from study, death, or study closure. For any patient who discontinues from study treatment for a reason other than disease progression or death, scans should occur at treatment discontinuation or the 28-day Safety Follow-up Visit if it has been ≥ 8 weeks since the last scan or if disease progression was noted on the last scan, and every 8 weeks (± 7 days) thereafter until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination, or initiation of subsequent anticancer treatments. Patients who have been on study at least 18 months may decrease the frequency of tumor assessments to every 16 weeks (± 7 days is permitted). A confirmatory scan to verify a CR or PR should occur at least 4 weeks after a response was first documented.

Disease/tumor assessments will comprise clinical examination and appropriate imaging techniques per RECIST v1.1 (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1); other assessments (MRI, X-ray, positron emission tomography (PET), bone scan, and ultrasound) may also be performed as clinically indicated. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with intravenous [IV] and oral contrast) then the CT portion of the PET/CT can be used for RECIST v1.1 measurements. MRI may be used in place of CT scans for assessment of target lesions if requested by local authorities. All sites of disease (including CNS) should be followed and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

For mCRPC patients, disease assessment by CT/MRI/PET/bone scans will be performed and modified RECIST v1.1/PCWG3 criteria will be used to evaluate efficacy; up to 10 lesions in any metastatic site shall be recorded for extra-skeletal disease according to PCWG3. For all other tumor types, up to 5 tumor lesions are allowed.

Tumor response will be interpreted using RECIST v1.1 (Appendix 2) or PCWG3 criteria in prostate cancer patients (Appendix 3). Disease progression will only be determined by RECIST v1.1.

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

7.3.3.2 Tumor Markers

Blood samples to assess tumor markers (eg, cancer antigen-125 [CA-125], prostate-specific antigen [PSA] or other markers that are standard of care for a specific tumor type) will be

collected at screening, on Day 1 of each cycle, at the treatment discontinuation, the 28-day Safety Follow-up Visit, and as clinically indicated. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging and ctDNA sampling. All tumor markers will be measured by a local laboratory.

7.3.4 Safety Evaluations

7.3.4.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. During the screening period, unless otherwise required by local regulations, SAEs related to protocol-mandated procedures will be reported. Patients will be monitored for AEs that occur after first administration rucaparib through 28 days, inclusive, after the last dose of rucaparib and any AEs will be recorded. After the 28-day safety follow-up window, 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 the AESIs of MDS and AML irrespective of causality, are to be reported. In the time after informed consent is provided but before rucaparib is administered, AEs/SAEs are to be recorded if they are the result of a protocol-mandated 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 (v5.0) and recorded on the 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. Any AE that occurs after first dose of study drug through 28 days after receiving the last dose of rucaparib will be recorded on the AE eCRF.

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

7.3.4.2 Clinical Laboratory Investigations

Samples for hematology, clinical chemistry, urinalysis, and serum/plasma hCG pregnancy test will be analyzed by a local laboratory. The panels of laboratory tests to be performed are shown below in Table 6.

Laboratory tests will be assessed for all patients at screening, during treatment per the Schedule of Assessments, at the EOT Visit, and Safety Follow-up Visit(s), and if toxicities are present.

Hematology and clinical chemistry results must be reviewed by the investigator before the start of rucaparib and throughout the study. Fasting is not required before blood sampling for clinical chemistry tests. Additional and more frequent tests may be performed at the investigator's discretion.

Table 6. Laboratory Tests

Hematology	Clinical Chemistry	
Red blood cell (RBC) count	Total protein	Glucose
Hemoglobin	Albumin	Sodium
Hematocrit	Creatinine (eGFR)[a]	Potassium
MCV	Blood urea nitrogen (BUN) or urea	Magnesium
MCH	Bilirubin (total, direct, indirect)	Chloride
MCHC	Alkaline phosphatase (ALP)	Bicarbonate (CO_2/HCO_3^-)
Reticulocyte count	Alanine aminotransferase (ALT)	Calcium
White blood cell (WBC) count	Aspartate aminotransferase (AST)	Phosphorus
Differential with absolute neutrophil count (ANC)	Lactate dehydrogenase (LDH)	Lipid panel (Total cholesterol, LDL, HDL, triglycerides)
Platelet count		

Abbreviations: eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume.

[a] Estimated GFR using the Cockcroft Gault formula or institutional standard formula may also be collected, as clinically applicable

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 (within 14 days prior to first rucaparib dose), during treatment per the Schedule of Assessments, at the EOT Visit, and Safety Follow-up Visit(s).

Pregnancy Test: For women of childbearing potential only. A serum or plasma hCG pregnancy test must be performed ≤ 3 days prior to first dose of rucaparib (a negative result is required before dosing can begin), ≤ 3 days prior to Day 1 of every cycle during treatment, and a serum/plasma hCG pregnancy test at the EOT Visit. A positive pregnancy test during study participation must be reported to the sponsor. Refer to Section 8.6 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 8.5 for guidelines on reporting of abnormal laboratory values as AEs.

7.3.4.3 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature. Vital signs will be taken predose, after the patient has been resting for at least 5 minutes, at the following time points:

during screening, Day 1 and Day 15 of Cycles 1 and 2, Day 1 of each cycle thereafter, at the EOT Visit and at the Safety Follow-up.

7.3.4.4 12-Lead Electrocardiograms

For all patients, local 12-lead ECGs (heart rate, PR interval, QRS, QT, QTc, and rhythm) will be taken during screening and at the EOT Visit.

The 12-lead ECGs may be repeated at other times as clinically indicated. The investigator or qualified designee will review the ECGs locally and assess the results as normal or abnormal (clinically significant or not clinically significant).

7.3.4.5 Physical Examinations, Body Weight, and Height

Physical examinations will include an assessment of all the major body systems. Complete physical examinations, along with measurement of body weight, will be performed at screening (within 28 days prior to first dose of rucaparib), on Day 1 of each cycle during each visit, at the EOT Visit, and at the 28-day Safety Follow-up Visit. Height will be measured at screening and at the EOT visit only.

7.3.4.6 ECOG Performance Status

ECOG performance status (Appendix 4) will be assessed at screening (within 28 days prior to first dose of rucaparib), on Day 1 of each cycle, at the EOT Visit, and at the 28-day Safety Follow-up Visit. ECOG performance status should be assessed by the same study site personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

7.3.5 Pharmacokinetic Assessments

Plasma samples are to be collected from patients for trough level PK analysis of rucaparib before the morning dose on Day 1 of Cycles 2 to 6 and as close as possible to 12 hours after the previous dose. If a new treatment cycle is delayed, the predose PK sample closest to 12 hours after the last dose should still be collected on that visit and should not be collected on Day 1 of the delayed treatment cycle. Refer to the Laboratory Manual for sample collection, handling, and storage details for PK samples.

7.3.6 Biomarker Analyses

7.3.6.1 Biomarker Analysis - Formalin-fixed Paraffin-embedded Tumor Tissue

All patients will be required to provide sufficient quantity of archival FFPE tumor tissue (10 to 15 x 5 µm sections [unstained], or equivalent) for central laboratory analysis. The tumor tissue should also contain at least 20% tumor content and 80% nucleated cellular content. If archival tumor tissue of sufficient quantity is not available, a screening biopsy must be submitted for central laboratory analysis, unless the biopsy location is inaccessible,

or the procedure is deemed unsafe by the investigator. FFPE tumor specimens that do not meet the tumor adequacy requirements may be depleted in the course of biomarker analysis. Refer to the Laboratory Manual for details.

DNA extracted from submitted FFPE tumor tissues will undergo next-generation sequencing to identify deleterious mutations in HRR genes and other cancer-related genes. Remaining tumor tissues may be used for gene expression profiling or immunohistochemistry to study biomarkers that are associated with sensitivity or resistance to PARP inhibitors in different cancer types.

A tumor tissue biopsy sample at the time of disease progression/ treatment discontinuation is optional; patients must provide additional consent for this optional tumor tissue biopsy sample. For patients who provided appropriate consent, an optional tumor biopsy may be collected within 30 days after the time of radiographic disease progression/treatment discontinuation and prior to the start of any subsequent treatment. If disease progression is caused by appearance of a new lesion(s), the lesion(s) should be prioritized for the optional biopsy to enable study of acquired resistance. Detailed sample handling instructions are located in the Laboratory Manual.

The Laboratory Manual will include details of the tissue sampling method, number of samples to be collected, processing, and handling. Handling of samples if a patient withdraws consent is described in Section 10.3. Results of the biomarker analysis on tumor samples will be provided to patients, if optional consent is signed, as described further in the Informed Consent Form. Results are provided to the study investigator for discussion with the patient.

7.3.6.2 Biomarker Analysis - Blood Sample for ctDNA

Blood samples for plasma ctDNA analysis will be collected during screening, before dosing beginning on Day 1 of Cycles 1 to 6 , before dosing every other cycle after Cycle 6, and at the EOT Visit as well as the 28 day Follow-Up Visit as outlined in Table 5. The planned ctDNA analysis can identify alteration in genes that may be associated with potential mechanisms of primary and acquired resistance to PARP inhibitors (eg, reversion mutations in HRR genes that restore wild-type function). Sample collection details will be provided in the Laboratory Manual.

7.3.6.3 Biomarker Analysis – Blood Sample for Genomic DNA

A whole blood sample for genomics analyses will be collected on Day 1 of Cycle 1 from all patients. If the genomics sample is missed on Day 1, it should be collected at the next clinic visit. Genomic DNA will be extracted from this blood sample and analyzed to determine whether the BRCA1/2 mutation or other HRR gene mutation is germline or somatic prior to final data analysis.

Because the germline analysis will be done near the end of the study, there are no plans to share these results with the investigator. However, if an actionable mutation, as defined by the American College of Medical Genetics and Genomics (https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/), is revealed that was not detected in

tumor or plasma, this incidental finding will be made available to the investigator provided the results are generated from a CLIA-certified laboratory.

7.3.6.4 Additional Research

Patients will have the option to provide additional consent to allow the sponsor to retain residual samples for future unspecified research. The sponsor will store samples for up to 7 years after the study is over and any remaining samples will be retained for future unspecified research use for patients who provide additional consent.

8 ADVERSE EVENT MANAGEMENT

8.1 Definition of an Adverse Event

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

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

8.2 Definition of a Serious Adverse Event

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

- Results in death. Any event resulting in death during the reporting period (from date of first dose of rucaparib 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; or
- Is an important medical event – Important medical events may not result in death, are not life-threatening, or do not require hospitalization but may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

8.3 Definition of an Adverse Event of Special Interest

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

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

8.4 Events or Outcomes Not Qualifying as Serious Adverse Events

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

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

8.5 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

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

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any 1 of the following criteria is met:

- an action on rucaparib is made as a result of the abnormality;
- intervention for management of the abnormality is required; or

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

8.6 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the study, rucaparib should be held immediately.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a study patient or partner of a male study patient during study participation or within 6 months of the last dose for female patients, and within 3 months of the last dose for partners of male study patients, must be reported to the sponsor using the Pregnancy Report Form within the same timelines as an SAE.

All pregnancies are to be followed through to outcome, if possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form is to 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.

If any female partner becomes pregnant by a male study patient while he is receiving rucaparib, or within 3 months after the last dose of rucaparib, she will be asked to provide optional consent to allow follow-up until final outcome/delivery to determine if rucaparib has any effect on the pregnancy and fetal development.

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

Events that occur after signing the ICF but prior to initiation of rucaparib, unless due to a protocol-mandated procedure, are to 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 rucaparib through 28 days after receiving the last dose of rucaparib is to be recorded on the AE eCRF.

After the 28-day reporting window after discontinuation of treatment, only SAEs assessed as potentially related to rucaparib should be reported per Clovis 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 Safety 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 Safety Follow-up Visit.

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

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

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

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

8.7.1 Onset Date of Adverse Events

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

8.7.2 Resolution Date of Adverse Events

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

8.7.3 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, v5.0 or later grading scale.[42]

Severity is not the same as serious.

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

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

8.7.4 Causal Relationship of Adverse Events to Study Drug

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease,

concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge with the study drug (Table 7).

Table 7. Causal Relationship of Adverse Events to Study Drug

Not Related to Study Drug	• An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.); • It does not follow a reasonable temporal sequence from administration of the study drug; • It does not follow a known pattern of response to study drug; • It does not reappear or worsen when study drug is restarted; or • 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; or • It is confirmed with a positive rechallenge or supporting laboratory data.

8.7.5 Outcome and Action Taken

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

Action Taken with Study Drug (note all that apply)

- Drug withdrawn;
- Dose reduced;
- Dose interrupted;
- Dose not changed;
- Unknown; or
- Not applicable.

Outcome

- Recovered/resolved;
- Recovering/resolving;

- Not recovered/Not resolved;
- Recovered/resolved with sequelae;
- Fatal; or
- Unknown/ Lost to follow-up.

8.8 Follow-up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition becomes the patient's new baseline, until fully characterized through 28 days after the last dose of rucaparib. Any SAEs, AESIs, and treatment-related Grade 3/4 AEs must be followed until resolution or stabilization, death, or until loss to follow-up. After the 28-day safety follow-up window, SAEs considered as potentially related to rucaparib (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, must be reported.

8.9 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria,[40] must be reported as SAEs (see Section 8.7 for reporting details).

Potential drug induced liver injury is defined as:

1. ALT or AST elevation > 3 × ULN
   AND
2. Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. **No other immediately apparent possible causes** of ALT/AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

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

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/AESIs or pregnancies can be found on each of the forms.

The sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the US FDA, according to 21 Code of Federal Regulations (CFR) 312.32; to the 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.

9 STATISTICAL METHODS

9.1 General Considerations

All statistical analyses will be conducted with the SAS® System, v9.4 or higher. Further details around the statistical analyses planned for this study will be outlined separately in the statistical analysis plan (SAP). Changes to or deviations from the SAP will be described in the clinical study report (CSR).

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.

Unless otherwise specified, all data will be used to their maximum possible extent but without any imputations for missing data. Unless otherwise specified, baseline is defined as the last measurement prior to the first dose of rucaparib.

9.2 Determination of Sample Size

Estimated enrollment is from 30 to 220 patients.

Evaluation of efficacy, safety, and tolerability of rucaparib will be focused on patients in Cohort A (patients harboring mutations in certain HRR genes with tumor types that have not been sufficiently evaluated previously in a Clovis-sponsored study of rucaparib monotherapy). The minimum expectation is to enroll 10 or more patients in at least 1 additional tumor type with multiple other tumor types represented with only a few patients each. These additional data could be collected in as few as 30 patients if many of the early enrolled patients are in a single tumor type. Conversely, if the study enrolls patients in a wide variety of tumor types, it may take more than 30 patients to collect data on at least 10 patients in a single tumor type. If enrollment to a given tumor type reaches 11 patients, a futility analysis is planned to gate further enrollment within that tumor type (see Figure 1). The total study sample size is dependent on enrollment of the various tumor types, risk:benefit assessments throughout the study, and regulatory considerations. If the risk:benefit is favorable, enrollment may reach up to 200 patients in Cohort A for potential regulatory purposes. Combined with the up to 20 patients to be enrolled in Cohort B, the total enrollment could reach a maximum of approximately 220 patients.

9.3 Analysis Populations

The following analysis populations are defined for the study:

- **Safety Population** – The safety population will consist of all enrolled patients who received at least 1 dose of protocol-specified treatment

- **Efficacy Population** – The efficacy population will consist of all patients evaluable for response by RECIST v1.1 (or modified RECIST v1.1/PCWG3 for mCRPC patients)
- **Pharmacokinetic (PK) Population** – The PK population will consist of all patients who received at least 1 dose of rucaparib and had at least 1 PK parameter analyzed.

9.4 Patient Disposition

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

9.5 Demographics and Baseline Characteristics

All demographic (eg, age, race, and ethnicity as allowed by local regulations) and baseline characteristics will be summarized for the Safety Population. The following variables, as appropriate, will be summarized descriptively and/or with frequency tabulations:

- Time since diagnosis (months): ≤ 12, > 12 to 24, > 24;
- Key baseline laboratory parameters.

9.6 Efficacy Analyses

The analysis of ORR, DOR, and PFS will be based on the RECIST v1.1 criteria (or modified RECIST v1.1 for mCRPC patients) as assessed by the investigator. ORR and DOR will be performed using the Efficacy Population and PFS will be analyzed for the Safety Population.

All patients identified as harboring a reversion mutation in an HRR gene at baseline will be removed from primary and secondary efficacy analyses. Sensitivity analyses will be performed that include any/all patients harboring these reversion mutations. The methodology used to identify patients with a reversion mutation will be specified in a separate document. Sensitivity analyses to investigate the effect of platinum-free intervals (eg, < 3, 3-6, and > 6 months) and response to previous platinum-based therapy will also be performed. Details of these and all other planned analyses will be described in the SAP.

9.6.1 Primary Efficacy Analysis

The primary efficacy endpoint will be analyzed by calculating the ORR. The ORR is defined as the proportion of patients with a documented and confirmed best overall response of CR or PR per RECIST v1.1 (or modified RECIST v1.1 for mCRPC patients) as assessed by the investigator. A confirmed CR or PR is a response that is maintained and documented on a subsequent tumor assessment at least 4 weeks after initial response.

The frequency and percentages of patients with a best overall response of CR, PR, SD, or progressive disease (PD) will be summarized. The ORR (confirmed CR+PR) will also be

summarized with frequencies and percentages. All summaries of response rates will be accompanied by 95% confidence intervals (CIs).

9.6.2 Secondary Efficacy Analysis

9.6.2.1 Duration of Response

For any patient who reaches a best confirmed overall response of CR or PR, DOR will be measured from the date that best response is first recorded until the first date that progressive disease is documented per RECIST v1.1 (or modified RECIST v1.1 for mCRPC patients). Patients without a documented event of radiologic progression will be censored on the date of the last adequate tumor assessment.

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

9.6.2.2 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients that reach a confirmed CR, confirmed PR, or SD for at least 16 weeks per RECIST v1.1 (or modified RECIST v1.1 and no progression in bone by PCWG3 criteria for mCRPC patients). DCR will be summarized and accompanied by 95% CIs.

9.6.2.3 Progression-free Survival

Progression-free survival will be calculated as the number of days from the first dose of rucaparib to documented radiologic progression, according to RECIST v1.1 (or modified RECIST v1.1 for mCRPC patients), as determined by the investigator, or death due to any cause, whichever occurs first. Patients without a documented event of radiologic progression will be censored on the date of their last adequate tumor assessment (ie, radiologic assessment), or date of first dose of rucaparib if no post-baseline tumor assessments have been performed. Only tumor scans prior to start of any subsequent anticancer treatment are included.

The Kaplan-Meier methodology will be used to summarize PFS. If able to be estimated, the 50th percentile (median) together with a 95% CI will be presented. The number of patients with events and the number of patients at risk at each timepoint will be presented, and censored patients will be graphically displayed.

9.6.2.4 Overall Survival

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

The Kaplan-Meier methodology will be used to summarize OS. If able to be estimated, the 50th percentile (median) together with a 95% CI will be presented. The number of patients with events and the number of patients at risk at each timepoint will be presented, and censored patients will be graphically displayed.

9.7 Safety Analyses

All safety analyses will be summarized for the Safety Population.

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

AEs, clinical laboratory results, vital signs, ECG results, ECOG performance status, body weight, and concomitant medications/ procedures will be tabulated and summarized.

9.7.1 Extent of Exposure

Duration of exposure will be summarized descriptively and categorically. The number and percentage of patients with dose reductions and dose interruptions will be provided.

9.7.2 Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v5.0 or later TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until 28 days after the last dose of study drug.

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;
- Treatment-related serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study;
- TEAEs resulting in interruption/delay of study drug; and TEAEs resulting in dose reduction of study drug.

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

If a patient experiences multiple occurrence of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of “Missing.” For each toxicity grade, the number and percentage of patients with at least 1 TEAE of the given grade will be summarized.

9.7.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology and serum chemistry. The laboratory values will generally be presented in International System of Units (SI). The on-treatment period will be defined as the time from the first dose of rucaparib to 28 days after the last dose of rucaparib or the last Safety Follow-up Visit, whichever is later. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

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

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

9.7.4 Vital Sign Measurements

The on-treatment period will be defined as the time from the first dose of rucaparib to 28 days after the last dose of rucaparib or the last Safety Follow-up Visit, whichever is later. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

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

9.7.5 Other Safety Measurements

Body weight will be summarized descriptively (N, mean, StD, median, minimum, and maximum). 12-lead ECG findings and ECOG status will be summarized categorically.

9.8 Pharmacokinetic Analysis

Individual C_{min} of rucaparib and summary statistics by visit time (N, mean, StD, median, minimum, and maximum) will be reported. The PK data and selected safety and efficacy endpoints may be included in exploratory PPK and exposure-response analyses, with the results to be reported separately.

9.9 Exploratory Analysis

Primary and acquired resistance mutations to rucaparib have been identified in ctDNA from ovarian and prostate cancer patients. A key exploratory objective will evaluate if these resistance mutations (eg, reversion mutations that restore the wild-type function of HRR genes) have an impact on rucaparib clinical efficacy across tumor types.

HRD typically results from biallelic inactivation of an HRR gene, such as homozygous mutations or deletion. Therefore, another key exploratory objective will evaluate if patients with homozygous mutations in HRR genes derive greater rucaparib clinical efficacy.

9.10 Interim Analysis

This study is designed primarily to explore the safety and efficacy and safety of monotherapy rucaparib in patients who harbor certain HRR genes (Cohort A) with a variety of tumor types and who have received prior therapy for their disease. As such, the efficacy will be monitored separately within each tumor type. For Cohort A, a response rate of < 20% within a tumor type will be deemed insufficient for further investigation in this study. If enrollment in a tumor type reaches 11 patients and 0 responses (as assessed by the investigator per RECIST v1.1, or modified RECIST v1.1 for mCRPC patients) are observed, then the study may be amended to discontinue enrollment of patients with that tumor type. Rejection error for such a decision is 10%.[43]

10 STUDY ADMINISTRATION

10.1 Regulatory and Ethical Considerations

10.1.1 Good Clinical Practice

The study will be conducted in accordance with the protocol and applicable standard operating procedures (SOP); and in compliance with:

- ICH E6(R2)
- The Code of Federal Regulations (21 CFR Parts 11, 50, 54, 56, and 312)
- EU Directives 2001/20/EC, 2005/28/E
- All applicable local requirements, and in accordance with the ethical principles of the Declaration of Helsinki.

The investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB/IEC, and local health authority (where applicable), except where necessary to eliminate an immediate hazard(s) to the study participants.

Noncompliance with the protocol, SOPs, Good Clinical Practice (GCP), and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor staff or its representatives will lead to prompt action by the sponsor to secure compliance. If monitoring and/or auditing identifies serious noncompliance on the part of an investigator/institution, the sponsor will take steps to secure compliance or terminate the investigator's/institution’s participation in the study. When an investigator's/institution’s participation is terminated because of noncompliance, the sponsor will promptly notify the regulatory authority(ies).

All potential serious breaches of GCP must be reported to sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study site personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

10.1.2 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, when participating in a US Investigational New Drug Application [IND] study) and provide the completed form according to written instructions to the sponsor (or designee). In addition, local statement of investigator documents must be provided where required. Each investigator must submit to the sponsor (or designee) financial disclosure information if required by national law and/or local regulations.

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

10.1.3 Institutional Review Board or Independent Ethics Committee Approval

This protocol, the Investigator's Brochure, 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 IRB/IEC. 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 IRB/IEC. The investigator will submit the study protocol for review and approval by an IRB/IEC, according to national law and/or local regulations, and will provide the IRB/IEC with all appropriate materials.

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

No patient will be admitted to the study until appropriate IRB/IEC approval of the study protocol and ICF/patient information sheet (PIS) have been received, the investigator has obtained the patient's signed and dated ICF/PIS, and the eligibility criteria have been satisfied and confirmed.

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

The IRB/IEC must be informed by the 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, according to institutional policies.

10.2 Patient Information and Consent

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

It is the responsibility of the investigator to obtain signed ICFs from 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 IRB/IEC 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 IRB/IEC. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legally authorized representatives [where acceptable according to national law and/or local regulations], 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 who explains the study and ICF to the patient will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original will be filed in the investigator file unless otherwise agreed.

10.3 Patient Confidentiality

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only identification codes (ie, not names or, in some regions, initials) according to country regulations should be recorded on any form submitted to the sponsor and the IRB/IEC. The investigator must record all screened and enrolled patients in the eCRF. The investigator must have a list where the identity of all treated patients can be found, but not intended for use by the sponsor.

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

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 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.

10.4 Study Monitoring

On behalf of the sponsor, a contract research organization (CRO) or contract monitor will contact and visit the investigator at the study center prior to the entry of the first patient (unless the sponsor or the CRO has worked with the center recently in the same or comparable indication, the site location and facilities have not changed significantly, and the potential investigator/site are in good standing with respect to previous regulatory compliance, in which case this initial visit maybe waived) and at predetermined 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; however, the investigator retains ultimate responsibility for the quality and integrity of data generated by the site.

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. Representatives from the sponsor may also contact and visit the investigators and monitor data during the study.

10.5 Case Report Forms and Study Data

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

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

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

Prior to study start, the investigator will prepare a list showing the signature and handwritten initials of all individuals delegated responsibility on this study. This "study site personnel and delegation list" must be kept current throughout the study.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant EDC system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted in the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

Laboratory data and investigator observations on the results and any other clinically significant test results are to be documented and input into applicable eCRFs.

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

Clinical data will be entered directly from the source documents.

10.6 Study Termination and Site Closure

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

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

The entire study will be stopped if:

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

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

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

10.7 Modification of the Study Protocol

Protocol modifications (ie, amendments) must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol modifications and changes to the informed consent document. The IRB/IEC 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. Protocol deviations are described in Section 10.9.1.

10.8 Retention of Study Documents

The study site will maintain a study file, which should contain all documents defined in the ICH E6(R2) Guideline for Good Clinical Practice. The investigator should have control of all essential documents generated by the site. Source documents must be maintained and attributable, legible, contemporaneous, original or certified copy, accurate, and complete, consistent, enduring, and available (ALCOA+) documentation practices used. Any changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (via an audit trail). The investigator must implement procedures to ensure the integrity of any data generated.

The sponsor and investigator will maintain a record of the location(s) of their respective essential documents including source documents. The storage systems used during the study and for archiving (irrespective of media used) must provide for documentation identification, version, history, search, and retrieval. The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor or its designees.

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

No data should be destroyed without the agreement of the sponsor. Copies of original documents should fulfill the requirements for certified copies. Should the investigator wish to

assign the study records to another party or move them to another location, the sponsor must be notified in writing of the new responsible person and/or the new location. The sponsor will inform the investigator, in writing, when the study-related records are no longer needed.

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

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site; but at a minimum, for the period defined by the applicable regulatory requirements.

10.9 Quality Control and Assurance

The sponsor will implement and maintain quality control and quality assurance procedures with written 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. Patient protection and safety and the reliability of study results are major areas of focus for the procedures.

10.9.1 Protocol 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 nonevaluable. Any deviation must be documented in the source documents and reported to the sponsor.

10.9.2 Study Site Training and Ongoing Monitoring

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

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

10.9.3 Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by the sponsor. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate study conduct and compliance with the protocol, SOPs, ICH GCP, and the applicable regulatory requirements. 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 patients' medical records. It is important that the investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

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

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

Representatives of the FDA, European Medicines Agency (EMA), or other regulatory agencies, as well as IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify the sponsor immediately. The investigator will ensure that the auditors have 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.

10.10 Clinical Study Report

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

10.11 Publication and Disclosure Policy

All data generated from this study will be maintained by the sponsor. All data generated from this study, and all information furnished by the sponsor, the investigators, and other participating study groups shall be held in strict confidence. Independent analysis and/or publication of these data by the investigator(s) or any member of their staff are not permitted without the prior written consent of the sponsor. Any collaborative publications will be authored in accordance with the applicable guidelines (eg, International Committee of Medical Journal Editors [ICMJE]).[44] Written permission to the investigator will be contingent on the review of the statistical analysis and manuscript/abstract by the sponsor and participating cooperative groups, and will provide for nondisclosure of the confidential or proprietary information. In all cases, the parties agree to provide all manuscripts or abstracts to all other parties 60 days prior to submission. This will enable all parties to protect

proprietary information and to provide comments based on information that may not yet be available to other parties.

10.12 Investigator Oversight

The investigator has a responsibility for supervising any individual or party to whom they delegate study-related duties and functions conducted at the study site. This includes the services of any party or individual retained by the investigator for this purpose. All staff delegated study responsibilities must be documented on an approved Delegation of Authority log for the study and this filed with the essential documents. In addition, the investigator must ensure that delegated staff are qualified by training, experience and licensure (as applicable). The investigator should implement procedures to ensure integrity of the study-related duties, functions performed, and any data generated.

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12 APPENDICES

Appendix 1 HRR Genes Associated With PARPi Sensitivity

	Prostate Cancer			Ovarian Cancer		Breast Cancer		Pancreatic Cancer		*In Vitro* Data	
Gene Symbol	**Frequency of deleterious gene alterations observed in mCRPC (%)**	**Frequency of germline deleterious alterations in mCRPC (%)[c]**	**Clinical activity of PARPi associated with gene defect[g]**	**Ovarian cancer susceptibility gene[d]**	**Clinical activity of PARPi associated with gene defect[h]**	**Breast cancer susceptibility gene**	**Clinical activity of PARPi associated with gene defect[h]**	**Pancreatic cancer susceptibility gene**	**Clinical activity of PARPi associated with gene defect[h]**	**References demonstrating *in vitro* sensitivity to PARPi**	**Reference(s) demonstrating role in HRR**
Cohort A											
BRCA1	2.0[b]	0.9	Yes	Yes	Yes[e,f]	Yes	Yes	Yes	Yes	Farmer, Nature 2005. Lord, DNA Repair 2008	Moynahan, Mol Cell 1999
BRCA2	13.3[a]	5.3	Yes	Yes	Yes[e,f]	Yes	Yes	Yes	Yes	Bryant, Nature 2005. Farmer, Nature 2005. Lord, DNA Repair 2008	Xia, PNAS 2001
PALB2	2.0[b]	0.4	Yes	Yes	NS[e], NR[f]	Yes	NR	Yes	Yes	Buisson, Nat Struct Mol Biol 2010. Shen, CCR 2013	Buisson, Nat Struct Mol Biol 2010
RAD51C	0.7[a]	0.1	NR	Yes	Yes[e]	Yes	NR	No	NR	Min, Mol Cancer Ther 2013	Kurumizaka, PNAS 2001
RAD51D	0.4[c]	0.4	NR	Yes	Yes[e]	Yes	NR	No	NR	Loveday, Nat Genet 2011	Kurumizaka, J Biol Chem 2002

Cohort B											
BARD1	NR[a,b,c]	NS	NR	Yes	NS[e], NR[f]	Yes	NR	No	NR	Clovis internal data	Westermark, Mol Cell Biol 2003
BRIP1	0.7[a]	0.2	NR	Yes	Yes[e,f]	Yes	NR	No	NR		Litman, Cancer Cell 2005
FANCA	6.1[b]	NE	Yes	NE	NS[e], NR[f]	No	NR	No	NR	McCabe, Cancer Res 2006	Yang, Carcinogenesis 2005
NBN	2.0[b]	0.3	Yes	No	Yes[e]	Yes	NR	No	NR	McCabe, Cancer Res 2006	Tauchi, Nature 2002
RAD51	NR[a,b,c]	NE	No	NE	NS[e], NR[f]	No	NR	No	NR	McCabe, Cancer Res 2006. Lord, DNA Repair 2008. Shen, CCR 2013	Shinohara, Cell 1992
RAD51B	0.7[a]	NE	NR	NE	NS[e], NR[f]	No	NR	No	NR		Takata, Mol Cell Biol 2000

Abbreviations: ADP = adenosine diphosphate; CA-125 = cancer antigen-125; HRR = homologous recombination repair; mCRPC = metastatic castration-resistant prostate cancer; NR = not reported; NS = not seen (this gene was evaluated, but a deleterious mutation or associated clinical activity was not observed); NE = not evaluated; PARP = poly(ADP-ribose) polymerase; PARPi = PARP inhibitor; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Robinson, Cell 2015

[b] Mateo, N Engl J Med 2015

[c] Pritchard, N Engl J Med 2016

[d] Norquist, JAMA Oncol 2016

[e] Clovis ARIEL2 study data (unpublished)

[f] Lheureux, ASCO Annual Meeting 2016

[g] As reported in Mateo, N Engl J Med 2016; clinical activity is defined as a response by RECIST v1.1; a reduction in prostate-specific antigen (PSA) level of ≥ 50%; or a conversion in the circulating tumor-cell count from ≥ 5 per 7.5 ml of blood at baseline to < 5 per 7.5 ml during treatment, with a confirmatory assessment ≥ 4 weeks later.

[h] Clinical activity is defined as a response by RECIST v1.1 or a reduction in serum CA-125 level of ≥ 50%.

Appendix 2 Response Evaluation Criteria In Solid Tumors (RECIST)

The RECIST v1.1 guidelines are described in Eisenhauer et al 2009[45] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least 1 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 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 1 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). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Evaluation of Best Overall Response			
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 = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

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.

Confirmatory Measurement/Duration of Response

Confirmation

If an initial CR or PR is noted, confirmatory scans should be performed at least 4 weeks after response was first documented.

Duration of Overall Response

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

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

Duration of Stable Disease

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

Appendix 3 Modified Response Evaluation Criteria in Solid Tumors v1.1 and Prostate Cancer Working Group 3 Criteria

The RECIST v1.1 guidelines are described in Eisenhauer, et al 2009[45] and at http://www.eortc.be/Recist/Default.htm and PCWG3 criteria as described by Scher, et al 2016.[46]

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 slice 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

For the purposes of this study, bone metastatic lesions should be recorded at baseline and followed during treatment using PCWG3 criteria. Bone lesions should not be recorded as target or nontarget lesions according to RECIST v1.1 criteria.

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 10 lesions per organ (per PCWG3), 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 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 v 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

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a $\leq$ 5 mm contiguous reconstruction algorithm. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Ultrasound, endoscopy, and laparoscopy should not be used to measure tumor lesions.

Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions.

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 extra-skeletal lesions is also considered progression. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

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 extra-skeletal lesions and/or unequivocal progression of existing nontarget lesions. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

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 = not evaluable; PD = progressive disease; PR = partial response; SD = 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 = not evaluable; PD = progressive disease.

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

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

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

Duration of Response

CT scans are required for this study at screening and every 8 calendar weeks (within 7 days before or after is permitted) thereafter. Patients who have been on study at least 24 weeks, may decrease the frequency of disease/ tumor assessments to every 12 calendar weeks (within 7 days before or after 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), including progression in bone per PCWG3 criteria.

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.

PCWG3 Criteria for Assessment of Bone Disease

PCWG3 criteria will be used to document evidence of disease progression in bone lesions as described by Scher, et al 2016.[46]

Imaging of Baseline Bone Disease

The use of bone scan as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial.

Different modalities for imaging bone metastases can provide different information for the same patient. However, because of the lack of standards for reporting disease presence or changes after treatment, positron emission tomography imaging with sodium fluoride, fluorodeoxyglucose, choline, or prostate-specific membrane antigen, bone marrow MRI (body MRI), and other modalities that are in use to image bone, should be approached as new biomarkers subject to independent validation.

Criteria for progression in bone at study entry

- Two new lesions observed on 99mTc-methylene diphosphonate radionuclide bone scintigraphy;
- Confirm ambiguous results by other imaging modalities (eg, CT or MRI) however only positivity on the bone scan defines metastatic disease to bone.

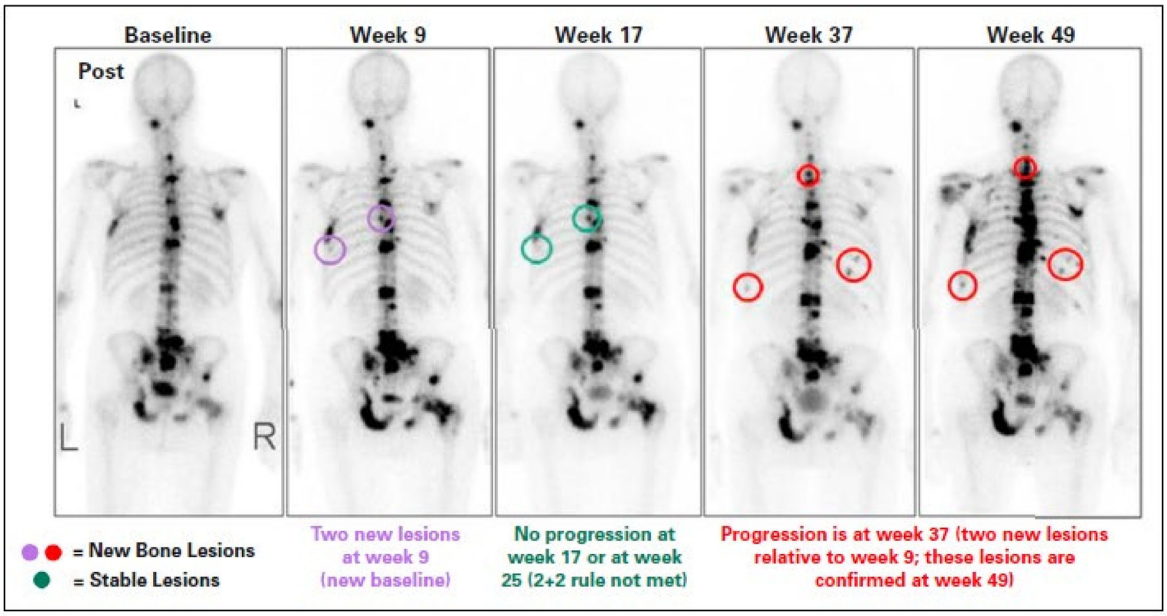
Documentation of baseline bone disease

- Presence or absence of metastasis recorded first
- A quantitative measure of disease burden, such as lesional number, the bone scan index, or lesion area, is required
- Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial.

Following for bone progression during the study

- Exclude pseudoprogression in the absence of symptoms or other signs of progression
- At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)
- If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented
- For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
- Date of progression is the date of the scan that first documents the second lesion
- Changes in intensity of uptake alone do not constitute either progression or regression

Appendix 3, Figure A: Controlling for Flare by Applying the 2+2 Rule using the First Post-treatment Scan as Baseline



PCWG3 Criteria For Confirmation of Radiographic Progression in Bone by Investigator Assessment (to be used in conjunction with modified RECIST v1.1 criteria for visceral and nodal disease)

Date Progression Detected (Visit)	**Criteria for Progression in Bone**	**Criteria for Confirmation of Progression in Bone**
Week 9 (1st on-treatment scan)	Two or more new lesions on bone scan compared to **baseline** bone scan by PCWG3	Two or more new bone lesions compared to Week 9 on bone scan obtained at least 6 weeks after progression identified (or at Week 17 assessment)
Week 17 (2nd on-treatment scan)	Two or more new lesions on bone scan compared to **Week 9** bone scan.	Persistent or increase in number of bone lesions compared to Week 17 assessment on bone scan obtained at least 6 weeks after progression identified (or at Week 25 assessment)
Week 25 and after (3rd on-treatment scan and after)	Two or more new lesions bone scan compared to **Week 9** bone scan	Persistent or increase in number of bone lesions compared to prior assessment on bone scan obtained at least 6 weeks after progression identified (or at next scheduled assessment)

Appendix 4 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	40	Disabled; requires special care and assistance	
	30	Severely disabled; hospital admission is indicated although death not imminent	4

may be progressing rapidly	20	Very sick; hospital admission necessary; active supportive treatment necessary	
	10	Moribund; fatal processes progressing rapidly	
	0	Dead	5

Appendix 5 Examples of Sensitive Clinical Cytochrome P450 (CYP) Substrates

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

Source: FDA Guidance on Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-mediated Drug Interactions, January 2020.[47] Refer to this website for an 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 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.