A Phase 2, Open-Label Study of Rucaparib in Patients with Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Protocol Number:	CO-338-017
Investigational Product:	Oral rucaparib (CO-338)
Eudra CT Number:	[redacted]
IND Number:	[redacted]
Development Phase:	Phase 2
Indication Studied:	Relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
Sponsor Name and Address:	Clovis Oncology, Inc. [redacted]
Responsible Medical Officer:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines ICH E6(R2). Essential study documents will be archived in accordance with applicable regulations.
[redacted]	[redacted]
Amendment 6 Date:	17 July 2019

CONFIDENTIALITY STATEMENT

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Protocol Approval Signature Page

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Date: 17 July 2019

Amendment: 6

[redacted]

Protocol Acceptance Form

Protocol: CO-338-017

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Date: 17 July 2019

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

Investigator's Signature Date

Name (printed)

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1 SYNOPSIS

Protocol Number	CO-338-017
Title	A Phase 2, Open-Label Study of Rucaparib in Patients with Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Study Phase	Phase 2
Introduction	Rucaparib is an orally available, small molecule inhibitor of poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) being developed for treatment of ovarian cancer associated with homologous recombination DNA repair deficiency. The safety and efficacy of rucaparib has been evaluated in Phase 1, Phase 2, and Phase 3 studies. Rucaparib (Rubraca®) is approved in the United States (US) as monotherapy treatment for 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 have a complete or partial response to platinum-based chemotherapy.[1] Rucaparib is also 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.[2] Normal cells repair single-strand breaks (SSBs) in DNA through base excision repair (BER). While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP-1 is the best characterized. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are repaired by homologous recombination repair (HRR) of DNA, a complex process involving multiple proteins, including those encoded by breast cancer susceptibility gene 1 and 2 (*BRCA1* and *BRCA2*), as well as RAD51, Fanconi anemia core complex, ataxia telangiectasia mutated (ATM), and ataxia telangiectasia and RAD3-related (ATR) protein, among others. HRR pathway defects, either as an initiating event or late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers. The Cancer Genome Atlas (TCGA), which completed an analysis of molecular changes associated with high-grade serous ovarian cancer (HGSOC), estimated that approximately 50% of patients with HGSOC have homologous recombination deficiency (HRD).[3] Germline mutations in the *BRCA1* and *BRCA2* genes (*gBRCA*) are the strongest known hereditary factors for epithelial ovarian cancer (EOC), accounting for up to 15% of all EOC.[4, 5] These patients carry heterozygous deleterious mutations in their germline DNA, and develop tumors when the remaining wild-type functional allele is inactivated (i.e., "second hit"). Approximately 6 – 8% of HGSOC patients have somatic mutations in *BRCA1* or *BRCA2* (*sBRCA*).[3, 6] HRD is not limited to mutations of *BRCA1*/2, however. Approximately 27% of HGSOC patients are estimated to

	have HRD due either to an alteration in a HRR gene other than *BRCA1/2* or due to other molecular alteration or modification (e.g., epigenetic silencing). Inhibition of DNA damage repair in cancer cells, which are intrinsically genetically unstable, represents an attractive opportunity for the development of new therapies. Given the overlap in various DNA repair pathways, inhibition of a single pathway is unlikely to have a significant effect. Inhibition of multiple pathways, such as BER with a PARP inhibitor, in the context of tumor with intrinsic HRD, may lead to cell death, a concept known as synthetic lethality. Normal cells, with only one DNA repair pathway affected by inhibition of PARP, still have an intact DNA repair pathway that can compensate. This concept of synthetic lethality has been demonstrated in key in vitro and in vivostudies, as well as in several clinical trials with PARP inhibitors.[7-12] While up to 15% of patients may have a hereditary form of ovarian cancer (based on germline mutations), the majority of cases are sporadic (based on somatic mutations).[3, 13-15] Both *gBRCA* and *sBRCA* mutations result in HRD, and patients whose tumors harbor these mutations derive clinical benefit from PARP inhibitor therapy.[16] Collectively, these mutations comprise a group known as tissue BRCA (tBRCA). Patients without evidence of a *gBRCA* or *sBRCA* mutation also derive benefit from PARP inhibitor treatment.[16, 17] The molecular signature associated with PARP inhibitor response in a non-BRCA setting is not yet fully understood, but may be linked to other mechanisms of HRD, termed non-BRCA HRD (nbHRD). This molecular signature, as well as s*BRCA* mutations, cannot be characterized by a blood-based diagnostic test. The purpose of this study is to define a tumor-based molecular signature of HRD in ovarian cancer that correlates with response to rucaparib and enables selection of appropriate ovarian cancer patients for treatment with rucaparib. Through a series of experiments and data analyses, the Sponsor has determined that measuring the extent of genomic scarring, a downstream consequence of HRD, is a potential method for identifying patients who may be sensitive to rucaparib. Genomic scarring can be assessed by quantifying the extent of loss of heterozygosity across the tumor genome (tumor genomic LOH). One of the main advantages of detecting tumor genomic LOH is that it can identify HRD tumors regardless of the underlying mechanisms, which include both known (i.e., *BRCA* mutations) and unknown genetic and other mechanisms. In this study, patients will be prospectively placed into 1 of 3 HRD subgroups prior to primary efficacy analysis. HRD subgroups include: tBRCA (HRD related to a deleterious *BRCA1* or *BRCA2* gene mutation in tumor tissue), nbHRD (no *BRCA1* or *BRCA2* mutation; LOH^+ - meets or exceeds a pre-specified tumor genomic LOH cutoff), or biomarker negative (no *BRCA1* or *BRCA2* mutation; LOH^- - tumor genomic LOH below the prespecifed cutoff). Additional sensitivity analyses will be performed to determine the optimal tumor genomic LOH cutoff to determine rucaparib sensitivity. Once the optimal response signature is defined, it will be prospectively applied in the final analysis of the planned Phase 3 pivotal study (CO-338-014), which will evaluate rucaparib as switch maintenance treatment following a response to platinum-based chemotherapy in a similar patient population. This Phase 2 study will also compare archival versus recently collected tumor tissue in order to validate the use of archival tumor tissue for assessment of HRD status in the planned Phase 3

	study.
Study Overview	This is a two-part study that will enroll patients with relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who have disease that can be biopsied and is measurable. Part 1 will enroll patients who received ≥1 prior platinum-based regimen and have platinum-sensitive disease. Part 2 will enroll patients who have received at least 3, but no more than 4, prior chemotherapy regimens. In Part 1, patients <55 years of age at diagnosis, or with prior history of breast cancer, or who have a close relative (first or second degree) with ovarian cancer or early onset (<age 50) breast cancer are required to have been previously tested for *gBRCA* mutation. Enrollment of patients known a priori to harbor a *gBRCA* mutation classified as deleterious (pathogenic), suspected deleterious, or favor deleterious (or the equivalent interpretation of any of these) on the most recent assessment by a testing laboratory will be limited to 15 in Part 1 in order to enrich for patients that have HRD associated with a defect other than germline *BRCA1/2*. Patients with a *tBRCA* mutation but no *gBRCA* mutation do not count toward this cap and will be eligible to receive treatment with rucaparib, provided all other eligibility criteria are met. In Part 2, at least 80 patients with a *tBRCA* mutation will be enrolled. All patients, with the exception of Part 2 patients known to harbor a deleterious *gBRCA* mutation, will be required to undergo a pre-dose biopsy for collection of tumor tissue. Archival tumor tissue will also be collected. *tBRCA* mutation and/or tumor genomic LOH analysis will be performed using Foundation Medicine's next generation sequencing (NGS) test. Analysis of tumor genomic LOH is expected to identify tumors with HRD regardless of the underlying mechanism(s). *tBRCA* mutation and/or the extent of tumor genomic LOH will be correlated with the clinical outcome with rucaparib. The NGS test also targets a large panel of other cancer-related genes and other HRR pathway genes. Results of the Foundation Medicine panel test will be provided to all patients who consent to receive this information. In the event a *BRCA1* or *BRCA2* mutation is identified in tumor tissue, the patient may be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline testing, this result will be entered in the clinical trial database for this study. Alterations detected in tumor tissue may be somatic or germline; however, the NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients at screening and stored. Prior to final efficacy analysis, genomic DNA may be subjected to exploratory analysis in order to determine whether the mutation is germline or somatic. These data will be generated in a research setting and will not be provided to the investigator or patient. The following correlative translational studies are planned: 1. Tumor genomic LOH and gene sequence alterations in archival and screening tumor tissue will be compared to assess the changes in a tumor's genomic LOH and genetic profile over time and determine if archival tumor tissue carries sufficient predictive utility and obviates the need for a contemporaneous biopsy. The frequency and nature of secondary *BRCA* mutations will also be assessed. Acquired secondary *BRCA* mutations (also

	known as reversions) may result in functional protein and restored HRR capability, leading to PARP inhibitor resistance.[18-20] 2. An alternative NGS test known as BROCA will be used to potentially identify mutations in other DNA repair genes that may confer sensitivity or resistance to rucaparib.[21] 3. Gene expression profiling on extracted RNA will be analyzed to potentially identify a signature associated with efficacy. A gene expression signature has been developed to identify BRCA and BRCA-like (also referred to as "BRCAness") tumors. Such a signature may predict response to platinum and PARP inhibitors.[22] 4. Immunohistochemistry (IHC) of non-homologous end joining (NHEJ) proteins will be investigated to assess whether NHEJ pathway integrity modulates efficacy. It has been hypothesized that cells with HRD must have functional NHEJ DNA repair in order to generate sufficient genomic instability for synthetic lethality with a PARP inhibitor.[23] 5. Circulating cell-free tumor DNA (ctDNA) will be analyzed as a potential molecular marker of efficacy. Tagged-amplicon deep sequencing (TAm-Seq) will be utilized to sequence ctDNA and identify mutations, including but not limited to, those in the tumor suppressor gene TP53, which is present in greater than 95% of high-grade serous ovarian tumors.[3, 24] Similar to CA-125, the fraction of TP53 mutant alleles in plasma of ovarian cancer patients has been shown to track with the clinical course of the disease.[24]
Number of Patients	**Part 1:** Approximately 180 patients will be enrolled. Patients known a priori to harbor a *gBRCA* mutation classified as deleterious (pathogenic), suspected deleterious, or favor deleterious (or the equivalent interpretation of any of these) on the most recent assessment by a testing laboratory will be limited to 15. Patients who do not harbor a known *gBRCA* mutation but are found to have a *tBRCA* mutation after their tumor tissue is analyzed by the Foundation Medicine NGS test are not subject to this cap and will be eligible to receive treatment with rucaparib. **Part 2:** Up to 300 patients will be enrolled, including at least 80 patients with a *tBRCA* mutation, as identified by the Foundation Medicine NGS test. Patients will enroll into either Part 1 or Part 2 of the study. Part 2 will begin once enrollment of Part 1 has been completed.
Number of Sites	This is a multicenter, multinational study. Patients will be enrolled from approximately 60 study sites.
Study Duration	Q4 2013 – Q4 2021 (estimated, LPLV)
Study Objectives	Unless otherwise specified, the objectives apply to both parts of the study. The primary objectives of this study are: • To determine progression-free survival (PFS) in patients with relapsed platinum-sensitive ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature (Part 1) • To estimate objective response rate (ORR) in heavily pre-treated patients with relapsed ovarian cancer classified into molecularly-defined

	subgroups by a prospectively defined HRD signature (Part 2) The secondary objectives of this study are: • To estimate ORR (Part 1) • To estimate ORR including cancer antigen 125 (CA-125) response criteria • To evaluate duration of response (DOR) • To determine PFS (Part 2) • To evaluate survival (Part 2) • To evaluate the safety and tolerability of rucaparib • To evaluate steady state trough level pharmacokinetics (PK) The exploratory objectives of this study are: • To assess efficacy in molecularly-defined HRD subgroups as defined by HRR gene alterations • To optimize the tumor LOH algorithm by testing additional signatures of interest based on higher or lower genomic LOH • To assess changes in HRD status over time • To assess whether the BROCA panel can identify mutations in additional HRR genes that may be associated with efficacy • To assess if a gene expression signature for HRD correlates with efficacy • To assess NHEJ pathway integrity and correlate it with efficacy • To assess ctDNA as a molecular marker of efficacy
Study Population	Unless otherwise specified, the criteria below apply to both parts of the study. **Inclusion Criteria** Eligible patients must meet the following inclusion criteria: 1. Have signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation 2. Be ≥ 18 years of age at the time the informed consent form is signed 3. Have a histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer – If mixed histology, > 50% of the primary tumor must be confirmed to be high-grade serous or endometrioid upon re-review by local pathology – Patients with a histology of other than serous or endometrioid are also eligible for Part 2 of the study if they are known to harbor a deleterious/ pathogenic *BRCA* mutation (germline or somatic) 4. Have relapsed/progressive disease as confirmed by radiologic assessment 5. **Part 1**: Received prior platinum-based therapy and have platinum-sensitive disease a. Received ≥1 prior platinum-based treatment regimen; AND

	b. Received a platinum-based regimen as their last treatment; continuous or switch maintenance treatment as part of this regimen is permitted (hormonal treatment may be permitted following the last platinum regimen with advance approval from the Sponsor); AND c. Was sensitive to the last platinum regimen. Platinum-sensitive disease is defined as documented radiologic progression ≥ 6 months after the last dose of platinum administered in the treatment setting. **Part 2**: Received at least 3, but no more than 4, prior chemotherapy regimens and had documented treatment-free interval of ≥ 6 months following 1st chemotherapy regimen received a. Hormonal agents (e.g., tamoxifen, letrozole, etc), anti-angiogenic agents (e.g., bevacizumab, pazopanib, cediranib, nintedanib, trebananib, etc), and other non-chemotherapy agents administered as single agent treatment will not be counted as a chemotherapy regimen for the purpose of determining patient eligibility b. Agents administered in the maintenance setting will not be counted as a separate regimen 6. **Part 1 only:** If < 55 years of age at diagnosis, or has prior history of breast cancer, or has close relative (first or second degree) with ovarian cancer or early onset (<age 50) breast cancer, must have been previously tested for *gBRCA* mutation; after 15 patients harboring the *gBRCA* mutation are enrolled, no additional patients with a known *gBRCA* mutation will be allowed to enroll. 7. Have undergone a biopsy of tumor tissue prior to first dose of study drug and had the tumor tissue confirmed by the central laboratory as being of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content). *Note: biopsy is optional for Part 2 patients known to harbor a deleterious gBRCA mutation* – If tumor tissue obtained from the biopsy is deemed inadequate, and the patient is unwilling or unable to have another biopsy, the patient may be considered for enrollment if archival tumor tissue is provided and deemed of adequate quality. This must occur prior to any treatment with rucaparib. a. Biopsy must be of solid tumor tissue; ascites is not acceptable b. Biopsy must be of sufficient yield for planned analyses 8. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue available for planned analyses; cytospin blocks from ascites are not acceptable – The most recently obtained tumor tissue that is of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content) should be submitted 9. Have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Appendix B) in addition to the lesion planned for biopsy; a single RECIST target lesion will suffice if, in the investigator's opinion, it is of sufficient size that the biopsy will not affect postdose RECIST evaluations. 10. Have adequate organ function confirmed by the following laboratory values

obtained within 14 days prior to the first dose of rucaparib:

a. Bone Marrow Function
   i. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L
   ii. Platelets > 100 × 10^9/L
   iii. Hemoglobin ≥ 9 g/dL

b. Hepatic Function
   i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, then ≤ 5 × ULN
   ii. Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubemia is due to Gilbert's syndrome
   iii. Serum albumin ≥ 30 g/L (3.0 g/dL) (Part 2 only)

c. Renal Function
   i. Serum creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft Gault formula

11. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Appendix C)

Exclusion Criteria

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

1. Active second malignancy, i.e., patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment
   a. Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant (BMT) > 2 years prior to first dose of rucaparib
2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib are eligible.
3. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
4. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib
5. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C
6. Pregnant or breast feeding. Women of childbearing potential must have a negative serum pregnancy test < 3 days prior to first dose of rucaparib.
7. Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of rucaparib and/or ongoing adverse effects from such treatment > National Cancer Institute (NCI)

	Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 (ongoing Grade 2 non-hematologic toxicity related to most recent treatment regimen may be permitted with prior advanced approval from sponsor) 8. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of rucaparib or have on-going requirements for these medications 9. Non-study related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of rucaparib; in all cases, the patient must be sufficiently recovered and stable before treatment administration 10. 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 11. Diagnosis of low-grade serous or Grade 1 endometrioid ovarian cancer **Part 2 Only** 12. Hospitalization for bowel obstruction within 3 months prior to enrollment Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Patients of childbearing potential and their male partners must practice a highly effective method of contraception during treatment and for 6 months following the last rucaparib dose. No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolled into the study.
Study Treatment	Patients will take 600 mg rucaparib orally twice daily (BID; as close to 12 hours apart as possible, preferably at the same times every day) with at least 8 oz (240 mL) of water starting on Day 1. Rucaparib may be taken with an empty stomach or with food. Rucaparib will be provided as 200 and 300 mg [as free base] 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 are permitted in the event of unacceptable toxicity.
Interim Safety Monitoring	A formal safety data review will occur after the first 20 patients have been enrolled, then quarterly until Part 1 of the study is fully enrolled, and then every 6 months thereafter until all patients are enrolled and have participated in the study for at least 6 months or have discontinued prior to 6 months, at which point safety reviews will occur on an as-needed basis. The review committee will include external experts and Sponsor personnel. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review. In the event that the recommended Phase 2 dose of 600 mg BID rucaparib is determined to be unsuitable for chronic dosing, the starting dose may be decreased to Dose Level -1 (480 mg / 500 mg BID rucaparib) for all subsequent patients if agreed upon between the Sponsor and the Principal Investigators.

<table>
<tr><td>Withdrawal Criteria</td><td>A patient must be discontinued from protocol-prescribed therapy if <u>any</u> of the following apply:
Consent withdrawal at the patient's own request or at the request of their legally authorized representative
Progression of patient's underlying cancer
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
A positive pregnancy test at any time during the study</td></tr>
<tr><td>Disease Assessments for Efficacy</td><td>Efficacy measures may include tumor assessments using computed tomography (CT) scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST, CA-125 measurement, and clinical examination; other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. As of implementation of Protocol Amendment 6, disease assessments should be performed according to local standard of care per Investigator during and at the end of treatment.</td></tr>
<tr><td>Statistical Procedures</td><td>Currently, there are few clinical studies that have prospectively evaluated response to treatment beyond the 3rd-line setting; however, retrospective analysis of patients in 3rd relapse and beyond indicate they have a short PFS (approximately 4-6 months) and OS (approximately 5-6 months).[25] Overall, there is a need for new treatments and alternatives to chemotherapy for heavily pre-treated ovarian cancer patients with advanced, relapsed disease to be explored in prospectively designed trials.
The table below provides 95% CIs for observed response rates ranging from 10 to 60% assuming a total of 80 patients within each HRD subgroup.
Confidence Intervals for Objective Response Rates (ORR)<table><tr><th>ORR(%)</th><th>[95% CI]</th></tr><tr><td>10</td><td>4.4, 18.8</td></tr><tr><td>20</td><td>11.8, 30.4</td></tr><tr><td>30</td><td>20.3,41.3</td></tr><tr><td>40</td><td>29.2,51.6</td></tr><tr><td>50</td><td>38.6, 61.4</td></tr><tr><td>60</td><td>48.4, 70.8</td></tr></table>CI=Confidence intervals of ORR using Clopper-Pearson methodology.[26]
An ORR ≥ 20% in any subgroup would be worthy of further exploration in that population.
Efficacy Analyses
Kaplan-Meier methodology will be used to summarize time to event variables. Response will be determined using RECIST Version 1.1 and Gynecologic Cancer InterGroup (GCIG) CA-125 criteria. The overall response rate will be summarized with frequencies and percentages. The duration of response will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically. The efficacy analyses will be</td></tr>
</table>

	evaluated for all patients treated in the study as well as for each of the HRD subgroups. **Safety Analyses** Adverse events (AEs), clinical laboratory results, vital signs, ECOG performance status, body weight, and concomitant medications/procedures will be tabulated and summarized. AEs will be summarized overall and separately for serious AEs, AEs leading to discontinuation, AEs leading to death, and NCI CTCAE Version 4.0 Grade 3 or higher AEs. Body weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG will be summarized categorically.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAG	alpha-1 acid glycoprotein
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under the curve
BER	base excision repair
BID	twice a day
BMT	bone marrow transplant
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
$BRCA^{mut}$	*BRCA1* and/or *BRCA2* gene(s) harboring a deleterious mutation
$BRCA^{unk}$	*BRCA1* and *BRCA2* genes with unknown mutation status
$BRCA^{wt}$	wild-type *BRCA1* and *BRCA2* gene sequences
BUN	blood urea nitrogen
CA-125	cancer antigen 125
ctDNA	circulating cell-free tumor DNA
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatinine kinase
C_{max}	maximum concentration
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (version 4.0)
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double-strand break
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOC	epithelial ovarian cancer

EOS	end of study
EOT	end of treatment
FFPE	formalin-fixed paraffin-embedded
FSH	follicle stimulating hormone
FTC	fallopian tube cancer
GALT	gut-associated-lymphoid tissue
gBRCA	germline *BRCA*
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GS	genomic scarring
h	hour
H & E	hematoxylin and eosin
HDL	high-density lipoprotein
hERG	human ether-a-go-go-related gene
HGSOC	high-grade serous ovarian cancer
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRR	homologous recombination repair
HRD	homologous recombination deficiency
HNSTD	highest non-severely toxic dose
IC_{xx}	concentration where maximum response is inhibited by XX%
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	international normalized ratio
IRB	Institutional Review Board
irr	independent radiology review
irrORR	objective response rate assessed by independent radiology review
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LDL	low-density lipoprotein
LOH	loss of heterozygosity
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	minute
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
nbHRD	non-BRCA homologous recombination deficiency
NCCN-FACT	National Comprehensive Cancer Network-Functional Assessment of Cancer
NCI	National Cancer Institute
NGS	next generation sequencing

NHEJ	non-homologous end-joining
NOAEL	no-observed-adverse-effect level
ORR	objective response rate
OS	overall survival
PARP	poly(adenosine diphosphate [ADP]-ribose) polymerase
PBL	peripheral blood lymphocytes
PD	progressive disease
PET	positron emission tomography
PLD	PEGylated liposomal doxorubicin
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPC	primary peritoneal cancer
PR	partial response
PT	prothrombin time
QD	once a day
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SD	stable disease and standard deviation
SI	international units
SNP	single-nucleotide polymorphism
SOA	schedule of assessments
SOC	system organ class
SSB	single-strand break
STD	severely toxic dose
SUSAR	suspected unexpected serious adverse reaction
TAm-Seq	tagged-amplicon deep sequencing
$t_{1/2}$	half-life
tBRCA	tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TMZ	temozolomide
TP53	tumor protein p53
ULN	upper limit of normal
UV	ultraviolet
WBC	white blood cell
WOCBP	women of childbearing potential
wt	wild-type

3 INTRODUCTION

3.1 Ovarian Cancer

3.1.1 General Overview

Ovarian cancer is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer.[27, 28] After initial therapy, most women will have a progression-free interval of approximately 1.5 to 2 years, depending on the extent of post-operative residual disease and response to chemotherapy.[29] Relapse still occurs, however, in the majority of cases, and only 10–30% of women experience long-term survival.[29] Advanced stage disease is associated with a 5-year survival rate of only 30–40%.[27]

Approximately 90% of ovarian tumors are surface epithelial in origin, and the papillary serous histology subtype accounts for approximately 75%, of which the large majority (70%) is high-grade.[29] The site of origin of epithelial ovarian cancer remains unclear. Some studies suggest that serous epithelial ovarian cancer (EOC) and primary peritoneal cancer (PPC) arise from the fallopian tube epithelium; however, other studies suggest an origin within stem cells of the ovarian surface epithelium.[29-33] EOC, PPC and fallopian tube cancer behave very similarly and are therefore treated in the same way.

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

3.1.2 Treatment of Ovarian Cancer

The standard approach to treatment of advanced high-grade serous ovarian cancer (HGSOC) is cytoreductive surgery (either at time of diagnosis or interval debulking), with the goal of minimizing residual tumor to no visible residual disease, a major prognostic indicator for improved survival. Six to eight cycles of platinum- and taxane-based chemotherapy is the global standard of care. If initial cytoreduction is not performed, interval debulking surgery is considered. This surgery may be carried out after three or four cycles of primary chemotherapy, followed by three further cycles of chemotherapy. Platinum analogues, such as carboplatin and cisplatin, are the most active agents, mediating their effects through the formation of inter- and intra-strand cross-links with deoxyribonucleic acid (DNA).[29, 34]

The choice of treatment for relapsed disease is based on the treatment-free interval relative to last therapy administered and chemotherapy agents used. Platinum-based regimens dominate ovarian cancer therapy and define treatment groups.[35] In general, patients whose disease progresses during treatment with a platinum-based regimen are considered to have platinum-refractory disease; patients whose disease relapses within 6 months after the last platinum agent was administered are considered to have platinum-resistant disease; and patients whose disease relapses more than 6 months after last platinum-based therapy was administered are considered to have platinum-sensitive disease. However, these classifications are somewhat arbitrary as resistance to platinum-based therapy is a time continuum, not a categorical variable, and a status of ‘platinum-resistant’ is not absolute as it can be partially overcome. In addition, ‘platinum-sensitivity’ was defined when there was no alternative to platinum-based treatment and in

clinical practice typically only refers to second-line treatment. These definitions also do not take into account the molecular characteristics of a patient's tumor (i.e. HRD such as BRCA mutations). In later lines of therapy, treatment choice is often restricted according to the individual patient situation (e.g., performance status, organ function, residual toxicities from prior treatment, other comorbidities, and patient choice).

As many patients experience multiple relapses, prognosis and response to therapy decreases as the interval between last chemotherapy exposure and disease relapse shortens. The treatment-free, or specifically the platinum-free interval, provides further prognostic information for patients, as therapeutic options lessen and survival shortens as a patient's tumor becomes less responsive to platinum-based therapy. Patients who have received several prior lines of treatment are known to have strongly diminished treatment-free intervals and response rates and the benefits of continued treatment with conventional chemotherapy often does not outweigh the risk of additional toxicity. This patient population is a group with limited treatment options that could benefit from treatment with a targeted agent that takes the molecular characteristics of their disease into account.[25, 36]

3.1.3 Role of BRCA and HRD in Ovarian Cancer

DNA is constantly damaged by both endogenous and exogenous (environmental) assaults. A common type of DNA damage is the formation of DNA single-strand breaks (SSBs). During normal cell cycling, DNA is replicated and replication forks are eventually stalled by persistent SSBs. If stalled replication forks are not rapidly repaired, they can often degenerate and form DNA double-strand breaks (DSBs), which are highly likely to be lethal to the cell.

Single-strand breaks are normally quickly repaired by a process known as base excision repair (BER). The BER process is initiated by the activity of the poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzyme. In normal cells, an additional DNA repair process known as homologous recombination repair (HRR) can repair DSBs. Homologous recombination is a complex, multistep process, in which two key components are the proteins encoded by the breast cancer susceptibility 1 and 2 genes (*BRCA1* and *BRCA2*).

Germline mutations in *BRCA1* and *BRCA2* genes are the strongest known hereditary factors for breast and EOC, accounting for up to 5% of all breast cancers and 15% of all EOCs.[4, 5] These patients carry heterozygous deleterious mutations in their germline DNA, and develop tumors when the remaining wild-type functional allele is inactivated (i.e., "second hit"). Approximately 6 – 8% of patients with HGSOC have somatic mutations in *BRCA1* or *BRCA2*.[3, 6]

If either the BER or HRR pathway is rendered non-functional, the remaining functional pathway can compensate to ensure ongoing DNA repair and cell cycling. For example, when the BRCA-associated HRR pathway is lost or dysfunctional, repair shifts towards the BER repair pathway that is dependent on PARP enzymes. In contrast, in the setting in which both repair pathways (BER and HRR) are rendered non-functional, the cell dies. This concept, where a defect in either of two pathways can be withstood by a cell, but defects in both are lethal, is referred to as synthetic lethality. This type of lethality can arise from a variety of different interactions. In the case of DNA damage repair, this state of dual non-functionality can be

achieved by enzymatic inhibition of PARP in the context of a genetic mutation in the *BRCA1* or *BRCA2* genes.

Two key in vitro and in vivo studies demonstrated the concept of synthetic lethality in DNA repair. Bryant and colleagues showed that cell lines and a tumor xenograft deficient in *BRCA2* were highly sensitive to PARP inhibition.[7] In a parallel set of experiments, Farmer and colleagues illustrated that chemical inhibition of PARP-1 was more potent in homozygous *BRCA1/2*-deficient cell lines than in heterozygous mutant or wild-type cell lines.[8] These findings were also supported by a *BRCA2*-deficient murine model. Taken together, these studies provide support for the treatment of patients with a *BRCA*-deficient tumor with a PARP inhibitor.

However, defects in the HRR pathway are not limited solely to mutations of *BRCA1*/2. Genetic alterations of many different HRR pathway genes are associated with human cancers, with the percentage of tumors affected by homologous recombination deficiency (HRD) varying considerably across different tumor types. The Cancer Genome Atlas (TCGA), which completed an analysis of molecular changes in HGSOC, estimated that approximately 50% of patients with HGSOC have alterations in genes involved in the HRR DNA repair.[3] Of those, approximately 27% are estimated to have HRD due to a gene mutation or other genomic alteration or modification (e.g., epigenetic silencing) that is not associated with a *BRCA1/2* mutation.[3] Approximately 15% of patients are estimated to have a gene mutation in a HRR pathway gene other than *BRCA1/2*.[3]

An alternative approach in identifying non-*BRCA* patients with HRD is to detect genomic scars within the tumor, which arise from the use of error-prone DNA repair pathways when HRR is compromised.[37, 38] Through a series of experiments and data analyses, the Sponsor has determined that a potential method for identifying patients who may be sensitive to rucaparib is to assess genomic scarring by quantifying the extent of loss of heterozygosity across the tumor genome (tumor genomic LOH). One of the main advantages of detecting tumor genomic LOH is that it can identify HRD tumors regardless of the underlying mechanisms, which include both known (i.e., *BRCA* mutations) and unknown genomic mechanisms.[39, 40]

3.2 PARP Inhibitors

Refer to the current Investigator's Brochure for comprehensive information on rucaparib.

PARP inhibitors have been evaluated in the clinic for the past decade. Iniparib (BSI-201) was initially the furthest advanced, with a Phase 3 randomized study in combination with gemcitabine and carboplatin conducted in patients with triple-negative metastatic breast cancer. Data from this study showed that patients receiving iniparib with chemotherapy did not experience significant improvements in overall survival (OS) or progression free survival (PFS) compared to patients receiving just the chemotherapy regimen.[41] Since then, several groups have determined that the primary mechanism of action for iniparib is not via inhibition of PARP activity.[42, 43]

Rucaparib has demonstrated compelling activity in ovarian cancer patients with a *BRCA* mutation as well as in patients without a *BRCA* mutation (see Section 3.3). Durable responses have been observed in both platinum-sensitive and platinum-resistant disease.

Olaparib (AZD-2281), another PARP inhibitor, has also demonstrated Phase 2 clinical activity, both in treatment and maintenance settings, in metastatic breast cancer patients with a germline *BRCA* (*gBRCA)* mutation and in relapsed HGSOC patients (both *BRCA* mutant and wild-type). The concept of synthetic lethality was exploited in two proof-of-concept clinical studies with olaparib in patients with *BRCA*-associated tumor types. These studies evaluated the efficacy and safety of continuous oral dosing with olaparib in women with either relapsed ovarian cancer or advanced breast cancer and included women with and without a *gBRCA* mutation.[10, 11] In these patients, who had received a median of three prior chemotherapy regimens, encouraging overall response rates of 33% and 41%, were observed, in ovarian and breast cancer, respectively. In a third study, olaparib treatment was associated with a greater overall response rate (ORR) in patients with *gBRCA*-associated ovarian cancer compared with the patients in the non-*BRCA* associated cohort (41% vs 24%, respectively).[12] In a fourth study that evaluated olaparib versus PEGylated liposomal doxorubicin (PLD) in patients with a *gBRCA* mutation and relapsed ovarian cancer, the efficacy of olaparib was consistent with that observed in previous studies.[44] More recently, olaparib demonstrated good clinical activity (31% ORR) in *gBRCA*^{mut} ovarian cancer patients (n=193) with platinum-resistant disease who received a mean of 4.3 prior treatment regimens.[45]

Activity in HGSOC has also been observed with switch maintenance therapy following response to platinum-based chemotherapy.[46] Patients with platinum-sensitive relapsed ovarian cancer who achieved a response to another regimen of platinum-based chemotherapy followed by olaparib as switch maintenance treatment experienced a statistically significant improvement in median PFS (8.3 months) compared to patients who received placebo as maintenance therapy (4.8 months); hazard ratio of 0.35 (95% CI, 0.25 – 0.49).[46] Patients with a *BRCA* mutation derived the most benefit (median PFS 11.2 vs 4.3 months; HR, 0.18; 95% CI 0.11-0.31; $P<0.00001$).[16] It should be noted that outcomes were the same in patients who had a *gBRCA* mutation and those who had a somatic *BRCA* (*sBRCA*) mutation, suggesting that it is appropriate to not differentiate between germline and somatic mutations. Patients without a *BRCA* mutation also experienced significant benefit from treatment with olaparib (HR=0.53; 95% CI 0.33-0.84; $P=0.007$).[16]

Niraparib (MK-4827), another PARP inhibitor with a similar mechanism of action to olaparib, exhibited clinical activity in both *BRCA*-mutated ovarian cancer (8 RECIST PRs) and sporadic ovarian cancer (2 RECIST PRs and/or GCIG CA-125 responses) patients in a Phase 1 study.[47, 48] In a Phase 1 evaluation of BMN 673, also a PARP inhibitor, 11 of 17 *BRCA*-mutated ovarian cancer patients treated at doses ≥100 µg/day exhibited a RECIST and/or CA-125 response.[49]

It is worth noting that PARP inhibitor monotherapy has elicited objective responses in patients with platinum-sensitive disease as well as in patients with platinum-resistant disease, although response rates are higher in the former population.[12, 44, 48] This indicates that using platinum-sensitivity alone as a selection marker for PARP inhibitor therapy is not an effective tool.

These data support the potential role for the PARP inhibitor rucaparib in the treatment of patients with *BRCA*-associated ovarian cancer. Furthermore, the 24% ORR in the non-BRCA cohort described above and the benefit of maintenance PARP inhibitor treatment in patients without a *BRCA* mutation suggest that the clinical utility of PARP inhibitors can be extended to a larger patient group with HRD based on HRR alterations other than *BRCA*, i.e., nbHRD.[12, 16]

Assessing tumor genomic LOH in this trial provides a mechanism to identify patients with HRR alterations who may benefit from treatment with rucaparib but do not harbor a deleterious *BRCA1* or *BRCA2* mutation.

Emerging data with PARP inhibitors also support evaluation of rucaparib in relapsed ovarian cancer patients with advanced disease who have received multiple prior lines of treatment, a patient population for whom there are limited treatment options currently.

3.3 Rucaparib

Rucaparib (CO-338; formerly known as PF-01367338 and AG-014447) is an orally available, small molecule inhibitor of PARP-1 and PARP-2. Rucaparib is specific for PARP-1 and PARP-2 based on results of direct biochemical assays and an off-target receptor panel. Rucaparib (Rubraca®) is approved in the United States (US) as monotherapy treatment for 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 have a complete or partial response to platinum-based chemotherapy.[1] Rucaparib is also 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.[2]

Nonclinical evaluation has demonstrated exquisite sensitivity of *BRCA1* and *BRCA2* homozygous mutant cell lines to rucaparib and provides a rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary deficiencies of *BRCA1* and/or *BRCA2*. Rucaparib has also shown antitumor activity as a single agent in the MDA-MB-436 (*BRCA1* mutant) xenograft mouse model.

Comprehensive nonclinical and clinical information for rucaparib is available in the current Investigator's Brochure.

3.3.1 Nonclinical Experience

3.3.1.1 Rucaparib Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetics (PK) and toxicokinetics of rucaparib camsylate following oral administration, the intended route of administration in humans, was evaluated in the mouse, rat, and dog. The time at which the peak plasma concentrations were observed (T_{max}) occurred at 1–3 hours post dose in the mouse and dog, with the rat generally exhibiting a later T_{max} (4–8 hours). The oral bioavailability was 17%, 36%, and 62%, respectively, in the mouse (50 mg/kg), rat (100 mg/kg), and dog (20 mg/kg). In the rat and dog, there were no marked gender-related differences and no accumulation after repeat oral administration. A less than dose-proportional increase in exposure was observed in the rat and dog when rucaparib was administered as a suspension in 0.5% methylcellulose; however, a greater than dose-proportional increase in

exposure was observed in the 1-month dog toxicity study when rucaparib was administered in capsules.

Rucaparib PK, following IV administration of salts of rucaparib, were evaluated in mice, rats, dogs, and monkeys. IV dosing with the glucuronate or phosphate salt of rucaparib resulted in moderate to rapid clearance and a large volume of distribution, indicating this compound is well distributed in the body. The half-life ($t_{1/2}$) ranged from 2.3 to 5.2 hours.

In vitro plasma protein binding studies in mouse, rat, and dog plasma showed moderate binding and ranged from 49.5% to 73%. Plasma protein binding in humans ranged from 55% to 75%.

In in vitro studies, rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, CYP3A, CYP2C8, and CYP2D6 (in the order of decreasing potency), as well as moderately inhibited uridine-diphosphate glucuronosyletransferase (UGT) 1A1. In hepatocyte incubation, rucaparib showed concentration-dependent induction of CYP1A2 and down regulation of CYP3A4 and CYP2B6 at clinically relevant concentrations. No time-dependent CYP inhibition was observed.

Based on in vitro CYP interaction data, the drug-drug interaction (DDI) potential of rucaparib as a CYP inhibitor and/ or inducer was assessed by calculating the ratio of AUC (AUCR) of CYP substrate drugs in the presence and absence of rucaparib at target clinical exposures (600 mg BID) using the mechanistic static modeling.[50, 51] AUCR allows a conservative estimation of the magnitude of DDIs. Based on this analysis, the DDI potential for rucaparib was estimated to be moderate (AUCR 2 to 5) for CYP3A (AUCR=5.0), CYP1A2 (AUCR=2.9), CYP2C8 (AUCR=2.6), and CYP2D6 (AUCR=2.3); but appeared to be strong (AUCR > 5) for CYP2C19 (AUCR=11) and CYP2C9 (AUCR=5.2). Clinical implication of CYP3A downregulation was unknown and thus not considered in the modeling. However, the downregulation could further increase AUCR for CYP3A and result in elevated exposures of drugs that are CYP3A substrates.

Based on bi-directional experiments of digoxin transport carried out using Caco-2 cells, it was determined that rucaparib is a moderate P-glycoprotein (P-gp) inhibitor. The inhibition potential for rucaparib on P-gp will likely be low at clinical oral doses ≤200 mg. At doses >200 mg, patients taking digoxin should have their digoxin levels monitored regularly via standard clinical practice.

Quantitative whole body autoradiography studies in Long-Evans rats showed [^{14}C] rucaparib radioequivalents were rapidly and widely distributed to tissues following IV administration, consistent with a large volume of distribution. At 2 minutes after dosing, highest concentrations were found in kidney, lung, thyroid gland, heart, stomach mucosa, liver adrenal glands, spleen, and blood. Little radioactivity was present in brain; levels were undetectable at 15 minutes after dosing. Activity was undetectable in most tissues by 96 hours after dosing, however levels in the choroid/retina declined more slowly, and persistent radioactivity was also found in hair follicles through 192 hours, indicating that drug equivalents have high affinity and long half-life in pigmented tissues. High levels of radioactivity were observed in ureters, bladder, and bile ducts, indicating both renal and biliary routes eliminated drug equivalents.

3.3.1.2 Multiple-Dose Toxicity Studies

Rucaparib was evaluated in both rat and dog in oral and IV infusion toxicity studies. Only the multiple-dose toxicity studies utilizing the oral formulation are summarized below. Details of these studies are provided in the Investigator's Brochure.

Target organs identified in studies where rucaparib was administered orally include the hematopoietic system and gastrointestinal tract. No cardiovascular findings were noted in any of the oral toxicity studies.

Multiple-Dose Oral Toxicity Studies in Rats

Administration of rucaparib camsylate salt via oral gavage was generally well-tolerated in the rat up to 1000 mg/kg/day for 7 days and up to 150 mg/kg/day for 28 days. Decreases in body weight gain and food consumption were noted in both studies. In the 7-day study, target organs identified microscopically were bone marrow, spleen, and thymus. Minimal to mild bone marrow hypocellularity was noted in all dose groups. The no-observed-adverse-effect-level (NOAEL) was established at 500 mg/kg/day.

In the 28-day study, there were 3 rucaparib-related deaths at 500 mg/kg/day immediately after blood collection on Day 28 (n=1) or Day 29 (n=2; first day of recovery phase). These deaths likely resulted from the marked anemia identified hematologically. Other rucaparib-related clinical signs at 500 mg/kg/day included thinning haircoat and pale eyes. Identified target organs included bone marrow, spleen, lymphoid tissue (thymus, gut-associated-lymphoid tissue [GALT], and lymph nodes), and cecum (at 500 mg/kg/day only). Following cessation of rucaparib dosing, most findings reversed. In this study, the severely toxic dose in 10% of the animals (STD10) was 500 mg/kg/day and the NOAEL was 50 mg/kg/day.

Rucaparib camsylate in capsules was also given orally to rats at doses of 10, 40, and 100 mg/kg/day for 91 consecutive days with a 28-day recovery period. Decreased body weight and body weight gain were observed for animals given ≥40 mg/kg/day. At the end of the recovery phase, mean body weight was still lower for males given 100 mg/kg/day and females given ≥40 mg/kg/day. Hematological findings included decreases in red blood cell mass parameters in animals given ≥40 mg/kg/day (which correlated with decreased bone marrow hypocellularity), and decreases in reticulocytes, white blood cells (WBC) and absolute lymphocytes at ≥40 mg/kg/day. The latter changes correlated with the microscopic findings of decreased lymphocytes in the mandibular lymph nodes and gut-associated lymphoid tissue. All effects were reversible. Microscopically, bone marrow hypocellularity at 100 mg/kg/day and minimally decreased lymphocytes in lymphoid tissues at ≥40 mg/kg/day were noted and were completely reversed at the end of the recovery period. The NOAEL was established to be 100 mg/kg/day.

Multiple-Dose Oral Toxicity Studies in Dogs

Oral gavage administration of the camsylate salt form of rucaparib to dogs for 7 days resulted in gastrointestinal clinical signs at the 80 mg/kg/day high-dose group. Hematopoietic effects of decreased reticulocytes were noted in mid- to high-dose groups and leukopenia was exhibited in

all treatment groups. Lymphoid atrophy occurred in both sexes and in all treatment groups. Decreased bone marrow cellularity was seen in both sexes (males at all doses; females at 80 mg/kg/day). A 7-day repeat-dose toxicity study using oral capsules in dogs was repeated in order to characterize the toxicity of a new lot of rucaparib camsylate. Similar to the results of the prior 7-day study in dog, gastrointestinal clinical findings were noted at 80 mg/kg/day. Vomiting was observed throughout the dosing phase for males as well as liquid and/or mucoid feces in both genders. Decreased food consumption was observed at 80 mg/kg/day that correlated with body weight loss that was considered adverse. Decreases in erythroid, platelet, and leukocyte parameters were observed primarily at 80 mg/kg/day and occasionally at 20 or 5 mg/kg/day. These data indicated that the drug targeted multiple bone marrow lineages in a dose-related pattern.

Rucaparib camsylate salt in capsules was administered orally to dogs for 30 consecutive days with a 29-day recovery. Gastrointestinal clinical signs were noted at ≥ 5 mg/kg/day, with decrease in food consumption at 75 mg/kg/day. Adverse hematological changes (decrease in erythroid, myeloid, and megokaryocytic lineages) occurred at ≥ 20 mg/kg/day. Effects were fully reversible. The NOAEL in this study was 5 mg/kg/day.

Rucaparib camsylate in capsules was also given orally to dogs at doses of 3, 15/10, 40/30/20 mg/kg/day for 91 consecutive days with a 29-day recovery period. Body weight losses and inappetance observed at the high dose in both sexes during the first quarter of the dosing phase were considered adverse and resulted in dose reductions (40 to 30 to 20 mg/kg/day for toxicity and 15 to 10 mg/kg day in order to maintain multiples of exposures for optimal testing of dose response) for the remainder of the study. Clinical pathology findings were indicative of bone marrow toxicity; these changes were nonprogressive over time suggesting potential adaptation to these initial effects. Hematological findings at 40/30/20 mg/kg/day correlated with erythroid atrophy of the bone marrow detected microscopically. By Day 29 of recovery, most effects reversed. The highest non-severely toxic dose (HNSTD) for this study was 20 mg/kg/day for male dogs. No HNSTD was established for female dogs. The NOAEL was 10 and 20 mg/kg/day for male and female dogs, respectively.

3.3.1.3 Additional Observations

In vitro genetic toxicology assays demonstrated oral rucaparib to be clastogenic. Bacterial mutagenicity data for rucaparib were clearly negative in four microbial tester strains, both with and without metabolic activation, and equivocal in a fifth tester strain.

In an in vitro assay for human ether-a-go-go-related gene (hERG) activity, the IC_{50} and IC_{20} for the inhibitory effects of rucaparib (50% inhibitory concentration and 20% inhibitory concentration) on hERG potassium currents were 24 µM (7761 ng/mL) and 7 µM (2264 ng/mL), respectively. These values are 7-fold and 2-fold higher, respectively, than the highest (unbound) steady state plasma concentrations observed to date in humans (3710 ng/mL x 0.298 F_u = 1106 ng/mL) at a dose of 600 mg BID rucaparib administered orally.

Effects on appearance and behavior, motor activity, body temperature, and a number of neurofunctional tests and reflexes were evaluated in rats. A dose of 50 mg/kg of rucaparib administered via IV infusion (mean C_{max}=13629 ng/mL) resulted in a significant reduction in

motor activity compared with vehicle-treated animals; however, there were no effects on neurofunctional or reflex testing at this dose. The plasma concentration measured at this dose is 3.7-fold above the highest steady state plasma concentration (3710 ng/mL) observed to date in humans at a dose of 600 mg BID rucaparib administered orally.

Administration of rucaparib to Long-Evans rats orally at doses up to 750 mg/kg/dose, followed by a single exposure to solar-simulated ultraviolet radiation approximately 4 hours after the final dose elicited no skin or ocular reactions indicative of phototoxicity. The no-observed-effect-level (NOEL) for phototoxicity was >750 mg/kg/day.

Additional information may be found in the current Investigator's Brochure.

3.3.2 Clinical Experience

The early clinical program assessed safety and efficacy in patients with malignancies commonly treated with chemotherapeutic agents, initially with the IV formulation of rucaparib administered in combination with a variety of chemotherapies, and later with the oral formulation of rucaparib administered as a monotherapy. The latter is the focus of current development efforts.

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

3.3.2.1 Rucaparib Monotherapy

Rucaparib monotherapy is currently being evaluated as treatment for relapsed ovarian cancer in two Clovis-sponsored clinical studies (Study CO-338-010 and this study, CO-338-017 [ARIEL2]. Over 200 patients have been treated with the oral formulation of monotherapy rucaparib in open-label trials; over 150 patients have been treated with the recommended Phase 2 dose of 600 mg BID.

Study CO-338-010

Study CO-338-010 is a 2-part, open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered daily for continuous 21-day cycles. Part 1 was a Phase 1 portion in patients with any solid tumor, including lymphoma, who have progressed on standard treatment. The primary objective of this portion of the study was to determine the optimal monotherapy dose for orally administered rucaparib. Measurable disease was not required and tumor marker assessments are optional. Part 2 is the ongoing Phase 2 portion in patients (up to n=41) with platinum-sensitive relapsed ovarian cancer with evidence of a gBRCA mutation who have received at least 2, but no more than 4, prior regimens. The primary objective of this portion of the study is to assess the overall objective response rate by RECIST v1.1 in this ovarian cancer patient population.

Study CO-338-010 was initiated in Q4 2011. In the Phase 1 portion, a total of 56 patients (median age 50 years [range 21–71]; 51 female; 27 breast cancer, 20 ovarian/peritoneal cancer, 2 pancreatic cancer; 7 other tumor) were treated at dose levels of 40, 80, 160, 300, and 500 mg QD, and 240, 360, 480 and 600 mg BID rucaparib administered continuously. Two patients are

still receiving treatment as of November 2014. One patient treated with 360 mg BID rucaparib experienced a dose-limiting toxicity (DLT) of Common Toxicity Criteria for Adverse Events (CTCAE) Grade 3 nausea despite maximal intervention in Cycle 1 of treatment. No DLTs were observed during Cycle 1 in the 480 mg BID and 600 mg BID cohorts however, similar to other PARP inhibitors, non-DLT myelosuppression was observed beyond Cycle 1, therefore the dose of 600 mg BID rucaparib was selected as the recommended dose for future Phase 2 and Phase 3 studies.

In the ongoing Phase 2 portion, 20 ovarian cancer patients (median age 56 [range 44-84]; ECOG performance status 0/1=12/8; median number of anticancer regimens=2 [range 2-4]; median number of platinum-based regimens=2 [range 2-3]) were enrolled as of September 2014.

Study CO-338-017 (ARIEL2)

In this ongoing trial, 143 ovarian cancer patients (median age 65 [range 31-86]; ECOG performance status 0/1/pending=95/47/1; median number of anticancer regimens=1 [range 1-6); median number of platinum-based regimens=1 [range 1-5]) have enrolled into Part 1 of the study as of October 2014. Full enrollment into Part 1 of the study is anticipated to be completed in December 2014.

3.3.2.1.1 Safety

As of November 2014, safety data are available for n=163 ovarian cancer patients treated with 600 mg BID rucaparib monotherapy in the ongoing Phase 2 studies, including Part 1 of this trial. Treatment-related adverse events (all grades) reported in ≥15% of patients treated with 600 mg BID rucaparib include: gastrointestinal and related symptoms (nausea, vomiting, dysgeusia, diarrhea, abdominal pain, and decreased appetite); anemia; fatigue/asthenia, and headache. Elevations of ALT and/or AST are also commonly observed. The ALT/AST elevations occur early (within first 2-4 weeks of treatment), are generally mild to moderate (Gr 1-2), are not accompanied by any changes in bilirubin levels, and often transient and resolved to within normal ranges, or stabilize. No patient has met the laboratory criteria for Hy's Law.[52] As has been observed with rucaparib and other PARP inhibitors, myelosuppression may be delayed and observed after a period of continuous dosing. Grade 3/4 adverse events assessed as treatment-related and occurring in >5% of patients include: anemia/decreased hemoglobin and increased ALT. All treatment-related adverse events have been successfully managed with concomitant medications, supportive care, and treatment interruption and/or dose reduction. No patient has discontinued rucaparib treatment due to a treatment-related adverse event. A total of five patients have died on study or within 30 days of last dose of rucaparib; all deaths were due to disease progression and were assessed as not related to rucaparib.

Extensive centrally-reviewed electrocardiogram (ECG) monitoring was conducted in the Phase 1 portion of study CO-338-010. ECG results (as triplicate reads) are available for all 56 treated patients. No patient had a QTcF measurement ≥500 msec at any time during study participation. Only one patient had a QTcF measurement ≥480 msec. This measurement occurred in a patient receiving 480 mg BID rucaparib and concomitant administration of citalopram, a medication with known potential to cause QT prolongation. This patient has continued to receive monotherapy rucaparib at a dose of 480 mg BID with no further QTcF measurement ≥480 msec.

No patient experienced a ≥60 msec increase in QTcF over baseline. A total of 11 patients experienced a QTcF increase ≥30 msec over baseline. Further analyses suggest a lack of relationship between QTcF increase ≥30 msec and dose or exposure. In addition, there were no adverse events suggestive of cardiac arrhythmia (e.g., presyncope, syncope, sudden death) in any patient. ECG and adverse event data to date in patients receiving monotherapy rucaparib at doses up to 840 mg BID suggest there is a minimal risk of QTc prolongation.

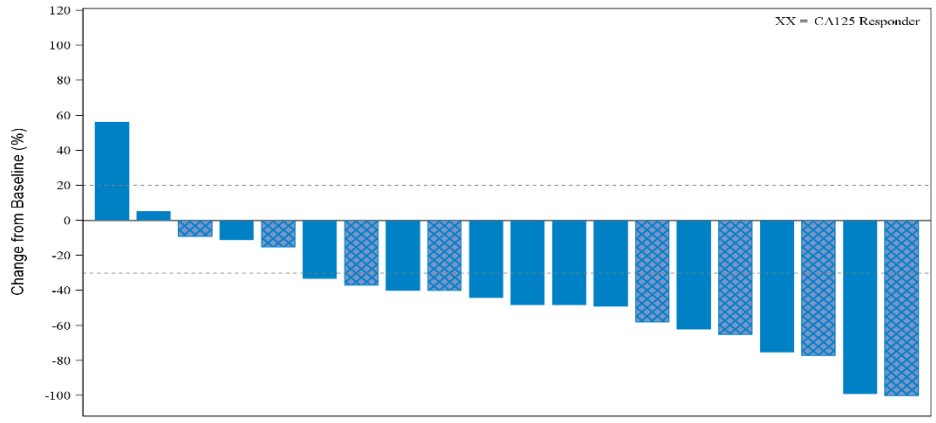
3.3.2.1.2 Efficacy

Study CO-338-010

In the Phase 1 portion, 2 patients (breast cancer and ovarian cancer, both *gBRCA*^{mut}) achieved a RECIST CRs and 7 patients (3 ovarian cancer, 4 breast cancer, 1 pancreatic cancer; all *gBRCA*^{mut}) achieved a RECIST PR during the dose escalation phase (n=2 at 300 mg QD; n=2 at 360 mg BID; n=3 at 480 mg BID; and n=2 at 600 mg BID). Response were durable across tumor types. In addition, 3 patients with ovarian cancer achieved a cancer antigen 125 (CA-125) response as defined by Gynecologic Cancer InterGroup (GCIG) criteria. The disease control rate (CR, PR, or SD>12 weeks) in evaluable ovarian cancer patients treated at doses ≥360 mg BID was 92% (11/12). Responses were observed in platinum-resistant as well as platinum-sensitive ovarian cancer patients. In platinum-resistant ovarian cancer patients treated with ≥360 mg BID rucaparib, 50% (4/8) achieved either a RECIST (25%, 2/8) or GCIG CA-125 response (25%, 2/8). The disease control rate (CR, PR, or SD>24 weeks) in this group was 75% (6/8) and median time on treatment was approximately 9 months (range 1.5-14.5).

In the Phase 2 portion of Study CO-338-010, compelling activity has been observed in patients who had received 2-4 prior chemotherapy regimens and a deleterious *BRCA* mutation, with 15 of 20 (75%) achieving a RECIST PR and 17 of 20 (85%) achieving a RECIST PR and/or a GCIG CA-125 response. The vast majority of patients had some level of target lesion measurement reduction as shown in Figure 1.

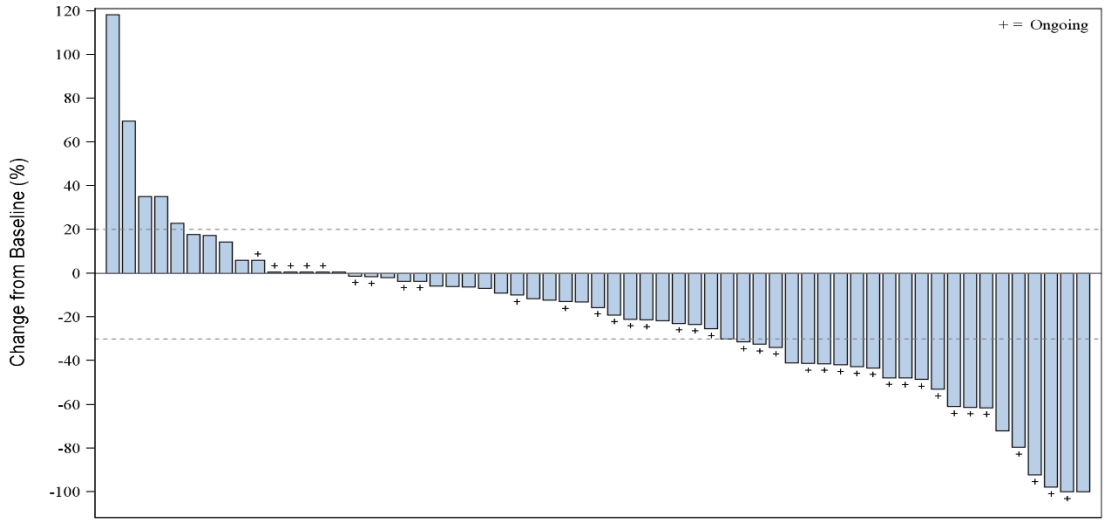
Figure 1 Best Target Lesion Response – Study CO-338-010 Phase 2



Study CO-338-017 (ARIEL2)

In Part 1 of this study, preliminary efficacy data as of October 2014 indicate target lesion reduction in the majority of patients currently evaluable for efficacy, as indicated in Figure 2. ORRs of 38% (RECIST) and 44% (RECIST & GCIG CA-125) have been observed in n=61 patients who had a baseline scan and at least one post-treatment scan, and who were able to be classified into 1 of 3 HRD subgroups based on analysis of their screening biopsy sample. The disease control rate (CR, PR or SD>24 weeks) in this group of patients is 78% and 61% of patients were continuing treatment with rucaparib at the time of this data analysis.

Figure 2 Best Target Lesion Response – Study CO-338-017 (ARIEL2) Part 1



Response and disease control rate data were also analyzed by HRD subgroup as shown in Table 1. Activity was enhanced, as expected, in the subset of patients with a BRCA mutation (n=23), with ORRs of 61% (RECIST) and 70% (RECIST and/or GCIG CA-125). Responses were observed in patients with germline as well as somatic mutations, indicating the importance of assessing tumor tissue rather than relying on a blood test that assesses germline mutation status only. Clinical activity was also observed in patients without a tBRCA mutation. In these patients, the nbHRD group (patients whose tumors had a high level of genomic LOH) (n=25) had ORRs of 32% (RECIST) and 40% (RECIST and/or GCIG CA-125), while the biomarker negative group (patients whose tumors had a low level of genomic LOH) (n=13) had a best ORR (RECIST/RECIST & GCIG CA-125) of 8%. The disease control rates across the 3 HRD subgroups displayed very similar differential results. While these preliminary results are very encouraging and indicate that the current analysis approach of assessing BRCA mutation status in tumor tissue and also assessing level of genomic LOH in tumors without a BRCA mutation does differentially identify patients likely respond to rucaparib, the individual group sizes are still small and more data is still required to complete the analysis and determine the optimal HRD signature, particularly with regards to the $BRCA^{wt}$ groups.

Table 1 Response Rates by HRD Subgroup in Part 1 of Study CO-338-017 (ARIEL2)

Efficacy Parameter	HRD Subgroup		
	$tBRCA^{mut}$	nbHRD ($tBRCA^{wt}$ / high LOH)	Biomarker Negative ($tBRCA^{wt}$ / low LOH)
RECIST ORR, % (n)	61 (14/23)	32 (8/25)	8 (1/13)
RECIST & GCIG CA-125 ORR, % (n)	70 (16/23)	40 (10/25)	8 (1/13)
Disease Control Rate* (CR, PR, or SD>12 wks), % (n)	94 (15/16)	75 (9/12)	50 (3/6)

*Patients with SD who are ongoing with <12 weeks on study are not included in denominator

SUMMARY

Refer to the current Investigator's Brochure for comprehensive information on rucaparib.

Monotherapy rucaparib has demonstrated clinical activity in ovarian cancer patients with and without a BRCA mutation. Overall, response to rucaparib occurs rapidly, with the majority of patients achieving a PR at the first disease assessment scan (weeks 6-8). Responses have been durable and most responders are continuing to receive treatment with rucaparib.

In addition to the data presented by study, the efficacy of rucaparib in $BRCA^{mut}$ ovarian cancer patients who received ≥3 prior chemotherapy regimens and were treated with 600 mg BID rucaparib has been evaluated. In this group, which included both patients with platinum-sensitive and platinum-resistant disease, ORRs of 47% (RECIST) and 73% (RECIST & GCIG CA-125) have been observed, suggesting that rucaparib may be a suitable treatment alternative in this patient population with advanced disease and limited treatment options.

3.3.2.1.3 Pharmacokinetics

After once daily oral administration of rucaparib for 15 days, steady state C_{max} and AUC_{0-24} generally increased dose proportionally. T_{max} and $t_{1/2}$ were independent of dose. Steady state exposure increased by an average of 89%, consistent with accumulation expected for a compound exhibiting a $t_{1/2}$ of approximately 17 hours administered once daily. Following BID oral administration of rucaparib for 15 days, steady state C_{max} and AUC_{0-24} generally increased dose proportionally. Moreover, BID dosing delivered a lower C_{max} with a low peak to trough plasma concentration variation. The target trough level of 2 μM was achieved in 100% of patients (n=14) at ≥240 mg BID with low inter-patient variability (<4-fold) within each dose group. Steady state trough levels also exhibited low intra-patient variability (24% CV). No sporadically high exposures were observed. The effect of food on rucaparib PK was evaluated at 40 mg (n=3) and 300 mg (n=6) doses administered once daily. There was no food effect; patients may take rucaparib on an empty stomach or with food.

3.3.2.2 Studies A4991002 and A4991005, and A4991014

Further details of these rucaparib combination studies are provided in the Investigator's Brochure.

3.4 Rationale for Study

Clinical data with PARP inhibitors indicate there is an ovarian cancer patient population beyond just those with *gBRCA* mutations and/or platinum-sensitive disease that may benefit from treatment with a PARP inhibitor. The purpose of this study is to test and optimize a molecular signature of HRD in ovarian cancer that is hypothesized to correlate with response to rucaparib and will enable selection of appropriate ovarian cancer patients for treatment with rucaparib. The HRD signature has been defined based on the presence of a deleterious *BRCA1* or *BRCA2* mutation and/or genomic tumor LOH. This study will test the ability of the signature to discriminate good from poor outcome on rucaparib. It is anticipated that patients with a *BRCA1* or *BRCA2* mutation and those with tumors exhibiting tumor genome LOH will derive the greatest clinical benefit from rucaparib treatment.

After optimization (if needed), this signature will be prospectively applied in the final analysis of the planned Phase 3 pivotal study (CO-338-014), which will evaluate rucaparib as switch maintenance treatment following a response to platinum-based chemotherapy in a similar patient population. This Phase 2 study will also compare archival versus recently collected tumor tissue in order to validate the use of archival tumor tissue for assessment of HRD status in the Phase 3 study.

This 2-part study will enroll patients with relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube, and primary peritoneal cancer who have disease that can be biopsied and is measurable. Part 1 of the study will enroll approximately 180 patients who received ≥1 prior platinum-based regimen and have platinum-sensitive disease. Enrollment of patients known to harbor a deleterious / pathogenic *gBRCA* mutation will be limited to 15 in Part 1 in order to enrich for patients that have HRD associated with a defect other than *BRCA1/2*. Part 2 will enroll up to 300 patients who received at least 3, but no more than 4, prior chemotherapy regimens, including at least 80 patients with a *tBRCA* mutation. Patients will enroll into either Part 1 or Part 2 of the study. Part 2 will begin once enrollment of Part 1 has been completed.

Tumor tissue collected at screening and/or an archival tumor tissue sample will be sequenced using Foundation Medicine's next generation sequencing (NGS) test, which analyzes a large panel of cancer-related genes, including tumor genome LOH, *BRCA*, and other HRR pathway genes. Genetic alterations, which include mutations and homozygous deletions, in specific HRR pathway genes may also be associated with clinical outcome on treatment with rucaparib.

The following correlative translational studies are also planned:

1. Tumor genomic LOH and gene sequence alterations in archival and screening tumor tissue will be compared to assess the changes in a tumor's genomic LOH and genetic profile over time and determine if archival tumor tissue carries sufficient predictive utility and obviates the need for a contemporaneous biopsy. The frequency and nature of

secondary *BRCA* mutations will also be assessed. Acquired secondary *BRCA* mutations (also known as reversions) may result in functional protein and restored HRR capability, leading to PARP inhibitor resistance.[18-20]

2. An alternative NGS test known as BROCA will be used to potentially identify additional mutations in other DNA repair genes that may confer sensitivity or resistance to rucaparib.[21]
3. Gene expression profiling on extracted RNA will be analyzed to potentially identify a signature associated with efficacy. A gene expression signature has been developed to identify *BRCA* and *BRCA*-like (also referred to as "BRCAness") tumors. Such a signature may predict response to platinum and PARP inhibitors.[22]
4. Immunohistochemistry (IHC) of non-homologous end joining (NHEJ) proteins will be investigated to assess whether NHEJ pathway integrity modulates efficacy. It has been hypothesized that cells with HRD must have functional NHEJ DNA repair in order to generate sufficient genomic instability for synthetic lethality with a PARP inhibitor.[23]
5. Circulating cell-free tumor DNA (ctDNA) will be analyzed as a potential molecular marker of efficacy. Tagged-amplicon deep sequencing (TAm-Seq) will be utilized to sequence ctDNA and identify mutations, including but not limited to, those in the tumor suppressor gene TP53, which is present in greater than 95% of HGSOC tumors.[3, 24] Similar to CA-125, the fraction of TP53 mutant alleles in plasma of ovarian cancer patients has been shown to track with the clinical course of the disease.[24]

Taken together, the analyses planned in this trial will provide valuable information on genomic abnormalities that may be associated with response or resistance to rucaparib and will identify a broader ovarian cancer patient population that may benefit from treatment than has previously been explored in most other PARP inhibitor studies.

4 STUDY OBJECTIVES

4.1 Objectives and Endpoints

This is a two-part, open-label efficacy study of oral rucaparib in patients with platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer to define a signature of HRD that correlates with efficacy.

Primary, secondary, and exploratory objectives and endpoints are shown in Table 2. Unless otherwise specified, the objectives below apply to both parts of the study.

Table 2 Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
1. To determine PFS in patients with relapsed platinum-sensitive ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature (Part 1)	1. Disease progression (RECIST v1.1) (Appendix B) as assessed by investigator, or death from any cause, in molecularly-defined subgroups identified by a prospectively defined HRD signature
2. To estimate ORR in heavily pre-treated patients with relapsed ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature (Part 2)	2. ORR by RECIST v1.1 in molecularly-defined subgroups identified by a prospectively defined HRD signature
Secondary Objectives	**Secondary Endpoints**
1. To estimate ORR (Part 1)	1. ORR by RECIST v1.1
2. To estimate ORR including CA-125 response criteria	2. ORR by RECIST v1.1 and GCIG CA-125 criteria
3. To evaluate duration of response (DOR)	3. DOR by RECIST v1.1
4. To determine PFS (Part 2)	4. Disease progression (RECIST v1.1) (Appendix B) as assessed by investigator, or death from any cause
5. To evaluate survival (Part 2)	5. Overall survival
6. To evaluate the safety and tolerability of rucaparib	6. The incidence of adverse events (AEs), clinical laboratory abnormalities, and dose modifications
7. To evaluate steady state trough level PK	7. Trough (C_{min}) level rucaparib concentrations

Table 2 Primary, Secondary, and Exploratory Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
1. To assess efficacy in molecularly-defined HRD subgroups as defined by HRR gene alterations	1. PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria. HRD subgroups as defined by HRR gene alterations
2. To optimize the tumor LOH algorithm by testing additional signatures of interest based on higher or lower genomic LOH	2. PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria. Additional signatures of interest based on higher or lower genomic LOH.
3. To assess changes in HRD status over time	3. Changes in HRD status (LOH and gene alterations) between fresh biopsy versus archival tumor tissue samples
4. To assess whether the BROCA panel can identify mutations in additional HRR genes that may be associated with efficacy	4. ORR by RECIST v1.1 and GCIG CA-125 criteria in relation to HRR gene mutations identified in BROCA
5. To assess if a gene expression signature for HRD correlates with efficacy	5. PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria in relation to gene signature defined by a gene expression profiling assay
6. To assess NHEJ pathway integrity and correlate it with efficacy	6. NHEJ protein expression by immunohistochemistry (IHC) and PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria
7. To assess ctDNA as a molecular marker of efficacy	7. Levels of ctDNA in relation to PFS and/or ORR by RECIST v1.1 and GCIG CA-125 criteria

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a two-part, open-label efficacy study of rucaparib in patients with platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer to characterize the relationship between HRD status and rucaparib efficacy in patients who received ≥1 prior platinum-based regimen and have platinum-sensitive disease (Part 1) and patients who received at least 3, but no more than 4, prior chemotherapy regimens (Part 2). Patients will enroll into either Part 1 or Part 2 of the study. Part 2 will begin once enrollment of Part 1 has been completed.

5.1.1 Screening Phase

All patients will undergo screening assessments within 28 days prior to the first dose of rucaparib. AEs that occur after signing of the informed consent form and before administration of the first rucaparib dose will also be collected during this period.

Screening assessments will include demographics and medical history, prior treatments for epithelial ovarian, fallopian tube, or primary peritoneal cancer (and other malignancies if applicable), prior and current medications, and procedures, 12-lead electrocardiogram (ECG), ECOG performance status, hematology, serum chemistry, serum pregnancy for women of childbearing potential, urinalysis, blood sample for ctDNA analysis, physical examination, vital signs, weight and height measurements, adverse events, radiological assessment by CT or MRI, and CA-125 measurement. All patients, with the exception of Part 2 patients known to harbor a deleterious *gBRCA* mutation, will be required to have a screening biopsy to collect fresh tumor tissue for determination of HRD status at study entry within 28 days prior to the first dose of rucaparib. The screening biopsy will be optional for Part 2 patients known to harbor a *gBRCA* mutation. This biopsy should be performed at least 7 days prior to the planned start of treatment to allow sufficient time for the sample to be sent to Foundation Medicine, the central laboratory for confirmation the tissue is of adequate quality for the planned analyses. If a biopsy was recently performed as standard of care prior to this patient consenting to this study or after study informed consent but outside the 28 day screening window this may be acceptable with advance approval from the Sponsor. In addition, archival tumor tissue samples must be confirmed as being available for all patients. While archival tumor tissue is not required to be shipped prior to initiation of treatment, it is highly recommended that the tissue be sent as close as possible to the time of sending the screening biopsy to enable timely enrollment in the event that the screening biopsy is deemed inadequate by Foundation Medicine.

In Part 1, patients <55 years of age at diagnosis, or with prior history of breast cancer, or who have a close relative (first or second degree) with ovarian cancer or early onset (<age 50) breast cancer are required to have been previously tested for *gBRCA* mutation. Germline *BRCA* test results must be obtained for all patients who are known to have been tested prior to enrollment in order to determine whether any mutation was reported and if so, whether the mutation was classified as deleterious / pathogenic or other. Enrollment of patients with a *gBRCA* mutation classified as deleterious (i.e., pathogenic), suspected deleterious, or favor deleterious (or the equivalent interpretation of any of these) on the most recent assessment by a testing laboratory

will be limited to 15 in Part 1. Patients not required to have been previously tested, or who tested negative for a *gBRCA* mutation, or who were found to have a mutation that was classified as other than deleterious, suspected deleterious, or favor deleterious or the equivalent of any of these, are eligible to enroll in Part 1 provided all other criteria are met. Patients with a *BRCA* mutation detected in tumor tissue (*tBRCA*), but who do not have a germline mutation, will not count toward the cap and will be eligible to receive treatment with rucaparib, provided all other eligibility criteria are met.

At least 80 patients with a deleterious / pathogenic *tBRCA* mutation will be enrolled into Part 2 of the study. There is no requirement for a patient enrolling into Part 2 to have been previously tested for a germline *BRCA* mutation, even if she meets the clinical criteria for testing being applied to patients entering Part 1 of the study.

Results of the Foundation Medicine panel test will be provided to all patients who consent to receive this information. In the event a *BRCA1* or *BRCA2* mutation is detected in tumor tissue, the patient may be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline testing, this result will be entered into the clinical trial database.

Mutations detected in tumor tissue may be somatic or germline; however, the central laboratory's NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients at screening and stored. Prior to final efficacy analysis, genomic DNA may be subjected to exploratory analysis in order to determine whether the mutation is germline. These data will be generated in a research setting and will not be provided to the investigator or patient.

Enrollment will require Clovis review of eligibility, including information on prior cancer therapies and dates administered, local *gBRCA* test result if patient has previously been tested, and, with the exception of Part 2 patients known to harbor a deleterious *gBRCA* mutation, confirmation that the screening biopsy sample has been submitted to the central laboratory and deemed adequate for the planned genetic analyses. Confirmation that an adequate amount of archival tumor tissue is available for analysis is also required.

5.1.2 Treatment Phase

For patients remaining on treatment as of implementation of Protocol Amendment 6, a more limited number of assessments will be performed during the treatment period as compared to previously; however, an appropriate level of safety monitoring will remain in place. A revised Schedule of Assessments (SOA) is provided in Section 9.1, which replaces all prior SOAs and should be followed for all patients who remain on treatment.

During the treatment phase (continuous 28-day treatment cycles), patients will be monitored for safety and efficacy. Assessments during the treatment phase will include AEs, complete blood count (monthly assessment advised), serum pregnancy test for women of childbearing potential, and study drug accountability; in addition, disease assessments (imaging/CA-125), clinical chemistry, urinalysis, and vital signs may be performed per local standard of care practices. Patients will be assessed for disease status per RECIST v1.1. Patients experiencing disease progression, as assessed by the investigator, will be discontinued from treatment.

A formal safety data review will occur after the first 20 patients have been enrolled, then every quarter until Part 1 enrollment is completed, and then every 6 months thereafter until all patients are enrolled and have participated in the study for at least 6 months or have discontinued prior to 6 months, at which point safety reviews will occur on an as-needed basis. The review committee will include external experts and Sponsor personnel. The external experts will include, but not be limited to, the coordinating PIs of the study (Dr. Elizabeth Swisher at Univ. of Washington and Dr. Iain McNeish at Imperial College London). Clovis reviewers will include the Medical Monitor, Chief Medical Officer, Head of Medical Safety (Pharmacovigilance), and Biostatistician. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review.

5.1.3 Post-Treatment Phase

As of implementation of Protocol Amendment 6, more limited post-treatment assessments will be performed while maintaining appropriate safety monitoring. A revised SOA is provided in Section 9.1, which replaces prior SOAs.

Upon discontinuation of treatment with rucaparib or study closure by the Sponsor, all patients will return to the clinic for an End of Treatment visit. Assessments at this visit will include AEs, complete blood count, serum pregnancy for women of childbearing potential, and study drug accountability; in addition, disease assessments (imaging/CA-125), clinical chemistry, urinalysis, and vital signs may be performed per local standard of care practices. An optional tumor biopsy sample, if available, will be collected from patients who experience disease progression and provide appropriate consent. Disease assessments should also be done at the time of treatment discontinuation if it has been ≥ 8 weeks since the last assessment.

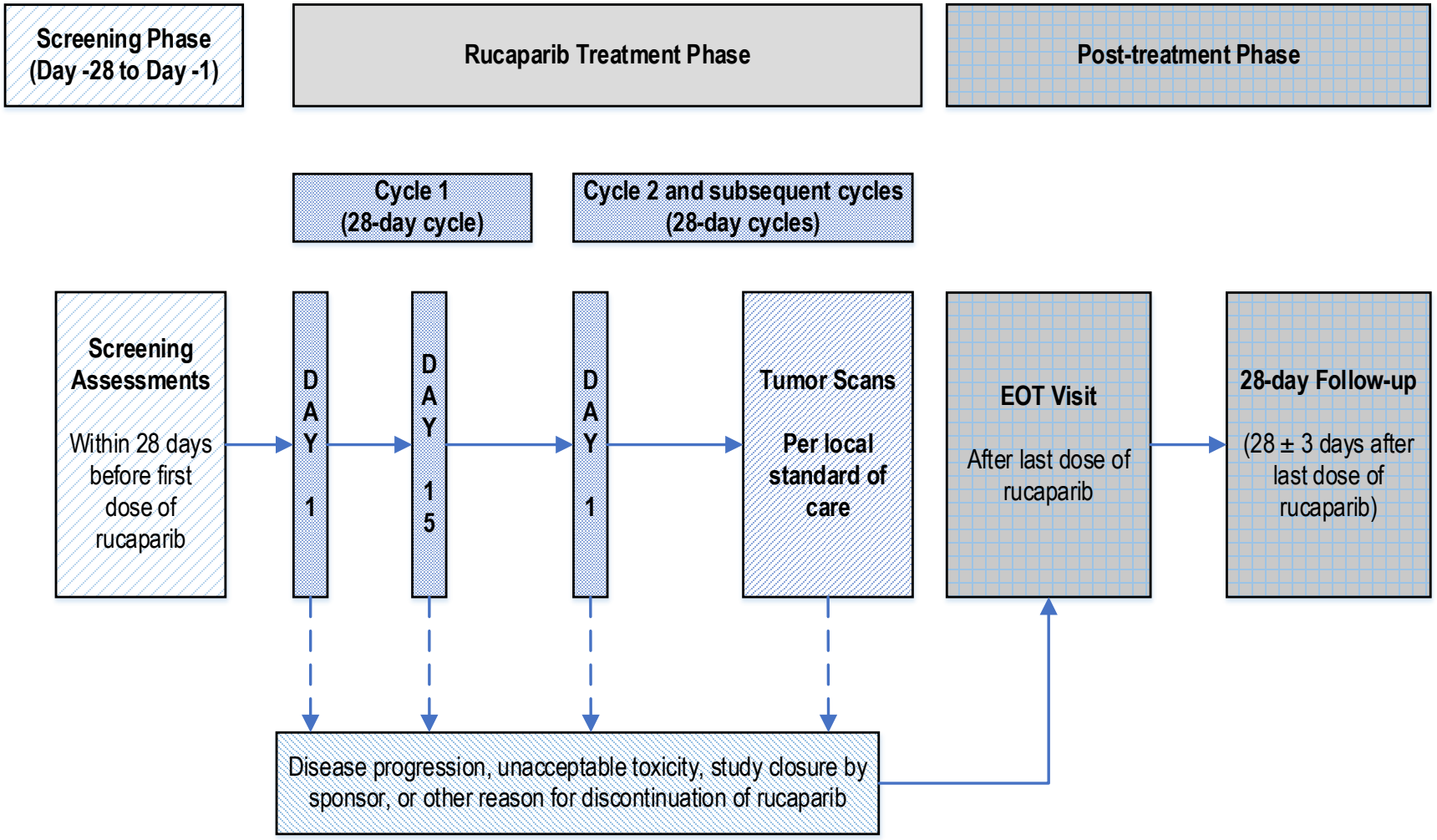
All patients will be assessed for AEs at 28 (±3) days following the last dose of rucaparib at the 28-Day Follow-up visit. All serious adverse events (SAEs) and adverse events of special interest (AESIs) are to be followed to resolution, stabilization, or lost to follow-up (refer to Section 10.7) even if the duration extends beyond the 28-day follow-up period.

All patients who discontinued treatment for any reason other than radiologically confirmed disease progression will continue to have scans according to local standard of care per investigator until radiologically confirmed disease progression, death, initiation of subsequent treatment, or study closure by the sponsor.

5.2 Study Schema

The study schema in Figure 3 summarizes the treatment design of the study.

Figure 3 Study Schema



5.3 End of Study

The study will close when all patients have discontinued the study, or by sponsor decision as stated in Section 13.6. If the study is closed by the sponsor, individual patients who are continuing to benefit from rucaparib treatment, and who do not meet any of the criteria for withdrawal, may have the option of entering an extension protocol, receiving rucaparib through compassionate use, or other acceptable study or option in which they can continue to receive rucaparib.

6 STUDY POPULATION

6.1 Number of Patients and Sites

Approximately 480 patients with platinum-sensitive, relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer will be enrolled into either Part 1 (n=180) or Part 2 (n=300) of the study at approximately 60 study sites. Enrollment of patients known a priori to have a deleterious / pathogenic *gBRCA* mutation will be limited to 15 in Part 1. At least 80 patients with a *tBRCA* mutation will be enrolled into Part 2.

6.2 Inclusion Criteria

Eligible patients must meet the following inclusion criteria. Unless otherwise specified, the criteria below apply to patients enrolling in either Part 1 or Part 2 of the study.

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form prior to any study-specific evaluation
2. Be ≥18 years of age at the time the informed consent form is signed
3. Have a histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer
   - If mixed histology, >50% of the primary tumor must be confirmed to be high-grade serous or endometrioid upon re-review by local pathology
   - Patients with a histology other than serous or endometrioid are also eligible for Part 2 of the study if they are known to harbor a deleterious / pathogenic *BRCA* mutation (germline or somatic)
4. Have relapsed/progressive disease as confirmed by radiologic assessment
5. **Part 1**: Received prior platinum-based therapy and have platinum-sensitive disease
   a. Received ≥1 prior platinum-based treatment regimen; AND
   b. Received a platinum-based regimen as their last treatment; continuous or switch maintenance treatment as part of this regimen is permitted (hormonal treatment may be permitted following the last platinum regimen with advance approval from the Sponsor); AND
   c. Was sensitive to the last platinum regimen. Platinum-sensitive disease is defined as documented radiologic progression ≥6 months after the last dose of platinum administered in the treatment setting.

   Part 2: Received at least 3, but no more than 4, prior chemotherapy regimens and had documented treatment-free interval of ≥6 months following 1st chemotherapy regimen received
   a. Hormonal agents (e.g., tamoxifen, letrozole, etc), anti-angiogenic agents (eg. bevacizumab, pazopanib, cediranib, nintedanib, trebananib, etc), and other non-chemotherapy agents administered as single agent treatment will not be counted as a chemotherapy regimen for the purpose of determining patient eligibility
   b. Agents administered in the maintenance setting will not be counted as a separate regimen

6. **Part 1 only:** If <55 years of age at diagnosis, or has prior history of breast cancer, or has close relative (first or second degree) with ovarian cancer or early onset (<age 50) breast cancer, must have been previously tested for *gBRCA* mutation ; after 15 patients harboring the *gBRCA* mutation are enrolled, no additional patients with a known *gBRCA* mutation will be allowed to enroll.
7. Have undergone a biopsy of tumor tissue prior to first dose of study drug and had the tumor tissue confirmed by the central laboratory as being of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content). *Note: biopsy is optional for Part 2 patients known to harbor a deleterious gBRCA mutation*
   - If tumor tissue obtained from the biopsy is deemed inadequate, and the patient is unwilling or unable to have another biopsy, the patient may be considered for enrollment if archival tumor tissue is provided and deemed of adequate quality. This must occur prior to any treatment with rucaparib.
     a. Biopsy must be of solid tumor tissue; ascites is not acceptable.
     b. Biopsy must be of sufficient yield for planned analyses
8. Have sufficient archival FFPE tumor tissue available for planned analyses; cytospin blocks from ascites are not acceptable
   - The most recently obtained tumor tissue that is of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content) should be submitted
9. Have measurable disease as defined by RECIST v1.1 (Appendix B) in addition to the lesion planned for biopsy; a single RECIST target lesion will suffice if, in the Investigator's opinion, it is of sufficient size that the biopsy will not affect post-dose RECIST evaluations.
10. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to the first dose of rucaparib:
    a. Bone Marrow Function
       i. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
       ii. Platelets $>100 \times 10^9$/L
       iii. Hemoglobin ≥9 g/dL
    b. Hepatic Function
       i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN); if liver metastases, then ≤5 × ULN
       ii. Bilirubin ≤1.5 × ULN (<2 × ULN if hyperbilirubemia is due to Gilbert's syndrome)
       iii. Serum albumin ≥30 g/L (3 g/dL) (Part 2 only)
    c. Renal Function
       i. Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate (GFR) ≥45 mL/min using the Cockcroft Gault formula
11. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Appendix C)

6.3 Exclusion Criteria

Patients will be excluded from participation if any of the following criteria apply. Unless otherwise specified, the criteria below apply to patients enrolling in either Part 1 or Part 2 of the study.

1. Active second malignancy, i.e., patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment
    a. Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed >6 months prior and/or bone marrow transplant (BMT) >2 years prior to first dose of rucaparib
2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib are eligible
3. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks
4. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib
5. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C
6. Pregnant or breast feeding. Women of childbearing potential must have a negative serum pregnancy test <3 days prior to first dose of rucaparib
7. Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤14 days prior to first dose of rucaparib and/or ongoing adverse effects from such treatment > NCI CTCAE Grade 1 (ongoing Grade 2 non-hematologic toxicity related to most recent treatment regimen may be permitted with prior advanced approval from sponsor).
8. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of rucaparib or have on-going requirements for these medications
9. Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤ 21 days, prior to first dose of rucaparib; in all cases, the patient must be sufficiently recovered and stable before treatment administration
10. 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
11. Diagnosis of low-grade serous or Grade 1 endometrioid ovarian cancer
12. **Part 2 Only:** Hospitalization for bowel obstruction within 3 months prior to enrollment

6.4 Patients or Partners of Patients of Reproductive Potential

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

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

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

Female patients of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to administration of the first dose of rucaparib. In addition, a serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle from Cycle 2 and beyond during the treatment phase. A serum pregnancy test will be performed at the End of Treatment visit. Pregnancy testing will be conducted locally.

Female patients of reproductive potential and their male partners must practice a highly effective method (failure rate < 1% per year) of contraception during treatment and for 6 months following the last dose of rucaparib.

Highly effective contraception includes:

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

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

6.5 Waivers of Inclusion/Exclusion Criteria

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

7 DESCRIPTION OF STUDY TREATMENTS AND DOSE MODIFICATIONS

7.1 Description of Investigational Product

Rucaparib camsylate (formerly known as PF-01367338 and AG-014447) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib tablets for oral administration will be supplied to the study sites by the sponsor. A brief description of the investigational product is provided below.

Drug Name:	Rucaparib camsylate (CO-338)
INN:	Rucaparib
Formulation:	Tablet; film coated; 200 mg – blue, 300 mg – yellow
How Supplied:	200 and/or 300 mg (as free base) strength in high-density polyethylene bottles or equivalent with child-resistant caps . Patients may receive one or more strengths.
Storage Conditions:	15–30 °C

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 Voice Response System/Interactive Web Response System (IVRS/IWRS).

7.2 Method of Assigning Patients to Treatment Groups

All patients enrolled in the study will receive rucaparib.

7.3 Preparation and Administration of Protocol-Specified Treatment

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.

All patients will ingest rucaparib twice a day. Patients may take rucaparib on an empty stomach or with food. Each dose should be taken with at least 8 oz (240 mL) of room temperature water. Tablets should be swallowed whole.

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 (i.e., does not take it within 4 hours of the scheduled time), she should skip the missed dose and resume taking rucaparib with her next scheduled dose. Missed or vomited doses should not be made up.

A sufficient number of tablets will be provided to the patient to last until the next scheduled 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.

Patients enrolled into Part 1 of the study will initially receive 120 mg tablets, and once available supplies are exhausted, patients receiving this dose strength will be transitioned to 300/200 mg tablets or combination of dose strengths at a dose agreed upon between the investigator and sponsor. Patients enrolled into Part 2 of the study will initially receive 300 mg tablets. (Tablets of 200 mg dose strength will also be available for patients in Part 2 to enable dose reductions in 100 mg increments – see Table 3).

7.3.1 Dietary Restrictions

All patients participating in the study should be instructed to use caution with CYP1A2, CYP2C9, CYP2C19, and CYP3A substrates noted in Appendix D.

7.4 Starting Dose and Dose Modifications of Protocol-Specified Treatment

7.4.1 Starting Dose

The starting dose in this study will be 600 mg rucaparib BID. This dose was selected as the recommended dose for future Phase 2 and Phase 3 studies based on safety, tolerability, overall PK, and preliminary efficacy profile observed in the CO-338-010 study, which evaluated monotherapy rucaparib in patients with advanced solid tumors. A summary of that study is provided in Section 3.3.2.1. In the event that the recommended Phase 2 dose of 600 mg BID rucaparib is determined to be unsuitable for chronic dosing, the starting dose may be decreased to Dose Level -1 (480 mg BID rucaparib) for all subsequent patients if agreed upon between the Sponsor and the Principal Investigators.

7.4.2 Dose Modification Criteria

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

- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below.
- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

MANAGEMENT OF RUCAPARIB TREATMENT-EMERGENT ALT/AST ELEVATIONS

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

- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:
  - Monitor liver function tests weekly until resolution to ≤ Grade 2.
  - Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN and alkaline phosphatase is < 3 x ULN.
  - If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before rucaparib can be resumed, either at the current dose or at a reduced dose.

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

Dose reduction steps are presented in Table 3.

Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 is permitted upon agreement between the investigator and sponsor.

Table 3 Dose Reduction Steps

Tablets	**300/200 mg**
Starting Dose	**600 mg BID**
Dose Level -1	500 mg BID
Dose Level -2	400 mg BID
Dose Level -3*	300 mg BID

*Consult with medical monitor before reducing to this dose

7.4.3 Criteria for Re-Treatment

A new cycle of treatment may begin if:

- ANC ≥1.0 x 10^9/L
- Platelet count ≥75 x 10^9/L
- Non-hematologic toxicities have returned to baseline or ≤CTCAE Grade 1 severity (or, at the investigator's discretion, ≤CTCAE Grade 2 severity if not considered a safety risk for the patient)

7.4.4 Treatment Beyond Progression

If the patient has met criteria for radiologic progression by RECIST, but the patient is still receiving benefit from rucaparib (e.g., 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, and must be documented prior to continuing treatment with rucaparib. Patients will continue to have all protocol-required assessments specified in Table 4 and may have the option of entering an extension protocol, receiving rucaparib through compassionate use, or other acceptable study or option in which they can continue to receive rucaparib either at the investigator's discretion at any time or if this study is closed by the sponsor.

7.5 Accountability of Protocol-Specified Treatment

Study personnel will maintain accurate records of study drug receipt, dispensation, use, return, destruction, and reconciliation. A web/phone-based drug management system will be used to manage study drug inventory at all sites. In order to function properly, the system will require real-time entry of study drug receipt, dispensation, destruction, etc. by study personnel at the study center.

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

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

7.6 Blinding/Masking of Treatment

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

7.7 Treatment Compliance

As of implementation of Protocol Amendment 6, drug dosing diaries will be discontinued.

Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose. Patients (or legally authorized representative) will be instructed to bring all unused tablets with them to scheduled clinic visits. A compliance check and tablet count will be performed by study personnel during clinic visits.

Every effort should be made to ensure patients return their study drug containers 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.

8 PRIOR AND CONCOMITANT THERAPIES

Patients who have received prior treatment with a PARP inhibitor including intravenous or oral rucaparib are not eligible to participate in this study. Patients having received prior treatment with iniparib are eligible.

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

All procedures performed (e.g., thoracentesis, etc.) and medications used during the study must be documented on the eCRF.

8.1 Anticancer or Experimental Therapy

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

8.2 Hematopoietic Growth Factors and Blood Products

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

8.3 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on results of 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 D).

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

8.4 Bisphosphonates

Bisphosphonates are permitted.

8.5 Anticoagulants

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

8.6 Other Concomitant Medications

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

Rucaparib marginally increased digoxin area under the plasma 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.

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. In addition, rucaparib is an inhibitor of the BCRP with 50% inhibitory concentration (IC_{50}) value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (eg, rosuvastatin).

8.7 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.

9 STUDY PROCEDURES

9.1 Schedule of Assessments

Table 4 summarizes the procedures and assessments to be performed for all patients remaining on treatment or in follow-up as of implementation of Protocol Amendment 6. The revised evaluations should commence immediately after the patient has provided appropriate informed consent, maintaining previous treatment cycle and day sequence.

The revised Schedule of Assessments (SOA) shown below in Table 4 replaces all prior SOAs.

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

The purpose of the revised SOA is to allow patients who continue to benefit from treatment with rucaparib to continue on treatment and follow-up but to reduce the number of assessments required at study visits (including at the end of treatment and follow-up assessments), while maintaining an appropriate level of safety monitoring.

Table 4 Revised Schedule of Assessments as of Implementation of Protocol Amendment 6

Procedure[a]	Treatment Phase (±3 days) Cycle X Day 1	Post-Treatment Phase	
		End of Treatment	28 Day Follow-up (FU) (±3 days after last dose)
Adverse Events[b]	The Investigator should monitor and educate patients on possible AEs observed with rucaparib		X
Complete Blood Count	Monthly assessments advised		
Clinical Chemistry, Urinalysis, Vital Signs	Local standard of care practices per Investigator		
Serum Pregnancy Test[c] (WOCBP only) (local lab)	X	X	
Disease Assessments (Imaging/CA-125)	Local standard of care practices per Investigator		
Tumor Tissue Biopsy[d]		X	
Rucaparib Dispensation/Administration/Accountability	X	X	

Abbreviations: AE = adverse event, AESI = adverse event of special interest, FU = follow up, SAE = serious adverse event, WOCBP = women of childbearing potential.

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

[b] = AEs will be monitored but only SAEs/AESIs are recorded through 28 days after last dose of rucaparib. Ongoing SAEs and AESIs will be followed until resolution, stabilization, or lost to follow-up.

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

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

9.2 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed during the 28-day period prior to the first dose of study drug. Assessments performed within this window, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care.

- Medical/oncology history, including demographic information (birth date, race, gender, etc.) and smoking status, including date of cancer diagnosis, and any surgical procedures
- Physical examination by body system, height, and weight
- ECOG performance status (Appendix C)
- Vital signs (blood pressure, pulse, and temperature)
- Prior and concomitant medications and any procedures
- 12-lead ECG
- Hematology (hemoglobin, hematocrit, WBC and differential [with ANC], and platelet count) ≤14 days prior to the first dose of study drug (all patients in Parts 1 and 2; patients in Part 2 will also have MCH, MCV, MCHC, and reticulocyte count measurements)
- Serum chemistry (total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, blood urea nitrogen [BUN] or urea, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus) and total cholesterol for all patients in Parts 1 and 2; patients in Part 2 will also have a lipid panel that includes LDL, HDL and triglycerides in addition to the total cholesterol measurement) ≤14 days prior to the first dose of study drug. *Note: fasting is not required for the lipid panel.*
- Serum pregnancy test for women of childbearing potential (within 3 days of first dose of study drug)
- Cancer antigen 125 (CA-125) measurements per GCIG criteria provided in Appendix E
  - To be evaluable for response by CA-125, at least 2 pretreatment samples must be collected at least 1 day, but not more than 3 months, apart. At least one pretreatment sample should be within 1 week prior to the first dose of rucaparib. Both must be at least twice the upper limit of normal.
- Urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH, and ketones). If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings.
- Tumor assessments should consist of clinical examination and appropriate imaging techniques, including CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST; other studies (MRI, X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. The same methods used to detect lesions at

baseline are to be used to follow lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment.

- Tumor tissue biopsy / sample collection (If a biopsy was recently performed as standard of care prior to this patient consenting to this study or after study informed consent but outside the 28 day screening window this may be acceptable with advance approval from the Sponsor). Tumor specimen must be processed locally as FFPE tissue. Sample must be sent to the central laboratory for review and confirmed as adequate (at least 20% tumor content with a minimum of 80% nucleated cellular content; 30% or greater tumor content is preferred) for planned analyses prior to enrollment. Refer to the Pathology Charter for detailed sample requirements and handling instructions.
  - To ensure sufficient viable tumor tissue is obtained, image-guided biopsies should be achieved with 14 to 18 gauge cutting needles to provide 1 to 3 cores measuring 1 to 1.5 cm in length.
  - Biopsy must be of solid tumor tissue; ascites is not acceptable.
  - If tumor tissue obtained from the biopsy is deemed not adequate, and the patient is unwilling or unable to have another biopsy, the patient may be considered for enrollment if archival tumor tissue is provided and deemed of adequate quality. This must occur prior to any treatment with rucaparib.
  - Note: screening biopsy sample is optional for Part 2 patients known to harbor a deleterious *gBRCA* mutation
- FFPE archival tumor tissue sample. Sufficient archival FFPE tumor tissue for planned analyses should be provided. Cytospin blocks from ascites are not acceptable. Refer to the Pathology Charter for detailed sample requirements and handling instructions.
  - The most recently obtained tumor tissue that is of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content) should be submitted
  - Sample need not be submitted prior to enrollment; however, confirmation that such tissue is available must be provided prior to enrollment approval.
- AE monitoring (after signing informed consent)
- Blood sample for ctDNA analysis
- Blood sample for storage (may be collected at a subsequent visit, if not collected during this visit)

9.3 Treatment Phase

9.3.1 Day 1 of Cycle 1

The following procedures will be completed before rucaparib is administered:

- Physical examination (abbreviated)
- Weight
- ECOG performance status (Appendix C)

- Vital signs
- Concomitant medications and procedures
- Hematology
- Serum chemistry
- CA-125 measurement
- AE monitoring
- Blood sample for ctDNA analysis

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until the next treatment cycle. Patients will ingest rucaparib twice daily at about the same times every day, at close to 12 hours apart as possible. Each dose of rucaparib should be taken with at least 8 oz (240 mL) of room temperature water. Patients may take rucaparib on an empty stomach or with food. Patients will record dosing information in their dosing diary.

9.3.2 Day 15 of Cycle 1

Patients will be instructed to refrain from taking their first dose of rucaparib at home on the day of their clinic visit because certain assessments should be performed prior to dosing.

- Hematology
- Serum chemistry
- A single plasma PK sample (as close to 12 hours after the last dose taken as possible and prior to the next dose)
- A single serum sample for AAG measurement (as close to 12 hours after the last dose taken as possible and prior to the next dose)
- Concomitant medications and procedures
- AE monitoring

9.3.3 Cycles 2 and Beyond

The revised Schedule of Assessments shown in Table 4 replaces all prior schedules of assessments as of implementation of Protocol Amendment 6.

The following procedures are advised:

- Hematology (complete blood count); monthly assessments advised
- Clinical chemistry, urinalysis, and vital signs according to local standard of care per Investigator
- CA-125 measurement according to local standard of care per Investigator

- Serum pregnancy test ≤ 3 days prior to start of cycle (for women of childbearing potential only)
- Tumor scans according to local standard of care per Investigator.
- AE monitoring
- Study drug accountability

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until the next clinic visit. A single dose of rucaparib will be administered with at least 8 oz (240 mL) of room temperature water during the current clinic visit. Patients may take rucaparib on an empty stomach or with food.

Patients will continue dosing with rucaparib at home on an empty stomach or with food, taking doses twice daily at about the same times every day. Rucaparib should be taken with at least 8 oz (240 mL) of room temperature water.

9.4 End of Treatment Visit

The revised Schedule of Assessments shown in Table 4 replaces all prior schedules of assessments as of implementation of Protocol Amendment 6.

The following procedures are advised as soon as possible after the last dose of rucaparib:

- Hematology (complete blood count)
- Clinical chemistry, urinalysis, and vital signs according to local standard of care per Investigator
- Serum pregnancy test for women of childbearing potential
- CA-125 measurement according to local standard of care per Investigator
- Optional tumor tissue biopsy sample collection at time of disease progression/treatment discontinuation (requires additional consent). If disease progression is caused by appearance of a new lesion(s), this lesion should be prioritized for biopsy. Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions
- AE monitoring
- Study drug accountability
- Disease assessments according to local standard of care per Investigator

9.5 28 Day Follow-up Visit

The following procedures will be performed for all patients at 28 (±3) days after the last dose of rucaparib:

- AE monitoring (ongoing SAEs and AEs of special interest [AESI]; Section 10.3) should be followed until resolution, stabilization, or lost to follow-up even if the duration extends beyond the 28-day follow-up period).

After the 28-day window, only SAEs assessed as related to study drug and all AESIs, irrespective of causality, should be reported.

9.6 Methods of Data Collection

Hematology, serum CA-125, and serum pregnancy will be performed locally. Central/core laboratories will conduct all other assays described below. Please refer to the Pathology Charter and/or Laboratory Manual for details on collecting and processing all samples that will be sent to central/core laboratories.

9.6.1 Pharmacokinetic Evaluations and AAG Measurement

As of implementation of Protocol Amendment 6, samples will no longer be collected for PK and AAG analyses.

9.6.2 Biomarker Analysis – FFPE Tumor Tissue

A tumor tissue biopsy sample is required to be collected during screening from all patients, except for Part 2 patients known to harbor a deleterious *gBRCA* mutation; the screening biopsy sample in this group of patients is optional. 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. If disease progression is caused by appearance of a new lesion(s), this lesion should be prioritized for the optional biopsy.

Sufficient archival FFPE tumor tissue (See Pathology Charter for details) must be available and located during the screening process and submitted to the central laboratory as soon as possible. Submission of archival tumor tissue is not required for enrollment; however, confirmation that such tissue is available is required.

Analysis of the tumor tissue samples may include, but not be limited to:

- DNA extraction and sequencing of single nucleotide polymorphisms (SNPs) to identify tumor genomic LOH and to determine whether tumor genomic LOH can be used as a predictor of efficacy
- DNA extraction and sequencing in order to identify:
- If the patient has a mutation in BRCA1, BRCA2, or another gene in the HRR pathway (Appendix A)
- If a patient has a BRCA reversion or other mutation(s) that may be associated with efficacy
- Gene expression profiling on extracted RNA to potentially identify a signature associated with efficacy
- Immunohistochemistry analysis to assess NHEJ pathway integrity

9.6.3 Biomarker Analysis – Blood

As of implementation of Protocol Amendment 6, blood samples will no longer be collected for biomarker analyses.

9.6.4 Safety Evaluations

9.6.4.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs during study participation (beginning at the time informed consent is obtained) and until 28 days after the last dose of rucaparib. Any ongoing SAEs and AESIs will be recorded and followed until resolution, stabilization, or lost to follow-up. Only treatment-related SAEs and all AESIs, irrespective of causality, need to be reported after the 28-day window. SAEs will be graded according to the NCI CTCAE grading system (Version 4.0) and recorded on the eCRF.

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

9.6.4.2 Clinical Laboratory Investigations

Certified local laboratories will perform study-related clinical laboratory tests according to institutional procedures, and the results will be reviewed by the investigator. The panels of laboratory tests to be performed are shown below:

Hematology: As of implementation of Protocol Amendment 6, monthly hematology assessment, consisting of a complete blood count, is advised.

Clinical Chemistry: As of implementation of Protocol Amendment 6, clinical chemistry assessments may be performed according to local standard of care per Investigator.

Urinalysis: As of implementation of Protocol Amendment 6, urinalysis may be performed according to local standard of care per Investigator.

Serum ß-hCG Pregnancy Test: For women of childbearing potential only. Serum pregnancy to be performed ≤ 3 days prior to first dose of rucaparib, ≤ 3 days prior to Day 1 of every cycle from Cycle 2 and beyond, and at End of Treatment.

Laboratory reports should be reviewed by the investigator or delegated physician who will assess clinical significance.

9.6.4.3 Vital Signs

As of implementation of Protocol Amendment 6, vital signs may be performed according to local standard of care per Investigator.

9.6.4.4 12-Lead Electrocardiograms

As of implementation of Protocol Amendment 6, ECGs will no longer be performed.

9.6.4.5 Body Weight and Height

As of implementation of Protocol Amendment 6, body height and weight assessments will no longer be performed.

9.6.4.6 Physical Examinations

As of implementation of Protocol Amendment 6, physical examinations will no longer be performed.

9.6.4.7 ECOG Performance Status

As of implementation of Protocol Amendment 6, ECOG performance status assessments will no longer be performed.

9.6.5 Efficacy Evaluations

9.6.5.1 Tumor Assessments

As of implementation of Protocol Amendment 6, tumor assessments will be performed per institutional standard of care during treatment and post-treatment (if patient discontinued treatment for any reason other than radiologically confirmed disease progression) until radiologically confirmed disease progression, death, initiation of subsequent treatment, or study closure by the sponsor. Tumor assessments should be done according to local standard of care per Investigator. Tumor response will be interpreted using RECIST Version 1.1 (Appendix B).

Tumor assessments may consist of clinical examination and appropriate imaging techniques (CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. If a patient has known brain metastases, this disease should be evaluated at each required assessment. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. Investigators should perform scans of the anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status.

Copies of CT scans will be collected from all patients in Part 2 of the study and may be collected from selected patients in Part 1 of the study. Independent radiology review may be conducted on all or a subset of CT scans.

9.6.5.2 Tumor Markers

CA-125 will be collected at Screening, on Day 1 of every cycle, at the End of Treatment visit, and as clinically indicated.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered a pharmaceutical product. The pharmaceutical product does not necessarily have a causal relationship with the AE. 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.

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/SAE.

It is the responsibility of the investigator to monitor all AEs that occur during the study. AEs should be elicited by asking the patient a nonleading question (e.g., "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). SAEs/AESIs will be reported on the AE eCRF. Symptoms reported spontaneously by the patient that meet seriousness criterion during the physical examination will also be documented on the AE eCRF.

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (including after informed consent is given and prior to dosing if deemed related to a protocol-mandated procedure) that:

- Results in death. Any event resulting in death during the reporting period (from date of first dose of study drug through 28 days after last dose) must be treated as an SAE and reported as such.
- Is immediately life-threatening (i.e., the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly or birth defect.
- Is an important medical event based upon appropriate medical judgment; it may jeopardize the patient or may require intervention to prevent one of the other outcomes noted above.

10.3 Definition of an Adverse Event of Special Interest (AESI)

An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., health authorities or ethics committees) might also be warranted.

Details on the sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib Investigator's Brochure. These AESIs are to be reported to the sponsor within 24 hours (see Section 10.8 for reporting instructions).

10.4 Exceptions to Serious Adverse Event Reporting

The following are not considered SAEs and therefore are not required to be reported to the Sponsor:

- Pre-planned or elective hospitalization, including social and/or convenience situations (e.g., respite care).
- Hospital visits of less than 24 hours duration (e.g., patient presents to the emergency room, but is not admitted to a ward).
- Overdose of study drug or concomitant medication, unless there is an associated SAE (e.g., hospitalization), as a direct consequence of the overdose. The accompanying SAE should be reported and overdose should be described in the report.
- 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/SAE.

10.5 Pregnancy or Drug Exposure During Pregnancy

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

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

All pregnancies should be followed through to outcome whenever possible. Once the outcome of a pregnancy is known, the Clinical Pregnancy Outcome Report form should be completed and submitted to the Sponsor.

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

All SAEs/AESIs will be fully documented on the appropriate eCRF. For each SAE/AESI, the Investigator must provide duration (start and end dates or ongoing), intensity, relationship to study drug, and indicate whether specific action or therapy was required.

Any SAE/AESI that occurs through 28 days after last dose of study drug administration will be collected, documented and reported to the Sponsor by the Investigator according to the specific definitions and instructions detailed within this protocol. After the 28-day window, only SAEs assessed as related to study drug and all AESI, irrespective of causality, should be reported. If a patient is determined to be a screen failure, no further AEs/ SAEs are required to be reported once that determination has been made, with the exception of AEs/SAEs deemed related to a protocol-specified procedure.

In order to avoid vague, ambiguous, or colloquial expressions, the SAE 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 SAE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

All SAEs/AESIs, regardless of relationship to study drug, must be reported to the Sponsor/designee within 24 hours of the Investigator's knowledge. This should be done by faxing or emailing the completed SAE/AESI report to the Sponsor/designee contact provided on the SAE/AESI report form.

Investigators must follow patients with SAEs/AESIs until the event has resolved or the condition has stabilized. If the patient is lost to follow-up with an ongoing SAE, this should be captured accordingly on a follow-up SAE report.

10.6.1 Intensity of Serious Adverse Events

Severity refers to the intensity of an SAE. The severity of each SAE will be categorized using the NCI CTCAE, Version 4.0 (http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).[53]

Severity is not the same as Serious

For any term that is not specifically listed in the CTCAE, intensity should be assigned a grade of 1-5 using the following CTCAE guidelines:

- Mild (Grade 1): mild or asymptomatic symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (Grade 2): limiting age-appropriate instrumental activities of daily living; minimal, local or noninvasive intervention indicated
- Severe (Grade 3): limiting self-care activities of daily living; hospitalization indicated

- Life threatening (Grade 4): life-threatening consequences; urgent intervention indicated
- Fatal (Grade 5): results in death

10.6.2 Causal Relationship of Serious Adverse Events to Investigational Product

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

Not Related To Study Drug	An SAE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medication, disease under study, etc.) An SAE that does not follow a reasonable temporal sequence from administration of the study drug. An SAE that does not reappear or worsen when study drug is restarted. An SAE for which an alternative explanation is likely, but not clearly identifiable.
Related to Study Drug	An SAE that is difficult to assign to alternative causes. An SAE that follows a strong or reasonable temporal sequence from administration of study drug. An SAE that could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. An SAE that is confirmed with a positive rechallenge or supporting laboratory data.

10.6.3 Outcome

The investigator will record the outcome for each SAE/AESI according to the following criteria:

Outcome

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Improving
- Ongoing
- Death
- Unknown/Lost to follow-up

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

All SAEs and AESIs occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 28 days after the last dose of study drug. Any SAE or AESI must be followed until resolution or stabilization, or until lost to follow-up. After the 28-day window, treatment-related SAEs and all AESIs, irrespective of causality, need to be reported.

10.8 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria,[52] must be reported as SAEs (see Section 10.9 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.

10.9 Regulatory Aspects of Serious Adverse Event Reporting

All SAEs and AESIs, regardless of relationship to study drug, and pregnancy must be reported to the Sponsor's SAE designee within 24 hours of knowledge of the event, according to the procedures below. After the 28-day specified window, only SAEs considered to be treatment-related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE to study treatment at the time of the initial report. The SAE/AESI Report Form must be used for reporting SAEs and AESIs. The contact information for reporting of SAEs can be found on the SAE/AESI Report Form. The Pregnancy Report Form must be used for reporting pregnancies.

Clovis Oncology, Inc. (Clovis Oncology), or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to 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 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), Clovis Oncology 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.

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

11 STATISTICAL METHODS

11.1 Analysis Populations

The following analysis populations are defined for the study:

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

Efficacy Population – The efficacy population will consist of all patients evaluable for response by RECIST (Appendix B) and/or GCIG CA-125 criteria (Appendix E). Patients evaluable for a RECIST response must have at least one measureable target lesion at baseline and at least one post-baseline tumor assessment. Patients evaluable for GCIG CA-125 response must have 2 pretreatment CA-125 values at least twice the upper limit of normal and at least 2 post-baseline values.

11.2 Statistical Methods

11.2.1 General Considerations

Data will be summarized separately for Parts 1 and 2 and may also be pooled as appropriate.

The summary tables will be presented for all treated patients and by the subgroups defined by HRD status.

Quantitative variables will typically be summarized using frequencies and percentages for appropriate categorizations and may also be summarized using descriptive statistics. For variables summarized with descriptive statistics, the following will be presented: N, mean, standard deviation, median, minimum and maximum. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier methodology will be used to summarize time-to-event variables. If estimable, the 25th, 50th (median), and 75th percentiles will be presented along with the Kaplan-Meier estimates of event rates at 6-month intervals. The number of patients with events and the number of censored patients will also be presented.

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

All statistical analyses will be conducted with the SAS® System, version 9.3 or higher.

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

11.2.2 Patient Disposition

Patient disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency counts, and the corresponding percentages.

11.2.3 Baseline Characteristics

All demographic and baseline characteristics will be summarized for the safety population.

The following variables will be summarized with frequency tabulations:

- Time since diagnosis (months): > 6-12, > 12-24, > 24;
- Baseline laboratory parameters: graded based on CTCAE;

Descriptive statistics may also be used to summarize these variables.

11.2.4 Efficacy Analyses

All primary and secondary efficacy evaluations will be presented by HRD status and study part (Part 1 or Part 2). Data may also be pooled across HRD status or Parts 1 and 2 as appropriate. Analyses of PFS will be presented for the safety population and ORR and CA-125 response rates will be presented for the appropriate subset of the efficacy evaluable population.

11.2.4.1 Primary Efficacy Analyses

Part 1: The primary efficacy endpoint of PFS will be calculated as 1+ the number of days from the first dose of study drug to disease progression, as determined by the investigator or death due to any cause, whichever occurs first, in molecularly defined subgroups. Patients without a documented event of progression will be censored on the date of their last adequate tumor assessment (i.e., radiologic assessment) or date of first dose of study drug if no tumor assessments have been performed.

Part 2: The primary efficacy endpoint of ORR is defined as the proportion of patients with a best response of CR or PR using RECIST v1.1 (Appendix B) as assessed by the Investigator. The ORR will be summarized with frequencies and percentages in the efficacy population.

Independent radiology review may also be performed as a supportive analysis for all or a subset of patients. The supportive analysis of ORR by independent radiology review (irrORR) is defined as the proportion of patients with a best response of CR or PR using RECIST v1.1 (Appendix B) as assessed by independent radiology review.

11.2.4.2 Secondary Efficacy Analyses

11.2.4.2.1 Objective Response Rate (ORR) (Part 1)

ORR is defined as the proportion of patients with a best response of CR or PR using RECIST v1.1 (Appendix B) as assessed by the Investigator. The ORR will be summarized with frequencies and percentages.

As a supportive analysis, the ORR will also be evaluated in the safety population. Patients who are not evaluable for a RECIST response will be considered to have experienced disease progression.

Independent radiology review may also be performed as a supportive analysis. The supportive analysis of ORR by independent radiology review (irrORR) is defined as the proportion of patients with a best response of CR or PR using RECIST v1.1 (Appendix B) as assessed by independent radiology review. The irrORR will be evaluated in the efficacy population for patients with measurable disease per the independent radiology review.

11.2.4.2.2 Duration of Response

The duration of response is measured from the time measurement criteria are met for CR/PR per RECIST or a 50% response in CA-125 (whichever is first recorded) until the first date that recurrent or PD is objectively documented using the earliest of the RECIST or CA-125 response.

The duration of response will also be evaluated separately for CR/PR RECIST responses and for CA-125 responses. In addition, the duration of overall CR will be measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

The duration of response will be summarized with descriptive statistics. Only patients with a response will be included in the summary.

11.2.4.2.3 ORR Assessed by RECIST and GCIG CA-125 Criteria

The endpoint of ORR defined as a best response of CR or PR using RECIST (Appendix B) will be summarized with frequencies and percentages in the appropriate efficacy population.

The endpoint of CA-125 response rate defined as a 50% reduction in CA-125 as assessed by GCIG criteria will be summarized with frequencies and percentages in the safety population. As a supportive analysis, the CA-125 response rate will also be evaluated in the patients evaluable for a CA-125 response as defined in Appendix E.

ORR will be reported separately and together for RECIST and GCIG. The combined ORR will be assessed as indicated in Table 5.

Table 5 Overall Response by RECIST[54] and GCIG CA-125 Criteria[55]		
RECIST Response	**GCIG CA-125 Response**	**RECIST + GCIG CA-125 Combined**
CR (requires normalization of CA-125)	CA-125 within normal range	Response
PR	Response	Response
PR	No Response	Response
SD	Response	Response
SD	No Response	No Response
PD	Response	No Response
PD	No Response	No Response

11.2.4.2.4 Overall Survival (Part 2)

Overall survival (OS) is defined as the number of days from the date of first dose of study drug 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.

11.2.4.3 Exploratory Efficacy Analyses

Statistical analysis of exploratory endpoints will be detailed in the Statistical Analysis Plan.

11.2.4.4 Diagnostic Test

The predictive utility of the HRD diagnostic test will be evaluated by comparing the primary and secondary endpoints in the t*BRCA* subgroup to that of nbHRD subgroup and the biomarker negative subgroup.

11.2.5 Pharmacokinetic Analyses

As a secondary endpoint of the study, trough (C_{min}) concentrations of rucaparib will be summarized with descriptive statistics overall and by cycle in all patients with at least one PK sample collected.

11.2.6 Safety Analyses

The safety analyses will be performed using the safety population (all patients who have received at least one dose of rucaparib).

11.2.6.1 Adverse Events

Adverse events will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE whenever possible. Treatment-emergent adverse events (TEAEs) are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days. Adverse events will be considered treatment-emergent if all or part of the date of onset of the adverse event is missing and it cannot be determined if the adverse event meets the definition for treatment-emergent.

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

Separate tables will be presented as follows:

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

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

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

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

11.2.6.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will be presented in SI units. The on-treatment period will be defined as the time from enrollment to 28 days after the last dose of study drug. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

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

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 (i.e., those that meet Grade 3 or 4 criteria according to CTCAE Version 4.0).

11.2.6.3 Vital Sign Measurements

The on-treatment period will be defined as the time from enrollment to 28 days after the last dose of study drug. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

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

11.3 Interim Analyses

No formal statistical interim efficacy analyses for the purpose of stopping early or altering the the sample size will be performed in this open-label study.

A formal safety data review will occur after the first 20 patients have been enrolled, then quarterly until Part 1 of the study is fully enrolled, and then every 6 months thereafter until all patients are enrolled and have participated in the study for at least 6 months or discontinued prior to 6 months, at which point safety reviews will occur on an as-needed basis. The review committee will include external experts and Sponsor personnel. The external experts will include, but not be limited to, the coordinating PIs of the study (Dr. Elizabeth Swisher at Univ. of Washington and Dr. Iain McNeish at Imperial College London). Clovis reviewers will include the Medical Monitor, Chief Medical Officer, Head of Pharmacovigilance, and Biostatistician. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review.

11.4 Sample Size Considerations

The total enrollment planned for this study is approximately 480 patients, N=180 in Part 1 and up to N=300 in Part 2.

Part 1: It is anticipated that approximately 180 patients will be required in order to ensure each subgroup of patients (tBRCA, nbHRD, and biomarker negative) will contain an adequate number of patients. Other than the cap on patients with a known deleterious *gBRCA* mutation, (n=15), there will be no specific requirement to enroll defined numbers of patients into each planned subgroup. The likely size of each subgroup has been estimated based on: a) frequencies of HRD-associated genetic abnormalities at initial diagnosis as reported in the literature and b) the hypothesis that the inclusion criterion of sensitivity to platinum following the most recent line of platinum therapy will enrich the population for patients with tumors harboring mutations of HRD pathway genes (i.e., that the frequency will be greater than that described in the newly-diagnosed population). Table 6 provides estimated HRD subgroup sizes in Part 1 of this trial.

Table 6 Estimated HRD Subgroup Sizes[a]

HRD Subgroup	Expected Frequency at Diagnosis	Estimated Frequency with Enrichment for Platinum Sensitivity	Estimated Number of Patients
tBRCA	21%	30%	15 with known deleterious *gBRCA* mutation (fixed) ***plus*** 20 – 25 with somatic *BRCA* mutation ***plus*** 5 – 25 additional with newly diagnosed *gBRCA* mutation
nbHRD	22 – 32%	30 – 50%	50 – 90
Biomarker Negative	60 – 70%	20 – 40%	36 – 72

[a]Expected frequency estimates are from TCGA[3]

Enrollment of patients known a priori to harbor a *gBRCA* mutation classified as deleterious (pathogenic), suspected deleterious, or favor deleterious (or the equivalent interpretation of any of these) on the most recent assessment by a testing laboratory will be limited to 15 in Part 1. Fifteen patients with a known *gBRCA* mutation are sufficient to establish that the frequency of *gBRCA* mutation reversions is low. In particular, if none of the 15 patients with a known *gBRCA* mutation is shown to have a reversion between archival tissue and tumor tissue collected at screening, then the frequency of *gBRCA* reversions is likely less than 20% as the upper bound on the 90% confidence interval (CI) is 18%. Additional patients, previously untested or tested and found to be $gBRCA^{wt}$, may be identified as having a *BRCA* mutation in tumor tissue, therefore the BRCA subgroup will likely contain at least 40 patients.

The benefit of rucaparib is expected to be the greatest in patients in the *tBRCA* subgroup, followed by patients in the nbHRD subgroup, and lowest in patients in the biomarker negative subgroup. This study will provide evidence as to whether the benefit of rucaparib is clinically meaningful in each of these subgroups, and particularly in the nbHRD subgroup.

With a total of 180 patients enrolled in Part 1 of the study, the comparison of any 2 subgroups will likely contain about 100 patients. Therefore with 100 patients, there is 80% power at a 2-sided 10% significance level to detect a difference in PFS distributions assuming the hazard ratio between 2 subgroups is 0.50.

Part 2: The objective of Part 2 is to estimate the ORR in each of the HRD subgroups in a more heavily pre-treated patient population (at least 3, but no more than 4, prior chemotherapy regimens). Up to 300 patients will be enrolled in Part 2 of the study in order to enroll at least 80 patients in each HRD subgroup. A total of 300 patients should be sufficient assuming an approximate 33.3% allocation to each HRD subgroup in the enrollment population.
Currently, there are few clinical studies that have prospectively evaluated response to treatment beyond the 3rd-line setting; however, retrospective analyses of patients in 3rd relapse and beyond indicate they have a short PFS (approximately 4-6 months) and OS (approximately 5-6 months).[25] Overall, there is a need for new treatments and alternatives to chemotherapy for heavily pre-treated ovarian cancer patients with advanced, relapsed disease to be explored in prospectively designed trials.

The table below provides 95% CIs for observed response rates ranging from 10 to 60% assuming a total of 80 patients within each HRD subgroup.

Confidence Intervals for Objective Response Rates (ORR)

ORR(%)	[95% CI]
10	4.4, 18.8
20	11.8, 30.4
30	20.3,41.3
40	29.2,51.6
50	38.6, 61.4
60	48.4, 70.8

CI=Confidence intervals of ORR using Clopper-Pearson methodology.[26]

An ORR ≥20% in any subgroup would be worthy of further exploration in that population.

12 PATIENT DISPOSITION

12.1 Patient Discontinuations

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

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative
- Progression of patient's underlying disease
- 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
- A positive pregnancy test at any time during the study
- In addition, the sponsor may discontinue the trial early for any of the reasons noted in Section 13.6.

The sponsor (or designee) should be notified of all study terminations as soon as possible. The date and reason for cessation of rucaparib must be documented in the eCRF and source documents. To the extent possible, the End of Treatment visit procedures should be performed on all patients who receive rucaparib as soon as possible following the last dose of rucaparib. Patients will be followed for 28 (±3) days after the last dose of rucaparib for safety; those with ongoing SAEs will be followed until either resolution or stabilization has been determined. Patients that discontinue treatment due to anything other than disease progression or death will be followed for tumor assessments until radiologic disease progression is confirmed, death or the initiation of new treatment.

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and applicable Standard Operating Procedures, and in compliance with: ICH E6(R2), the Code of Federal Regulations (21 CFR Parts 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.

13.1.1 Regulatory Authority Approvals

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

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

The study will be registered on regionally relevant registries, including www.clinicaltrials.gov, EudraCT, and the Spanish Clinical Studies Registry using the Protocol Registration System. 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).

13.1.2 Independent Ethics Committee/Institutional Review Board

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

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

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

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

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

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

13.2 Confidentiality of Information

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

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

13.3 Patient Informed Consent

All information about the clinical study, including the patient information and the informed consent form, 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 informed consent forms 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 informed consent form, prepared by the investigator with the assistance of the sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the sponsor.

The patient must be provided with the patient information and informed consent form consistent with the study protocol version used and approved by the relevant IEC/IRB. The informed consent form must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their

participation in the study with the investigator concerned. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the informed consent form. A copy of the signed informed consent form will be retained by the patient and the original will be filed in the investigator file unless otherwise agreed.

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

13.4 Study Monitoring

On behalf of Clovis Oncology, a CRO monitor will contact and visit the investigator at the study center prior to the entry of the first patient (unless Clovis or the CRO has worked with the center recently, 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 Clovis Oncology 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 (i.e., 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 (i.e., 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 Clovis Oncology may also contact and visit the investigators and monitor data during the study.

13.5 Case Report Form

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 trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the eCRF should be consistent with the data recorded on the source documents.

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

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

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

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

Clinical data will be entered directly from the source documents.

13.6 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, Clovis Oncology and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

Clovis Oncology 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.
- The sponsor discontinues the development of rucaparib.

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

If the study is terminated prematurely the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The investigators will promptly inform their

IRB/IEC, providing the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

13.7 Modification of the Study Protocol

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

13.8 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, ALCOA-C (attributable, legible, contemporaneous, original, accurate, and complete) 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 informed consent forms, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and Clovis Oncology or its designees. The investigator should have control of and continuous access to the eCRF data.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by Clovis Oncology. 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 Clovis Oncology. Copies of original documents that are used for source document verification should fulfill the ICH E6(R2) requirements for certified copies. Should the investigator wish to assign the study records to another party or move them to another location, Clovis Oncology must be notified in writing of the new responsible person and/or the new location. Clovis Oncology will inform the investigator, in writing, when the trial-related records are no longer needed.

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

13.9 Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of Clovis Oncology and signed by the sponsor's chief medical officer, head of biostatistics, and head of regulatory affairs, or a designee, 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.

13.10 Study Publication

All data generated from this study are the property of Clovis Oncology and shall be held in strict confidence along with all information furnished by Clovis Oncology. 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 Clovis Oncology. Written permission to the investigator will be contingent on the review by Clovis Oncology. Any collaborative publications will be authored in accordance with the applicable guidelines (eg, International Committee of Medical Journal Editors [ICMJE]). Written permission to the investigator will be contingent on the review of the statistical analysis and manuscript/abstract by the sponsor, and will provide for nondisclosure of the confidential or proprietary information. In all cases, the parties agree to submit 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.

13.11 Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by Clovis Oncology. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, SOPs, ICH GCPs, and the applicable regulatory requirements. The investigator and the sponsor may also be subject to an inspection by FDA, EMA, other 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.

13.12 Investigator Oversight

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

The investigator should implement procedures to ensure integrity of the study-related duties, functions performed, and any data generated.

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15 APPENDICES

Appendix A. List of Candidate Genes That May Comprise an HRD Signature

Appendix B. Response Evaluation Criteria in Solid Tumors Criteria

Appendix C. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Appendix D. Examples of Sensitive Clinical CYP Substrates

Appendix E. Gynecological Cancer Intergroup (GCIG) Guidelines for Response by CA-125

15.1 Appendix A

List of Candidate Genes That May Comprise an HRD Signature

Note: this list may be revised prior to initiation of the trial and/or prior to final analysis.

BRCA	nbHRD	
BRCA1	*ATM*	*FANCL*
BRCA2	*ATR*	*FANCM*
	ATRX	*MRE11A*
	BARD1	*NBN*
	BLM	*PALB2*
	BRIP1	*RAD50*
	CHEK1	*RAD51*
	CHEK2	*RAD51B*
	FANCA	*RAD51C*
	FANCC	*RAD51D*
	FANCD2	*RAD52*
	FANCE	*RAD54L*
	FANCF	*RPA1*
	FANCG	
	FANCI	

15.2 Appendix B

Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009) and at http://www.eortc.be/Recist/Default.htm.[54] A short summary is given below.

Measurable Disease:

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

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

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

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

Nonmeasurable Disease:

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

Bone Lesions

Bone lesions, cystic lesion, 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 two lesions per organ and five 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 one or more new lesions is also considered progression.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one 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
NE = Not evaluable.			

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

CT scans are required at screening and every 8 weeks (± 4 days) thereafter. Patients who have been on study at least 18 months, may decrease the frequency of disease assessments to every 16 (±2) weeks. If an initial CR or PR is noted , confirmatory scans must be performed at least 4 weeks later.

Duration of Overall Response

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

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

Duration of Stable Disease

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

15.3 Appendix C

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 (e.g., light house work or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

Karnofsky Performance Status			ECOG Performance Status
General Description	**Score**	**Specific Description**	**Score**
Able to carry on normal activity and to work; no special care needed	100	Normal; no complaints; no evidence of disease	0
	90	Able to carry on normal activity; minor signs or symptoms of disease	1
	80	Normal activity with effort; some signs or symptoms of disease	
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do active work	2
	60	Requires occasional assistance, but is able to care for most of personal needs	
	50	Requires considerable assistance and frequent medical care	3
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance	
	30	Severely disabled; hospital admission is indicated although death no imminent	4
	20	Very sick; hospital admission necessary; active supportive treatment necessary	
	10	Moribund; fatal processes progressing rapidly	
	0	Dead	5

15.4 Appendix D

Examples of Sensitive Clinical CYP Substrates

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

[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 Drug-drug interaction (DDI) studies.

Source: Draft FDA Guidance on Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications, 2017.[56] More example drugs can be found at the FDA's website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

15.5 Appendix E

Modified Gynecological Cancer Intergroup (GCIG) Guidelines for Response Using CA-125

Adapted from Rustin et al., Int J Gynecol Cancer. 2011[55]

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

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

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

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

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

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

In patients who have measureable disease by RECIST v1.1 and CA-125, the date of response will be the date of the earlier of the two events. When assessing progression, the objective change in tumor size should be used for treatment decisions. For example, if a patient has a reduction in measurable disease, but an increase in CA-125 that suggests progression, treatment should continue.