A Phase II Study of Rucaparib Monotherapy in Nonmetastatic, Hormone-Sensitive Prostate Cancer Demonstrating "BRCAness" Genotype (ROAR)

CTO ID # HCI-17-GU-24 – Lead Trial ID # HCI111833 – NCT03533946

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NCT Number *(CT.gov)*	NCT03533946

Drug Manufacturer Protocol ID	338-IIT-086
Investigational agent	Rucaparib
IND Number	Exempt

Historical Protocol Versions

Version 1: 28JUN2018

Version 2: 12SEP2018

Version 3: 19MAR2019

Version 4: 29JAN2020

Version 5: 26MAR2021

Version 6: 09JUL2021

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group

Abbreviation or Term[1]	**Definition/Explanation**
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level

Abbreviation or Term[1]	**Definition/Explanation**
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	A Phase II Study of Rucaparib Monotherapy in Nonmetastatic, Hormone-Sensitive Prostate Cancer Demonstrating "BRCAness" Genotype.
Short Title	**R**ucaparib Nonmetastatic pr**O**st**A**te with B**R**CAness **(ROAR)**
Protocol Number	IRB# 111833
IND	Exempt
Phase	Phase II
Design	This is a single arm, open label, phase II trial to assess efficacy of rucaparib.
Study Duration	Expected enrollment duration is 12 months, patients will remain on study treatment until PSA progression defined by PCWG3[22]. We estimate 2-3 years for total study duration.
Study Center(s)	This study will be conducted at the Huntsman Cancer Institute.
Objectives	**Primary Objective:** To assess PSA progression free survival (PSA-PFS) . Patients will have PSA values measured every month. **Secondary Objectives** 1. To assess the safety of rucaparib. 2. To assess the proportion of patients with a 50% reduction in PSA levels (PSA50) compared to the baseline value 3. To assess the proportion of patients with an undetectable PSA after initiation of PARP therapy.
Number of Subjects	15 evaluable subjects will be enrolled
Diagnosis and Main Eligibility Criteria	1. Histologically proven adenocarcinoma of the prostate with BRCAness (defined as an alteration in one or more of the following genes: BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, NBN, PALB2, RAD51C, RAD51D, RAD51, RAD51B based on soft tissue or liquid biopsy. 2. Rising PSA without radiographic evidence of metastatic disease and with PSA doubling time of ≤10 months. 3. ECOG/Zubrod score of 0-2. 4. Subject must not have received any prior systemic therapy for prostate cancer *unless used in the context of definitive treatment for prostate cancer*. Patients may have not received ADT treatment for longer than 24 months.
Study Product, Dose, Route, Regimen	Rucaparib 600mg orally twice daily No patients will be on ADT therapy either by surgical castration or with GnRH agonist or antagonist or on androgen synthesis blocker or androgen receptor antagonists during the study period.
Duration of administration	Subjects will remain on study treatment until unacceptable toxicity, PSA progressive disease (unless they meet the criteria for continued treatment post-progression as defined by section 6.4.1), or patient withdrawal.

Reference therapy	None
Statistical Methodology	Primary Objective: The total sample size is 15 patients. The null hypothesis is that median PSA-PFS is 3 months. With an alternative hypothesis that median PSA-PFS is 12 months, a sample size of 15 provides 90% power at one-sided alpha = 0.05. The proportion of subjects who achieve PSA50 will be reported along with a 95% exact binomial confidence interval. Descriptive analysis methods will be used to analyze tabulated safety characteristics. Kaplan-Meier methods will be used to assess the proportion of patients with an undetectable PSA after initiation of PARP therapy.

1 OBJECTIVES

1.1 Primary Objective and Endpoint

1.1.1 To assess PSA progression-free survival (PSA-PFS).

Endpoint: the levels of PSA will be monitored monthly for comparison to baseline levels until the time of PSA progression, as defined by Prostate Cancer Working Group 3 (PCWG3)[22] criteria (See Appendix B).

1.2 Secondary Objectives and Endpoint

1.2.1 To assess the safety of rucaparib in patients with biochemically recurrent hormone-sensitive prostate cancer.

Endpoint: adverse events will be monitored regularly during patient enrollment and follow up to assess the toxicity of rucaparib using validated CTCAE v5.0 criteria.

1.2.2 To assess the proportion of patients with a 50% reduction in PSA levels (PSA50) compared to the baseline value at the time of study enrollment.

Endpoint: the levels of PSA will be monitored monthly for comparison to baseline levels.

1.2.3 To assess the proportion of patients with an undetectable PSA after initiation of PARP therapy at 6 and 12 months.

Endpoint: the levels of PSA will be monitored monthly for comparison to baseline levels to determine when PSA becomes undetectable.

1.2.4 To evaluate overall survival (OS) in nonmetastatic hormone-sensitive prostrate cancer patients treated with rucaparib.

Endpoint: Subjects will be evaluated for survival using Kaplan-Meier estimation.

1.3 Exploratory Objectives and Endpoint

1.3.1 To evaluate exploratory biomarkers predictive of response and resistance to treatment with rucaparib.

Endpoint: blood and other tissue will be collected at baseline and during treatment to correlate clinical responses with various potentially predictive biomarkers.

1.3.2 To evaluate concordance between PSA-PFS and radiographic progression

Endpoint: levels of PSA will be monitored monthly and compared to the detection of any measureable new lesions by radiographic detection.

2 BACKGROUND

For decades, hormonal therapy using gonadotropin releasing hormone agonists/antagonists or surgical castration have been the first-line treatment in patients with metastatic hormone-sensitive prostate cancer. Androgen deprivation therapy (ADT) has repeatedly been shown to be effective in palliating symptoms and in prolonging survival for patients.[1] This is not curative therapy, so invariably patients will progress on ADT and develop metastatic castration-resistant

prostate cancer. Common practice is to continue with ADT despite progression. All of the subsequent treatments including abiraterone,[2] enzalutamide,[3] chemotherapy[4] and radium[5] have been tested in conjunction with ADT. With improved treatments for metastatic prostate cancer, patients are often surviving longer, with a median overall survival of approximately 5 years for patients with metastatic disease at diagnosis[6] to over 8 years for patients progressing to metastatic disease after definitive local treatment.[7] The long-term adverse effects of continued androgen deprivation therapy are becoming more apparent and clinically important with improved disease control. ADT increases the risk for cardiovascular disease, osteoporosis and metabolic syndrome.[8] Finding treatment strategies that control prostate cancer and delay ADT use can further improve the care of patients with prostate cancer by both directly controlling metastatic disease progression, and preventing the health complications of long-term ADT use.

Prostate cancer patients with DNA repair defects are an important population of prostate cancer. A common term used for these genomic alterations associated with DNA repair gene defects is "BRCAness".[9] The estimated incidence of BRCAness is 12-19% in prostate cancer.[10,11] This population generally has more aggressive disease and therefore a worse overall prognosis compared to men without BRCAness. Men with BRCAness prostate cancer often get diagnosed with prostate cancer earlier, and develop metastatic disease earlier compared to those who do not harbor BRCAness. Furthermore, BRCAness may portend a poor prognosis, including a poor overall survival.[12,13] The risk of disease progression to metastatic disease is significant in patients with BRCAness prostate cancer. The percentage of BRCAness patients free from metastatic disease was 90%, 72%, and 50% at 3, 5, and 10 years, respectively, compared to 97%, 94%, and 84% at 3, 5 and 10 years for patients with intact DNA repair ($p < 0.001$).[14]

Treatment using PARP inhibitors along with ADT in this population has demonstrated significant clinical activity.[15] In the seminal study, 50 patients with castration-resistant prostate cancer were enrolled regardless of BRCAness status and treated with olaparib, a PARP inhibitor. These patients were resistant to many prior therapies including docetaxel, abiraterone, or enzalutamide and many had been treated with cabazitaxel as well. 49 patients were evaluable for response. Sixteen patients demonstrated a response, including 4 patients with a durable response (treatment ≥ 12 months). 16 of the 49 patients were positive for BRCAness. 14 out of the 16 (88%) biomarker-positive patients had a composite response to olaparib, rather than a RECIST evaluable response. Only 2 of 33 (6%) biomarker-negative patients experienced a response. This strongly suggests significant clinical activity of PARP therapy in patients with BRCAness.

Given debilitating physical and psychological side effects of ADT in relatively younger men with BRCAness prostate cancer, delaying ADT in these men may be an attractive strategy. Given the proven efficacy of PARP inhibitors in the CRPC setting, PARP inhibitor monotherapy has the potential to result in PSA responses, and delay onset of metastatic disease.

We hypothesize that treatment with PARP inhibitor monotherapy in men with high risk biochemically recurrent prostate cancer (i.e., PSA only relapse with no radiographic evidence of disease with a PSA doubling time of < 9 months) will result in acceptable disease control in terms of PSA response, allow delay of androgen deprivation therapy, and delay the onset of metastasis.

3 DRUG INFORMATION

3.1 Rucaparib

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

Clovis Oncology, Inc. (Clovis) is developing rucaparib for oral administration in patients with advanced ovarian cancer and metastatic castration-resistant prostate cancer (mCRPC) associated with HRD, including patients with a deleterious mutations in BRCA1, BRCA2, and other HR gene mutations.

3.1.1 Summary of Nonclinical Experience with Rucaparib

An overview of data from nonclinical and clinical studies with rucaparib are summarized below. Further detail is provided in the most recent rucaparib Investigator's Brochure (IB).

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

In pharmacokinetic (PK) studies, rucaparib demonstrated species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier.

In vitro data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and dogs. In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UDP-glucuronosyltransferase 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion protein 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1), and may inhibit P-gp and BCRP in the gut.

Oral dosing of rucaparib in single and repeat dose toxicity studies in rats and dogs resulted in toxicity to the hematopoietic, lymphopoietic, and gastrointestinal systems. These toxicities were generally both reversible upon recovery and predictive of toxicities observed in patients. Rucaparib was shown to be clastogenic in an in vitro chromosomal aberration assay suggesting potential genotoxicity in humans. Reproductive and development toxicity studies

in rat showed that rucaparib caused maternal toxicity and was embryo-toxic. Although no rucaparib related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility.[17-20]

3.1.2 Summary of Clinical Experience with Rucaparib

Rucaparib has been evaluated in Phase 1 and 2 clinical studies and is being evaluated in ongoing Phase 2 and Phase 3 clinical studies. The early clinical program assessed safety and efficacy of rucaparib in patients with malignancies commonly treated with chemotherapeutic agents.

Initially, an intravenous [IV] formulation of rucaparib was administered in combination with a variety of chemotherapies; later, the oral formulation of rucaparib was administered in combination with chemotherapy and as a monotherapy. The oral formulation as monotherapy is the focus of current development efforts. The IV formulation is no longer in use.

Four studies (A4991002, A4991005, A4991014, CO-338-023 [RUCAPANC]) have been completed and 8 studies (CO-338-010, CO-338-014 [ARIEL3], CO-338-017 [ARIEL2], CO-338-044 [DDI], CO-338-043 [ARIEL4], CO-338-045 [ADME], CO-338-052 [TRITON2], and CO-338-063 [TRITON3]) are ongoing.

Details of all completed, ongoing, and planned studies are described briefly below. Additional information is provided in the rucaparib IB.

Completed Studies

- A4991002: a Phase 1 open-label, dose-escalation study of IV rucaparib in combination with temozolomide (TMZ) in patients with advanced solid tumors (Part 1) or malignant melanoma (Part 2).
- A4991005: a Phase 2, open-label study of IV rucaparib in combination with TMZ in patients with metastatic melanoma.
- A4991014: a Phase 1, open-label, dose-escalation study of IV and oral rucaparib administered with different chemotherapeutic agents in patients with an advanced solid tumor.
- CO-338-023 (RUCAPANC): a Phase 2, single-arm, open-label study of monotherapy oral rucaparib as treatment for patients with previously treated locally advanced or metastatic pancreatic ductal adenocarcinoma and a known deleterious BRCA mutation.

Ongoing Studies

- CO-338-010: 3-part, open-label, Phase 1/2 study of monotherapy oral rucaparib.
  - Part 1: a Phase 1 portion evaluating PK and safety of escalating doses of rucaparib in patients with solid tumors; this portion identified 600 mg twice daily (BID) as the recommended starting dose for future studies (n = 56; completed).
  - Part 2: a Phase 2 portion evaluating the efficacy and safety of rucaparib in patients with relapsed, high-grade ovarian cancer associated with a BRCA mutation.

        - Part 2A enrolled patients with a gBRCA mutation who had received 2 to 4 prior treatment regimens (n = 42; enrollment complete).
        - Part 2B enrolled patients with a gBRCA or sBRCA mutation who received at least 3 prior chemotherapy regimens (n = 9 as of the 27 June 2016 cut-off date [closed to enrollment on 1 July 2016]).
    - Part 3: a Phase 2 portion in patients with a relapsed solid tumor associated with a BRCA mutation in order to characterize the PK, food effect, and safety profile of a higher dose strength tablet (n = 26; enrollment complete).

- CO-338-017 (ARIEL2): a 2-part open-label Phase 2 study of monotherapy oral rucaparib for treatment of relapsed, high-grade ovarian cancer patients. It is designed to identify tumor characteristics that may predict sensitivity to rucaparib. Patients will be classified into molecularly-defined subgroups, including tumor BRCA (tBRCA, inclusive of both germline and somatic BRCA) and BRCA-like, by a prospectively defined genomic signature.
    - Part 1 enrolled patients with platinum-sensitive, relapsed disease who received ≥ 1 prior platinum regimen (n = 204; enrollment complete).
    - Part 2 is enrolling patients with relapsed disease who received at least 3 prior chemotherapy regimens (n = 262 as of the 27 June 2016 cut-off date [closed to enrollment on 29 July 2016]).

- CO-338-014 (ARIEL3): a Phase 3, randomized, double-blind study of monotherapy oral rucaparib versus placebo as switch maintenance treatment in patients with platinum-sensitive-, relapsed, high-grade ovarian cancer who achieved a response to platinum-based chemotherapy (n = 560 as of the 27 June 2016 cut-off date [closed to enrollment on 19 July 2016]).

- CO-338-044 (DDI study): a 2-part, Phase 1, open-label, multiple-probe drug-drug interaction (DDI) study to determine the effect of rucaparib on PK of caffeine, S-warfarin-, omeprazole, midazolam, and digoxin in patients with advanced solid tumors in Part 1, followed by optional continued treatment with rucaparib in Part 2 (n = 5; enrollment ongoing).

- CO-338-043 (ARIEL4): a phase 3 study evaluating rucaparib versus chemotherapy as treatment for patients with relapsed high-grade ovarian cancer associated with a deleterious BRCA1/2 mutation

- CO-338-045 (ADME): a 2-part open-label Phase 1, single-dose study of the disposition of [14C]-radiolabel rucaparib in patients with advanced solid tumors, with the option to continue rucaparib therapy.

- CO-338-052 (TRITON2): a Phase 2 study evaluating rucaparib efficacy in mCRPC whose tumors are associated with HRD by enrolling mCRPC patients with mutations in BRCA1/2, ATM, or other HR genes. All patients will be required to have progressed on prior AR-targeted therapy (abiraterone acetate, enzalutamide, or investigational AR-targeted agent) and also have progressed after one prior taxane-based chemotherapy for mCRPC.

- CO-338-063 (TRITON3): a Phase 3, randomized, 2-arm study evaluating rucaparib vs. physician's choice (abiraterone acetate, enzalutamide or docetaxel) in patients with mCRPC associated with a deleterious BRCA1/2 or ATM mutation (n = ~300).

3.1.3 **Overview of Clinical Pharmacokinetics**

Assessment of rucaparib PK in cancer patients showed an approximate dose-proportional exposure after once daily (QD) or BID dosing, rapid absorption with maximum plasma concentration (C_{max}) achieved within 1.5 to 6 hours, and distribution into tissue. The oral bioavailability was 36% and terminal half-life ($T_{1/2}$) ranged from 9.23 to 33.6 hours. Rucaparib was moderately bound to human plasma proteins in vitro.

At a dose of 600 mg BID rucaparib, steady-state was achieved after approximately 1 week. At the target clinical dose of 600 mg, a high-fat meal increased the C_{max} and area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24h}) of rucaparib by 20% and 38%, respectively, and delayed the median time to occurrence of C_{max} (T_{max}) by approximately 2.5 hours as compared with these parameters under fasted conditions. The effect of food on rucaparib PK is not considered to be clinically significant, thus rucaparib can be taken with or without food.

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

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

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

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

3.1.4 **Overview of Efficacy**

An overview of data are provided below and described in detail in the rucaparib IB.

Efficacy analysis was based on pooled efficacy data from 106 patients with BRCA mutant ovarian cancer, who received two or more prior chemotherapy regimens, and who initiated treatment with rucaparib at 600 mg BID in Part 2A of Study CO-338-010 and Parts 1 and 2 of Study CO-338-017. The enrollment cut-off date was 1 October 2015 (all 42 patients enrolled) and the visit data cut-off date was 30 November 2015 for Study CO-338-010 Part 2A. The enrollment cut-off was a 1 October 2015 and the visit data cut-off was 29 February 2016 for Part 1 (24 patients) and Part 2 (40 patients) of Study CO-338-017.

Efficacy data indicate that many patients with advanced ovarian cancer associated with a BRCA1/2 gene mutation and who had two or more prior therapies achieve RECIST and/or GCIG cancer antigen 125 (CA125) responses. The confirmed objective response rate (ORR) per RECIST by investigator review was 53.8% (57/106) and the confirmed response by RECIST or GCIC CA-125 was 70.8% (75/106). The confirmed ORR per RECIST by independent review was 41.5% (44/106). In addition, patients without a BRCA1/2 gene mutation in tumor tissue are also deriving benefit, with 43% achieving RECIST and/or GCIG CA-125 responses. Three mCRPC patients with a BRCA mutation received rucaparib monotherapy in Study CO-338-010 or under named patient access, most of whom experienced tumor stabilization, decrease of PSA levels, and symptom improvement.

3.1.5 **Overview of Safety**

Pooled safety data in the treatment setting are provided as of the 01 September 2017 cut-off date for the ongoing Studies CO-338-010 (Parts 2A and 2B) and CO-338-017 (ARIEL2; Parts 1 and 2), in which 545 patients with relapsed ovarian cancer received 600 mg BID rucaparib. Safety data in the maintenance setting are provided as of the 15 April 2017 cut-off date for Study CO-338-014 (ARIEL3), in which a total of 561 patients have been treated (372 patients in the rucaparib group and 189 patients in the placebo group). Pooled safety data from the treatment setting as well as safety data in the maintenance setting are presented in Table 3.1

Patients with ovarian cancer who received 600 mg BID rucaparib in pooled Studies CO-338-010 (Parts 2A and 2B) and CO-338-017 (Parts 1 and 2) (treatment setting), as well as in Study CO-338-014 (maintenance setting), the most common TEAEs reported were primarily mild to moderate (Grade 1-2) in severity and include gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, decreased appetite, and dysgeusia. The most common TEAE ≥ Grade 3 include anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased ANC, and asthenia/fatigue.

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

Table 3.1: Incidence of TEAEs (all causality; all grades and ≥ Grade 3) reported in ≥ 20% of patients - safety population

Preferred Term	Treatment Setting Pooled Studies CO-338-010 (Parts 2A and 2B) and CO-338-017 (ARIEL2 Parts 1 and 2)[a]		Maintenance Setting Study CO-338-014 (ARIEL3)[b]			
	600 mg BID Rucaparib (N = 545) n (%)		600 mg BID Rucaparib (N = 372) n (%)		Placebo (N = 189) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Nausea	428 (78.5%)	29 (5.3%)	280 (75.3%)	14 (3.8%)	69 (36.5%)	1 (0.5%)
Asthenia/fatigue[c]	409 (75.0%)	64 (11.7%)	258 (69.4%)	25 (6.7%)	83 (43.9%)	5 (2.6%)

Vomiting	250 (45.9%)	23 (4.2%)	136 (36.6%)	15 (4.0%)	28 (14.8%)	2 (1.1%)
Anemia/decreased hemoglobin	240 (44.0%)	132 (24.2%)	139 37.4%)	39 (10.5%)	11 (5.8%)	1 (0.5%)
ALT/AST increased[c]	214 (39.3%)	59 (10.8%)	126 (33.9%)	39 (10.5%)	7 (3.7%)	0
Decreased appetite	209 (38.3%)	16 (2.9%)	87 (23.4%)	2 (0.5%)	26 (13.8%)	0
Constipation	205 (37.6%)	8 (1.5%)	136 (36.6%)	7 (1.9%)	45 (23.8%)	2 (1.1%)
Dysgeusia	200 (36.7%)	1 (0.2%)	146 (39.2%)	0	13 (6.9%)	0
Abdominal pain	177 (32.5%)	22 (4.0%)	111 (29.8%)	9 (2.4%)	49 (25.9%)	1 (0.5%)
Diarrhea	176 (32.3%)	11 (2.0%)	118 (31.7%)	2 (0.5%)	41 (21.7%)	2 (1.1%)
Thrombocytopenia/ decreased platelets[c]	128 (23.5%)	33 (6.1%)	104 (28.0%)	19 (5.1%)	5 (2.6%)	0
Blood creatinine increased	120 (22.0%)	3 (0.6%)	57 (15.3%)	1 (0.3%)	3 (1.6%)	0
Dyspnea	120 (22.0%)	5 (0.9%)	50 (13.4%)	0	14 (7.4%)	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; N or n = number of patients; TEAE = treatment-emergent adverse event.

a. The treatment setting pooled data presented are from the 01 September 2017 cut-off date for the ongoing Studies CO-338-010 (Parts 2A and 2B) and CO-338-017 (ARIEL2; Parts 1 and 2).

b. Safety data in the maintenance setting are provided as of the 15 April 2017 cut-off date for Study CO-338-014 (ARIEL3).

c. Combined MedDRA preferred terms.

Note: Data are presented by decreasing frequency for TEAEs of all grades for the treatment setting pooled data.

The laboratory abnormalities reported in Study CO-338-014 (ARIEL3) were consistent with the TEAEs, with decreased hemoglobin, increased ALT, increased AST, and increased serum creatinine, most common in patients in the rucaparib group. Decreased platelets, neutrophils, leukocytes, lymphocytes, increased alkaline phosphatase and increased cholesterol were observed to a lesser extent.

ALT/AST elevations occurred early in treatment (i.e., by Day 1 of Cycle 2) and then resolved or stabilized over time. Treatment with rucaparib was continued at either the initial 600 mg BID dose or a lower dose. Elevations in ALT/AST were rarely accompanied by a concomitant elevation in bilirubin.., and there have been no cases of Hy's Law attributed to the use of rucaparib. Continued dosing with rucaparib in the presence of Grade 3 ALT/AST elevations is permitted if there are no other signs of liver toxicity.

Creatinine elevations were also observed early in treatment (i.e., by Day 1 of Cycle 2) and then stabilized with continued rucaparib treatment.

3.1.6 **Adverse Events of Special Interest**

A review of all reports of MDS and AML that have occurred in the entire clinical development program up to 10 April 2017 revealed a total of 10 reports in patients exposed to rucaparib in Studies CO-338-010, CO-338-017, and CO-338-014.

The rate of MDS/AML was 0.5% for patients on treatment and during the 28 day safety follow-up, and 0.9% for all patients including during the long-term safety follow-up (rate is calculated based on overall safety population of 1077 patients exposed to at least one dose of oral rucaparib in all clinical studies).

There was one case of AML in 189 patients exposed to placebo in Study CO-338-014.

All of the patients diagnosed with MDS or AML had received multiple cycles and regimens of prior chemotherapy, including platinum- and/or taxane-containing regimens. One patient had also received prior treatment with an alkylating agent (cyclophosphamide) and 2 patients had received radiation for breast cancer (1 patient received rucaparib and 1 received placebo). One patient was discontinued from rucaparib 14 months prior to MDS diagnosis and was treated with olaparib for 13 months between rucaparib discontinuation and MDS diagnosis. One patient discontinued rucaparib 9 months prior to MDS diagnosis and was treated with cisplatin and trabectedin for an unspecified time between rucaparib discontinuation and MDS diagnosis. Exposure to DNA-damaging therapies for ovarian and breast cancer present an increased risk of developing MDS or AML

In patients diagnosed with MDS, duration from start of primary disease treatment to diagnosis was between approximately 1 and 23 months (i.e., 35 days to approximately 693 days). In patients diagnosed with AML, duration from start of primary disease treatment to AML diagnosis was between approximately 3.5 and 28.5 months (i.e., 106 to 868 days). In the patient with MDS that evolved into AML, the duration of time from starting treatment with rucaparib to diagnosis of MDS was approximately 12.5 months (i.e., 380 days) and from start of rucaparib to diagnosis of AML was approximately 18 months (i.e., 541 days).

Nearly every patient who developed MDS/AML reported having experienced multiple/persistent cytopenias prior to the diagnosis of MDS/AML. The cytogenetic abnormalities currently available in 3 of the 4 patients diagnosed with AML were consistent with aberrations (primarily abnormalities in chromosome 5) typically observed in patients with secondary MDS/AML due to prior chemotherapy. One patient who developed both MDS and AML had chromosomal abnormality in chromosome 7.35. The patients who have developed MDS and AML have significant confounding risk factors, including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation presenting a higher risk of developing one or more malignancy (ies).

Based upon the above confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib.

4 STUDY DESIGN

4.1 Description

This is a single arm, open label, phase II trial to assess efficacy of rucaparib.

4.2 Number of Patients

15 evaluable subjects will be enrolled.

4.3 Number of Study Centers

This study will be conducted at Huntsman Cancer.

4.4 Study Duration

Expected enrollment duration is 12 months, patients will remain on study treatment until PSA progression defined by PCWG3 (unless they meet the criteria for continued treatment outlined in section 6.4.1), with 2 years of follow up after study treatment. We anticipate a total of 2-3 years until completion of the clinical trial.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with enrolling investigator's signature in the patient research chart.

Patient No. _____
Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria
Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Hormone-sensitive, histologically proven adenocarcinoma of the prostate with BRCAness (defined as an alteration in one or more of the following genes BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, NBN, PALB2, RAD51C, RAD51D, RAD51, RAD51B) from soft-tissue based genomic testing or liquid biopsy based genomic or genetic testing. Pathogenic or likely pathogenic alterations are accepted.

5.1.2 _____ ECOG/Zubrod score of 0-2.

5.1.3 _____ At a minimum, subjects must have received definitive local therapy with curative intent (i.e., prostatectomy and/or radiation therapy) with or without systemic therapy .

5.1.4 _____ Testosterone level is > 50 ng/dL.

5.1.5 _____ Be at least 18 years old at the time the informed consent form is signed.

5.1.6 _____ Demonstrate adequate organ function as defined in the table below, all screening labs should be performed within 28 days of treatment initiation.

- **Hematologic:**
  - Absolute neutrophil count (ANC) ≥ 1.5 k/µL.
  - Platelets ≥ 100 k/µL.
  - Hemoglobin ≥ 9 g/dL.
- **Hepatic:**
  - Serum total bilirubin ≤ 1.5 times upper limit of normal (× ULN) OR ≤ 2 × ULN for subjects with Gilbert's syndrome.
  - AST or ALT ≤ 2.5 × ULN
- **Renal:**
  - Creatinine < 1.5 × ULN OR
  - Creatinine clearance > 40 mL/min for subject with creatinine levels > 1.5 × ULN.
  - *Note: GFR may also be used in place of creatinine or CrCl*
- **Coagulation:**
  - PT or INR, PTT ≤ 1.5 × ULN

- If on active anticoagulants prior to study treatment, levels must be within standard therapeutic ranges per investigator

5.1.7 _____ Highly effective barrier methods must be used with all sexual activity and contraception methods must be practiced for all subjects throughout the study and for at least 6 months after last rucaparib treatment administration if the risk of conception exists (section 7.2).

5.1.8 _____ Recovery to baseline or Grade ≤ 1 CTCAE v5.0 from toxicities related to any prior treatments within the context of their definitive local therapy for their prostate cancer, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

5.1.9 _____ Subject is able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.1.10 _____ Subject must have confirmed PSA progression based on at least two time points taken at least one week apart to confirm rising trend.

5.2 Exclusion Criteria
Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Subjects with metastases defined by conventional scans (CT, MRI, NM Bone Scan). Disease identified on molecular imaging (e.g., fluciclovine-PET) is not exclusionary.

5.2.2 _____ Arterial or venous thrombi (including cerebrovascular accident), myocardial infarction, admission for unstable angina, cardiac angioplasty, or stenting within the last 90 days prior to screening.

5.2.3 _____ Pre-existing duodenal stent, recent (within ≤ 3 months) or existing bowel obstruction, and/or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib.

5.2.4 _____ Inability to swallow tablets.

5.2.5 _____ Evidence or history of clinically significant bleeding disorder per the determination of the treating investigator.

5.2.6 _____ Prior systemic therapy within the past 30 days prior to Day 1 (or 5 half-lives of the drug, whichever is shorter).

5.2.7 _____ Diagnosis of another malignancy within 2 years before first dose of study treatment only if the cancer will either interfere with patient safety or interfere with the primary endpoint, per the judgement of the Principal Investigator. Patients who have been diagnosed with superficial skin cancers, or localized, low grade tumors deemed cured or with a prolonged natural history (e.g., estimated overall survival > 5 years), may be included.

5.2.8 _____ Prior treatment with any PARP inhibitor, mitoxantrone, cyclophosphamide, or any platinum based chemotherapy.

5.2.9 _____ Clinically significant (i.e., active) cardiovascular disease at the time of enrollment: congestive heart failure (> New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

5.2.10 _____ Other severe acute or chronic medical conditions including cardiovascular, endocrine, neurologic, pulmonary or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

5.2.11 _____Major surgery (e.g., GI surgery, removal or biopsy of brain metastasis) within 8 weeks before first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before first dose and from minor surgery (e.g., simple excision, tooth extraction) at least 28 days before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

6 TREATMENT PLAN

6.1 Administration Schedule

Treatment with rucaparib will begin on Cycle 1 Day 1 and continue daily at 600 mg PO BID. Therapy continues according to criteria in Section 6.4.

All trial treatments will be administered on an outpatient basis.

6.2 Rucaparib Treatment

6.2.1 How Supplied, Stored, Packaged and Labeled

All tablets are provided in high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers between 15 °C and 30 °C (59 °F and 86 °F). Patients will be dispensed one or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 30 days treatment per cycle.

Study drug containers with rucaparib tablets will be labeled according to national regulations for investigational products by the drug manufacturer.

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 by Clovis. A brief description of the investigational product is provided below:

Drug Name	Rucaparib
INN	Rucaparib
Formulation	Tablet; film coated; 200 mg, 250 mg, 300 mg
How Supplied	200, 250, and/or 300 mg strength (based on free base) in high-density polyethylene bottles or equivalent with child-resistant caps. Patients may receive 1 or more strengths. Each bottle contains 60 tablets
Storage Conditions	15–30 °C (59–86 °F)

6.2.2 Preparation and Administration

Daily oral rucaparib at 600 mg BID with 8 oz (240 mL) of room temperature water, taken on an empty stomach or with food. Tablets should be swallowed whole without crushing or chewing.

6.2.3 Accountability and Compliance

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until Day 1 of the next treatment cycle. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next visit.

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

Patients will be instructed to record daily doses taken or not taken in a patient diary. Treatment with rucaparib is continuous and each cycle will comprise 28 days.

All study drugs will be stored at the Huntsman Cancer Institute Investigational Pharmacy in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor, and will be inaccessible to unauthorized personnel. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent.

An adequate record of receipt, distribution, and return of all study drugs must be kept in the form of a Drug Accountability Form. Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

Instructions on medication resupply and destruction will be made available to affected parties as applicable.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Clovis.

6.3 Concomitant Medications

6.3.1 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.

6.3.2 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the *in vivo* CYP interaction study (CO-338-044), rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used in patients on rucaparib taking concomitant medicines that are substrates of CYP1A2, CYP2C9, CYP2C19, and/or CYP3A with narrow therapeutic windows. Examples of such drugs are provided in table 6.1.

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. Selection of an alternative concomitant medication is recommended.

Table 6.1: Examples of CYP substrates with narrow therapeutic range

CYP Enzyme	Substrates with Narrow Therapeutic Range[a]
CYP1A2	Tizanidine, theophylline
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin

CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

The table is based on the Draft FDA Guidance on Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012

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

6.3.3 **Anticoagulants**

Caution should be exercised in patients receiving rucaparib and concomitant warfarin (Coumadin) as rucaparib showed a mixed inhibition of CYP2C9 in vitro. If appropriate, low molecular weight heparin should be considered as an alternative treatment. Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard clinical practice.

6.3.4 **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 increase 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 (e.g., rosuvastatin).

6.3.5 **Photosensitivity**

Patients should use typical precautions when going outside, such as applying sunscreen and/or covering exposed skin with clothing and wearing a hat and sunglasses, as photosensitivity has been observed.

6.4 **Duration of Therapy**

6.4.1 Treatment after PSA Progression

If PSA progression per PCWG3 is demonstrated, patients may continue on study therapy if it is felt by the treating physician to be of clinical benefit to the patient. Study therapy may be continued after PSA progression at the discretion of the treating physician. However, the following criteria must be met:

- No decline in ECOG performance status;
- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression;
- Absence of rapid progression of disease;
- PSA ≤100% increase or absolute increase of 5 ng/mL from baseline value, whichever is greater.
- Absence of progressive tumor at critical anatomical sites (i.e. cord compression) requiring urgent alternative medical intervention.

Before continuation of treatment after initial PD, the patient must be re-consented via informed consent addendum and informed that, by continuing to receive investigational products, the patient may be foregoing approved or investigational therapies with possible clinical benefit(s). Patients should continue to follow all assessments as outlined in the Study Calendar.

Once PSA progression has been documented, disease assessments should continue per the Study Calendar to ensure the above criteria is consistently met.

6.4.2 Criteria for discontinuation of treatment ("off-treatment")

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in Dose Modification Section and the Dose Limiting Toxicity Section, the following will result in treatment discontinuation:

- Unacceptable Toxicity
- Subject withdraws consent from the study treatment and/or study procedures.
- Demonstration of continued non-compliance with protocol requirements as determined by the principle investigator
- Significant protocol violation as determined by the principal investigator
- The patient refused further treatment
- Study terminated
- Lost to follow-up
- Death

- The patient does not meet the criteria for continued treatment post-progression as outlined in section 6.4.1.

6.4.3 Criteria for discontinuation of study ("off study")

Subjects will be taken off study for the following:

- Screen failure.
- If, in the investigator's opinion, the continuation of the trial would be harmful to the subject's well-being.
- Development of intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Participant requests to be withdrawn from the study.
- Subject is lost to follow-up.
- The patient completed the study follow-up period.
- Death.
- Deterioration of ECOG performance status to 4

7 TOXICITIES AND DOSAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting.

7.1 Dose Modifications

The most common effects of rucaparib treatment include gastrointestinal disorders (nausea, vomiting, diarrhea, and constipation), asthenia/fatigue, clinical chemistry elevations (ALT/AST, creatinine, and cholesterol), myelosuppression (decreases in hemoglobin, lymphocytes, platelets, and neutrophils), dysgeusia, and decreased appetite. Modification of rucaparib dose may be a necessary component of AE management, and study specific protocol guidelines for dose modifications should be followed. Dose interruptions, with or without subsequent dose reductions, may help to ameliorate AEs attributed to rucaparib therapy.

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.

7.1.1 Management of anemia including evaluation for MDS/AML and follow-up of patients who discontinue treatment with ongoing anemia

- If the patient develops anemia CTCAE Grade ≥ 3, rucaparib treatment should be held until the anemia improves to CTCAE Grade ≤ 2 whereupon daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion.
- If the duration of dosing is interrupted for > 14 consecutive days due to anemia CTCAE Grade ≥ 3, treatment should be permanently discontinued, unless otherwise agreed between the investigator and Clovis.
- In addition, if anemia CTCAE Grade ≥ 3 persists for > 14 consecutive days, or a dependence upon blood transfusion occurs, then weekly complete blood counts should be performed until resolution of the event.
- If, after 42 days of interruption of rucaparib, the anemia has not improved to CTCAE Grade ≤ 1 then the patient should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice.
- The bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

7.1.2 Management of rucaparib treatment-emergent ALT/AST Elevations

Grade 3 ALT/AST elevations have been successfully treated with treatment interruption and/or a reduction in dose. The data reported as of the data cut-off date suggest that many patients have been able to continue treatment with 600 mg BID following a dose interruption, without any further elevation or recurrence of Grade 3 ALT/AST. The following guidelines have been suggested for managing Grade 3/4 ALT/AST elevations.

- Grade 4 ALT/AST elevations: hold rucaparib until values have returned to Grade 2 or better, then resume rucaparib with a dose reduction. Monitor liver function tests weekly for 3 weeks after rucaparib has been restarted.
- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:
  - Monitor liver function tests weekly until improvement to ≤ Grade 2.
  - Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN and alkaline phosphatase is < 3 x ULN.
  - If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and improvement to ≤ Grade 2 will be required before rucaparib can be resumed, either at the current dose or at a reduced dose.

7.1.3 Management of rucaparib treatment-emergent cholesterol elevations

Grade 3 cholesterol elevations have been successfully managed with dose interruption and/or dose reduction and concomitant treatment with a HMG-CoA reductase inhibitor (commonly known as statin). Study drug must be held for Grade 3-4 elevated cholesterol but can be resumed after improvement to Grade 2 or less. Supportive care treatment will be based on

approved risk categories for patients found to have elevated levels. Treatment will be determined by the patients primary care physician or cardiologist based on current CHEST guidelines. Caution should be noted for the use of certain statin drugs, see section 6.3.

7.1.4 Management of rucaparib treatment-emergent myelosuppression

Grade 3/4 myelosuppressive events have been successfully treated with supportive care and dose interruption/reduction. Additional diagnostic evaluation, including bone marrow examination, should be considered for patients with persistent myelosuppression that does not stabilize or recover with rucaparib treatment modification.

Dose reduction steps are presented in Table 7.1.

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

Table 7.1. Rucaparib Dose Reduction Steps

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 Principal Investigator and Medical Monitor before reducing to dose level 3. Further dose reduction may be possible, but require consultation with the investigator-sponsor.

7.1.5 Rucaparib Re-treatment Criteria

Following a dose interruption, treatment may resume if:

- ANC ≥ 1.0×10^9/L
- Platelet count ≥ 100×10^9/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). Grade 3 or Grade 4 ALT/AST elevations should be managed as described above.

7.2 Contraception

It is not known if rucaparib has transient adverse effects on the composition of sperm. The investigational product may be transferred to a partner through semen and condoms must be used with all sexual activity.

For this trial, subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition). Subjects of non-reproductive potential must agree to use condoms with all sexual activity.

Subjects of reproductive potential must agree to avoid impregnating a partner or donating sperm while receiving study drug and for 6 months after the last dose of study drug by complying with the following:

(1) Males must agree to use condoms with all sexual activity.

AND

(2) Use (or have their partner use) highly effective contraception during heterosexual activity, if their partner is of reproductive potential.

Highly effective methods of contraception are‡:

- Intrauterine device (IUD)
- Vasectomy
- Contraceptive rod implanted into the skin
- Tubal ligation of female partner
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Of note: spermicides, diaphragm, sponge, and caps are NOT acceptable as they are not included in the highly effective methods.

‡ If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as a highly effective method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 6 months after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

7.3 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

8 STUDY CALENDAR

1 cycle = 28 days (± 3 days)

Examination	**Screening[1]**	**C1D1[2]**	**C(2+)D1[3]**	**PSA Progression Confirmation[20]**	**End of Treatment[18]**	**Follow-up[16]**
Informed consent	**X**					
Treatment after PSA Progression ICF[20]				**X**		
Medical history	**X**					
Eligibility criteria[4]	**X**					
Vital signs	**X**	**X**	**X**	**X**	**X**	
Physical examination	**X**	**X**	**X**	**X**	**X**	
ECOG performance status	**X**	**X**	**X**	**X**	**X**	
Hematology[5]	**X**	**X**	**X**	**X**	**X**	
Chemistry[6]	**X**	**X**	**X**	**X**	**X**	
Lipid Panel[7]	**X**	**X**	**X**	**X**	**X**	
PSA[8]	**X**	**X**	**X**	**X**	**X**	**X[8]**
Urinalysis	**X**					
Coagulation Panel[17]	**X**					
Testosterone	**X[19]**					
ECG	**X**					
Adverse Event Assessment		**X**	**X**	**X**	**X**	
Concomitant Medication Review	**X**	**X**	**X**	**X**	**X**	
CT scans (c,a,p)	**X**			**X[15]**		
NM Bone Scans	**X**			**X[15]**		

Examination	**Screening[1]**	**C1D1[2]**	**C(2+)D1[3]**	**PSA Progression Confirmation[20]**	**End of Treatment[18]**	**Follow-up[16]**
Rucaparib administration[9]		**X**	**X**			
Blood for Correlative Studies[10]	**X**		**X[10]**	**X[10]**	**X[10]**	
Urine for Correlative Studies[11]	**X**		**X[11]**	**X[11]**	**X[11]**	
Archival Tissue for Correlative Studies[12]	**X**					
BRCAness Test[13]	**X**					
Optional biopsy[14]				**X**		
Survival Follow-up						**X**

1. All Pre-study/Screening procedures should be completed within 4 weeks of study enrollment. CT Scan and NM Bone scan do not need to be repeated if done within preceding 90 days of visit.
2. C1D1 procedures do not need to be repeated if screening procedures have been done within 7 days of start of treatment.
3. Cycles will continue at 28 ± 3 days according to criteria in Section 6.4.
4. Confirmation of BRCAness by previous result or prospective analysis of archival tissue or blood sample biopsy. If archival tissue is unavailable, a new biopsy will NOT be required.
5. Hematology includes CBC with differential and platelets.
6. Chemistry includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen.
7. Lipid panel to consist of cholesterol, triglycerides, LDL cholesterol HDL Cholesterol, VLDL, and non-HDL Cholesterol.
8. If treatment is discontinued prior to PSA progression, PSA testing will continue throughout follow-up until PSA progression or start of another treatment. Patients who have PSA progression prior to discontinuing treatment do not need to have PSA testing performed during follow-up.
9. Rucaparib will be administered as described in Section 6.
10. Blood collection for biomarkers will be collected at screening, C3D1, C7D1, and confirmed PSA disease progression (± 7 days), if applicable, or at EOT visit (whichever occurs first).

11. For patients enrolled with an intact prostate, urine collection for biomarkers will be collected at screening,C3D1, C7D1, and confirmed PSA disease progression (± 7 days), if applicable, or at EOT visit (whichever occurs first).
12. Archival tissue will be collected at screening (if available). Archival tissue should not be cut until instructed by the central lab.
13. Genomic or genetic testing for 'BRCAness' will be confirmed with either blood or tissue based testing.
14. An optional fresh tissue biopsy may be obtained at PSA Progression Confirmation Visit (± 28 days) for subjects with radiographic disease progression.
15. CT scans of the chest/abdomen and pelvis and NM bone scans will be done at the time of PSA Progression Confirmation Visit (± 28 days) as defined in section 10.1.
16. Follow-up should occur every 90 days (± 14 days) for 2 years following End of Treatment as per standard of care (section 9).
17. Coagulation Panel includes PT/INR, PTT.
18. The end of treatment visit should occur within +/-3 days of the decision to discontinue treatment. If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed.
19. To be performed only if the subject has completed hormone therapy. Screening testosterone may be performed within 84 days of study enrollment.
20. Only patients who have suspected PSA progression during a regular study visit will have testing to confirm PSA progression at their next regularly scheduled visit. **Before continuation of treatment after confirmed PSA progression, the patient must agree to sign the Treatment After Progression Informed Consent Form.** Patients may complete the assessments required for PSA progression in conjunction with the next regularly scheduled cycle visit or at EOT.

9 STUDY PROCEDURES

9.1 Screening

- Informed Consent
- Physical exam (including weight and vital signs)
- Review of medical history/baseline symptoms
- Confirmation of BRCAness by previous result or prospective analysis of archival tissue or blood sample biopsy. If archival tissue is unavailable, a new biopsy will NOT be required
- 12-lead ECG (if medically indicated)
- ECOG Performance status
- Laboratory assessments:
  - Complete Blood Count (CBC) with differential (w/diff)
  - Complete Metabolic Panel (CMP) to include Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen (fasting is not required)
  - Coagulation to include PT, PTT, INR
  - Lipid Panel to include cholesterol, triglycerides, LDL cholesterol HDL Cholesterol, VLDL and non-HDL Cholesterol (fasting not required)
  - PSA
  - Testosterone (for subjects who have previously been treated with hormone therapy)
- Blood collection for correlative studies (see Section 14.1.1 for details)
- Urine collection for correlative studies. Prior to collection of the urine specimen, a prostate exam will be performed by the treating physician (see Section 14.1.2 for details)
- Archival tissue collection for correlative studies (see Section 14.1.3 for details)

9.2 On-Treatment Evaluations (Day 1 of each cycle)

- Physical Exam (including weight and vital signs)
- ECOG Performance Status
- Laboratory assessments (do not need to be repeated at C1D1 if screening labs were performed within 7 days prior to treatment initiation):
  - CBC w/diff
  - CMP as defined in Section 9.1
  - Lipid Panel as defined in Section 9.1
  - PSA
- Blood collection for biomarkers at C3D1 and C7D1 (see Section 14.1.1 for details)
- Urine collection for biomarkers at C3D1 and C7D1. Prior to collection of the urine specimen, a prostate exam will be performed by the treating physician (see Section 14.1.2 for details).

- Safety assessment: monitoring and recording all adverse events and serious adverse events using the CTCAE version 5.0
- Review of concomitant medications
- Study drug administration & patient resupply (enough to last until Day 1 of the next treatment cycle).

9.3 PSA Progression Confirmation Visit

Only for patients who have suspected PSA Progression at one of their regularly scheduled visits. Before continuation of treatment after confirmed PSA progression, the patient must agree to sign the Treatment After Progression Informed Consent Form. Patients may complete the assessments required for PSA progression in conjunction with the next regularly scheduled cycle visit or EOT Informed consent to treatment beyond PSA Progression

- Physical Exam (including weight and vital signs)
- ECOG Performance Status
- Laboratory assessments
    - CBC w/diff
    - CMP as defined in Section 9.1
    - Lipid Panel as defined in Section 9.1
    - PSA
- Blood collection for biomarkers (± 28 days) (see Section 14.1.1 for details)
- Urine collection for biomarkers ± 28 days). . Prior to collection of the urine specimen, a prostate exam will be performed by the treating physician (see Section 14.1.2 for details).
- Safety assessment: monitoring and recording all adverse events and serious adverse events using the CTCAE version 5.0
- Review of concomitant medications
- CT scans of the chest abdomen and pelvis (± 28 days)
- Nuclear Medicine (NM) Bone Scan (± 28 days)
- Optional biopsy (± 28 days) only for subjects who demonstrate radiographic progression. See Section 14.1.3 for details

9.4 End of Treatment

- Physical Exam (including weight and vital signs)
- ECOG Performance Status
- Laboratory assessments:
    - CBC w/diff
    - CMP as defined in Section 9.1
    - Lipid Panel as defined in Section 9.1
    - PSA
- Blood collection for biomarkers (± 28 days) (see Section 14.1.1 for details). (At confirmed PSA progression or EOT, whichever comes first).

- Urine collection for biomarkers ± 28 days). Prior to collection of the urine specimen, a prostate exam will be performed by the treating physician (see Section 14.1.2 for details). (At confirmed PSA progression or EOT, whichever comes first).
- Safety assessment: monitoring and recording all adverse events and serious adverse events using the CTCAE version 5.0
- Review of concomitant medications

9.5 Follow-up Evaluations Q 90 days (± 14 days)

Survival follow-up, including survival status and post-study treatments. Follow-up may be conducted via phone call or record review if laboratory assessments are not required.

- Laboratory assessments:
  - If treatment is discontinued prior to PSA progression, PSA testing will continue throughout follow-up until PSA progression or start of another treatment. Patients who have PSA progression prior to discontinuing treatment do not need to have PSA testing performed during follow-up.

10 CRITERIA FOR EVALUATION AND ENDPOINT

10.1 Efficacy

Patients must receive one full cycle of rucaparib and have PSA assessed after that cycle to be evaluable for efficacy. Patients who do not meet evaluable criteria will be replaced.

PSA levels will be monitored monthly while on treatment for comparison to baseline levels with the objective of assessing the proportion of patients with a 50% reduction in PSA levels (PSA50).

PSA progression-free survival (PSA-PFS) is defined as the time from study enrollment until the time of PSA progression as defined by PCWG3[22] criteria or death.

Patients who start another anti-cancer treatment prior to PSA progression or who complete one year of follow-up without PSA progression will have their data censored at that time point.

Overall survival is defined as the time from study enrollment until death. Survival will be monitored while on study and every 90 days for 2 years after study discontinuation.

10.2 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

10.2.1 Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician or appropriately delegated personnel as noted in the calendar (Section 8).

10.2.2 Vital Signs

Vital signs (weight, blood pressure, respiratory rate, pulse rate and temperature) will be obtained as noted in the calendar (Section 8).

10.2.3 Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the calendar (Section 8).

10.3 Stopping Rules

The protocol has no formal stopping rules.

11 STATISTICAL CONSIDERATIONS

11.1 Primary Objective

The total sample size is 15 patients. The null hypothesis is that median PSA-PFS is 3 months. With an alternative hypothesis that median PSA-PFS is 12 months, and assuming PSA-PFS is exponentially distrubuted, a sample size of 15 provides 90% power at one-sided alpha = 0.05. The median progression-free survival in the PROfound trial of olaparib treated patients was 7.4 months for Arm A (ie paitents with BRCA1, BRCA2 or ATM alterations). This trial evaluated patients who's cancer was highly refractory and had more advanced disease. The median PFS in the TOPARP-A trial was 9.8 months in biomarker selected patients. In the ROAR trial, the patients have early disease which is hypothesized to be more responsive to treatment. We hypothesize that the median PFS will be longer than that observed in prior studies where olaparib was tested in a more advanced setting.

11.2 Secondary Objectives

Descriptive analysis methods will be used to analyze tabulated safety characteristics. Kaplan-Meier methods and associated confidence intervals will also be used to analyze PSA progression-free survival and OS. The proportion of subjects who achieve PSA50 will be reported along with a 95% confidence interval. The proportion of subjecs with an undetectable PSA after initiation of PARP therapy at 6 and 12 months will be assessed using Kaplan-Meier methods and associated confidence intervals. The proportion of subjects who exhibit an objective response will be reported along with an exact binomial confidence interval.

11.3 Exploratory Objectives

Descriptive methods will be used to analyze the exploratory objectives. Circulating tumor DNA alterations and response category will be cross-tabulated. The mean and standard deviation of enumerated tumor cell characteristics will be reported separately for each response category. The mean and standard deviation at the time of radiographic progression will be reported for subjects with documented radiographic progression.

12 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to CTORegistrations@hci.utah.edu.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

14 SPECIAL INSTRUCTIONS

14.1 Correlative Studies

To support exploratory objectives and correlative studies, blood and tissue samples will be collected at the time points indicated on the Schedule of Events. After completion of the described correlative studies, any remaining blood or tissue will be stored for future unspecified cancer research. With the participant's approval and as approved by the Institutional Review Board (IRB), de-identified biological samples will be stored at Huntsman Cancer Institute's Biorepository.

At the time of consent, subjects will be given the opportunity to authorize the biobanking of their remaining samples for use in future undisclosed research. During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, the withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

Correlative studies will evaluate exploratory biomarkers predictive of response and resistance to treatment with rucaparib. Patients will have a baseline assessment at the time of enrollment.

14.1.1 Collection of Blood for Correlative Analysis

30-40 mL of blood will be collected at screening, C3D1, C7D1, and confirmed PSA Progression or EOT (whichever occurs first).

Testing may include, but is not limited to:

- Circulating tumor cells (CTC) detection, enumeration, and characterization
- Cytokine/chemokine/interferon assays
- Genomic analysis
- Proteomic analyses
- Flow Cytometry

Specimen collection and processing instructions can be found in the lab manual.

14.1.2 Collection of Urine samples for Correlative Analysis

For patients with an intact prostate, 10-20 mLs of urine will be collected at screening, C3D1, C7D1, and confirmed PSA progression or EOT (whichever occurs first). Prior to collection of the urine specimen a prostate exam will be performed by the treating physician.

Testing may include, but is not limited to:

- Androgen receptor isoform splice variant (AR-V7).

Specimen collection and processing instructions can be found in the lab manual.

14.1.3 Collection of Tumor Tissue

Available archival tissue will be used for correlative testing. If archival tissue is not available, a new biopsy will NOT be required. Archival tissue slides should not be cut until requested by the central lab.

An optional fresh biopsy will be obtained at the PSA Progression Confirmation Visit only for subjects who demonstrate radiographic progression. Up to 6 cores will be obtained.

Testing may include, but is not limited to:

- Multiomics platforms
- Immunohistochemistry
- Flow cytometry

Instructions for processing and analysis will be detailed in the lab manual.

14.1.4 BRCAness Testing

Genomic or genetic testing for ‘BRCAness’ will be confirmed with either blood or tissue based testing.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

15.2 Human Subjects Protections

15.2.1 Participation of Children

Patients must be at least 18 years of age to participate.

15.2.2 Participation of Subjects Unable To Give Consent

Patients must be able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

15.3 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures. Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a Phase II study classified as moderate risk per the NCI-approved DSM plan. Each moderate risk study may be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). SAEs occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly. The full committee will also review all toxicities for patients on treatment and within 30 days of their last treatment on a quarterly basis.

Each moderate-risk study will be assigned a dedicated research compliance officer who will monitor the trial. Moderate-risk trials will be monitored by RCO personnel after the first patient is enrolled and every six months thereafter during active enrollment. The RCO

monitor will review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. Moderate-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then semi-annually thereafter.

An initial audit of moderate-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of moderate-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

15.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

15.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Collection of adverse events will begin after the first dose of study treatment and end 30 days after the last dose of study treatment.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v.5.0 (grade 1-5)
2. Its relationship to the study drug(s) (definite, probably, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see Section

7.1 for guidance). Once an adverse event is detected, it should be followed until a new baseline is reached, death, or when patient is lost to follow up. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the rucaparib is described in the Drug Information section (Section 3) as well as Section 6.6 and Table 19 of Investigator Brochure. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

15.4.2 **Serious Adverse Event (SAE)**

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission > 24 hours.
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

Collection of adverse events will begin after the first dose of study treatment and end 30 days after the last dose of study treatment.

Any death (except those due to progression of disease) from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the SAE definitions above or AESIs in section 15.5.3 must simply be documented as AEs in the patient research chart.

15.4.3 **Adverse Events of Special Interest**

AESIs (serious or nonserious) are defined as AEs of scientific and medical concern specific to the Clovis's product or program, for which ongoing monitoring and rapid communication by the investigator to Clovis 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 Sponsor-Investigator to other parties (e.g., regulators) might also be warranted.

Details on Clovis's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to Clovis expeditiously within 48 hours of knowledge of the event, during the study through 30 days after receiving the last dose of study treatment, according to the procedures below.

15.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and drug manufacturer according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to HCI-RCO@utah.edu as soon as possible, but no later than 1 business day after first knowledge or notification of event.

DSMC Notifications:

An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.

The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

FDA Notifications:

This study is IND exempt; therefore, there are no SAE reporting requirements to the FDA

IRB Notification:

Events meeting the University of Utah IRB or local IRB reporting requirements will be submitted per local guidelines.

Drug Manufacturer Notifications:

All SAEs and AESIs, regardless of relationship to study drug, must be reported to Clovis Pharmacovigilance within 24 hours of knowledge of the event, during the study through 30 days after receiving the last dose of study treatment, according to the procedures below. After the 30 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 or AESI to study treatment at the time of the initial report.

Reporting will be done via email: drugsafety@clovisoncology.com.

15.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 6 months of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

15.7 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

15.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The sponsor requires the **prompt reporting** to HCI RCO of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.9 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

15.10 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

15.11 Record Keeping

Per 21 CFR 312.57, Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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APPENDIX A — Rucaparib Dosing Diary

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Patient Initials: _____ **Patient Study ID: _____**

Treatment Cycle #: _____ **Dose: _____**

1) Take the number of pills prescribed by your study doctor twice a day at approximately the same time each day. Take your pills with an 8oz glass of water with or without food.
2) If you forget to take your pills at the right time, you can take them as soon as you remember on that day as long as it's not more than 4 hours after the usual time.
3) If you miss taking your pills by more than 4 hours, the dose is missed. Do not take extra pills with your next dose to try and make up for the missed dose.
4) Complete one line of the diary each day and write the total number of pills taken in the morning and in the evening. If you've missed a dose, briefly explain why in the comments.
5) Please bring this diary as well as all empty containers and any unused supplies to your next clinic visit.

Day	**Date** mm/dd/yy	**Morning dose** hh:mm	**Evening dose** hh:mm	**Number of Pills Taken**	**Comments**
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					
Day 8					
Day 9					
Day 10					
Day 11					
Day 12					
Day 13					
Day 14					
Day 15					

APPENDIX A - Rucaparib Dosing Diary

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Patient Initials: _____ **Patient Study ID: _____**
Treatment Cycle #: _____ **Dose: _____**

1) Take the number of pills prescribed by your study doctor twice a day at approximately the same time each day. Take your pills with an 8oz glass of water with or without food.
2) If you forget to take your pills at the right time, you can take them as soon as you remember on that day as long as it's not more than 4 hours after the usual time.
3) If you miss taking your pills by more than 4 hours, the dose is missed. Do not take extra pills with your next dose to try and make up for the missed dose.
4) Complete one line of the diary each day and write the total number of pills taken in the morning and in the evening. If you've missed a dose, briefly explain why in the comments.
5) Please bring this diary as well as all empty containers and any unused supplies to your next clinic visit.

Day	Date mm/dd/yy	Morning dose hh:mm	Evening dose hh:mm	Number of Pills Taken	Comments
Day 16					
Day 17					
Day 18					
Day 19					
Day 20					
Day 21					
Day 22					
Day 23					
Day 24					
Day 25					
Day 26					
Day 27					
Day 28					
Day 29					
Day 30					
Day 31					

Patient Signature _____ Date_____

APPENDIX B – PROSTATE CANCER CLINICAL TRIALS WORKING GROUP 3 (PCWG3)

The PCWG3 was created to more accurately assess bone lesions and to describe PSA based progression. PCWG3 rules were designed to be used in conjunction with radionuclide (^{90m}Tc) bone scintigraphy and therefore should be used for all bone response assessments. Only bone lesions seen on bone scans will be followed for assessment of response.

Bone Assessments

Baseline Assessment

All bone lesions may be recorded as non-target lesions only and the number of lesions should be noted.

Response Assessment

While on treatment, follow-up scans should be assessed for progressive disease (PD), progressive disease unconfirmed (P Du), no progressive disease (Non-PD), no evidence of disease (NED), or non-evaluable (NE).

Table 1: Bone response assessment categories

Bone Response	Definition
PD	2 new lesions, not flare, persistent
P Du	2 new lesions, but confirmation is required by the second scan. The temporary marker of PD should be updated to PD or non-PD upon subsequent scans. If P Du is determined on the last scan, sponsor should update to PD upon analysis.
Non-PD	At least 1 bone lesion present, but not enough to trigger PD.
NE	Status of bone lesions cannot be determined.
NED	No lesions are seen on bone scan (either none at baseline or all have resolved).

Rules of Progressive Disease

- 2+2 Rule: If 2 new lesions appear on the first scan after the initiation of treatment, the response is classified as P Du and another scan is performed ≥ 6 weeks.
    - If the next scans show at least 2 new bone lesions in addition to those seen in the prior scan, the prior scan is to be considered confirmed PD.
    - If the next scan does not show at least 2 additional new bone lesions the lesions seen on the prior scan are considered pre-existing lesions. The bone response on the prior scan is updated to non-PD and new lesions seen on the first scan are ignored.
- Once outside of the flare window (the first 12 weeks of treatment) the appearance of new lesions must be confirmed with a second scan ≥ 6 weeks after the first scan.

- If ≥ 2 new lesions appear on a scan the scan will be classified as P Du until a second scan confirms lesion persistence.
  - If lesions are persistent on the second scan, the prior response will be updated to PD.
  - If the lesions disappeared on the second scan, the prior response is updated to non-PD.

- If 1 new bone lesion is seen on one scan classifying the scan as non-PD, but the following scan shows an additional new lesion (2 new lesions total between subsequent scans) the second scan will be classified as PD.
- Diffuse skeletal tumor involvement may result in a superscan. In this case, distinguishing between individual new bone lesions may be impossible. If a superscan occurs after baseline, the response will be considered PD and no further confirmation scans are required.

PSA Progression
PSA should be monitored at the beginning of every cycle. Any rise in PSA during the first 12 weeks of treatment should be monitored but should not be deemed evidence of progression. Record the percent change from baseline at 12 weeks. After a decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (i.e., a confirmed rising trend).

Nodal and Soft Tissue Progression
Nodal and soft tissue documentation, tracking, and determination of progression will follow RECIST 1.1.