Phase II Trial of Rucaparib in Patients with Metastatic and Non-Metastatic Hormone-Sensitive Prostate Cancer Harboring DNA Repair Gene Mutations (TRIUMPH)

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INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: **Phase II Trial of Rucaparib in Patients with Metastatic and Non-Metastatic Hormone-Sensitive Prostate Cancer Harboring DNA Repair Gene Mutations (TRIUMPH)**

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

SYNOPSIS

Title	Phase II Trial of Rucaparib in Patients with Metastatic and Non-Metastatic Hormone-Sensitive Prostate Cancer Harboring DNA Repair Gene Mutations (TRIUMPH)
Lead site	Johns Hopkins University
Sponsor	Clovis Oncology
IND holder	IND 137691(EXEMPT IND)
Investigational agent	Rucaparib 600mg by mouth twice daily, continuous dosing
Phase	2
Target population	• adult male > 18 years of age • Histologic or cytologic diagnosis of adenocarcinoma of the prostate. • Either (1) Metastatic disease as defined for one or more bone metastases confirmed by bone scintigraphy or radiographic soft tissue metastasis. Pelvic lymph nodes will be considered as metastatic disease if they measure ≥15 mm in short-axis diameter. Or (2) biochemically recurrence disease as defined by a PSA >0.2 ng/ml post prostatectomy or a PSA rise of 2ng/ml or more from the nadir after radiation therapy. • Germline or somatic mutation in one or more homologous recombination DNA-repair genes (BRCA1, BRCA2, ATM, CHEK2, NBN, BRIP1, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM) as documented by a clinical-grade, saliva, tissue, or blood based genetic test or molecular sequencing. • Patients must be informed about and must decline androgen deprivation therapy (ADT)-based systemic therapy • Serum PSA at screening ≥ 2.0 ng/mL • Serum testosterone level: ≥ 100 ng/dL at time of screening • patients with biochemical recurrence must have a PSADT ≤ 9 months, based upon ≥3 consecutive measurements collects in the past 12 months, at least 4 weeks apart, calculated using MSKCC calculator • life expectancy >12 months • ECOG performance status ≤ 2 • Adequate bone marrow, renal and liver function (ANC >1.5K, Plt >100K, Hgb >10 g/dL; Cr <1.5 mg/dL; AST/ALT < 3x ULN; Total Bilirubin <1.5x ULN).
Study centers	Two sites in the United States
Start date/Duration	First patients are expected to be enrolled in March 2018. Accrual is estimated to last 2 years with up to 12 months of follow-up after the last patient has been entered.

Expected enrollment	30 patients (Up to a max of 10 patients with non-BRCA1/BRCA2/ATM homologous recombination DNA-repair mutations allowed, ensuring at least 20 BRCA1/BRCA2/ATM-positive patients).
Rationale	At the time of metastatic disease, continuous ADT (+/- docetaxel, +/- abiraterone) is commonly initiated for the treatment of prostate cancer. However, many men find it difficult to tolerate treatment-related toxicities, including sexual impotency, decreased libido, hot flashes, and weight gain. These symptoms can persist with the development of castration resistance. Treatment with non-AR targeted agents, such as PARPi, may avoid or delay the toxicities of hormonal therapy. Therefore, there is an **unmet medical need to develop non-hormonal therapies** for men with newly diagnosed metastatic prostate cancer who wish to avoid or defer the initiation of chronic ADT. There is also a similar need for those patients with biochemically recurrence prostate cancer at high risk of developing metastatic disease (i.e. PSADT $\leq$ 9 months). The clinical activity of PARPi in patients with homologous recombination DNA-repair mutations and metastatic prostate cancer has now been established. Focusing specifically on patients with an inactivating mutation in a pre-specified group of DNA-repair genes, we hypothesize that targeted therapy with PARPi should be sufficient to induce a clinical response irrespective of hormonal (castration-sensitive or castration-resistant) status. Our hypothesis is based largely on the data from Mateo et al (NEJM 2015) showing a clinical response rate to olaparib of 88% in a heavily pre-treated population of mCRPC patients with a DNA repair mutation, with the most pronounced responses being in men with germline inactivation.(1) For men with metastatic hormone sensitive prostate cancer (mHSPC) and high risk biochemically recurrent disease (BCR), this trial would also provide an alternative to ADT. However, given that primary ADT (in mHSPC and high risk BCR) is a standard first-line therapy, all patients on trial must be ineligible for or decline standard-of-care hormonal treatment. For patients with mHSPC who do not respond to PARPi, we have incorporated safety rules into the trial design to take patients off study at first signs of progression. Primary ADT (+/- docetaxel, +/- abiraterone) would still remain a treatment option upon progression. The primary hypothesis of this study is that outcomes for patients with mHSPC and high risk BCR with an inactivating homologous repair mutation will be improved by this therapeutic agent (rucaparib)
Objectives	<u>Primary</u>

To estimate the PSA_{50} response rate to rucaparib in patients with metastatic and non-metastatic prostate cancer that harbor an inactivating mutation in a homologous recombination DNA repair gene while on treatment with rucaparib, defined as a decline in PSA to 50% of baseline level, confirmed with a second measurement at least 4 weeks apart (PCWG3).

Secondary

- To estimate the median PSA progression-free survival (PCWG3).
- To estimate the median progression-free survival (PCWG3).
- To estimate the objective response rate (ORR) in those patients with measurable disease.
- To determine the safety/tolerability of rucaparib in a population of men with hormone sensitive prostate cancer.

Correlatives/Tertiary

- To measure the quantitative change in gamma-H2AX, RAD51, 53BP1 formation in tumor tissue following treatment with rucaparib (M1 disease only).
- To develop an RNA expression signature associated with response to rucaparib (M1 disease only).
- To estimate the percentage of patients with a loss-of-function mutation or total allelic loss of second somatic gene allele (i.e. LOH, or biallelic inactivation) (In all patients undergoing biopsy or with archived tissue).
- To investigate any association between PARP-1 and PARP-2 protein and mRNA expression levels in tumor with response to rucaparib (In all patients undergoing biopsy or with archived tissue).
- To examine the incidence of reversion mutations in circulating tumor DNA at clinical progression.

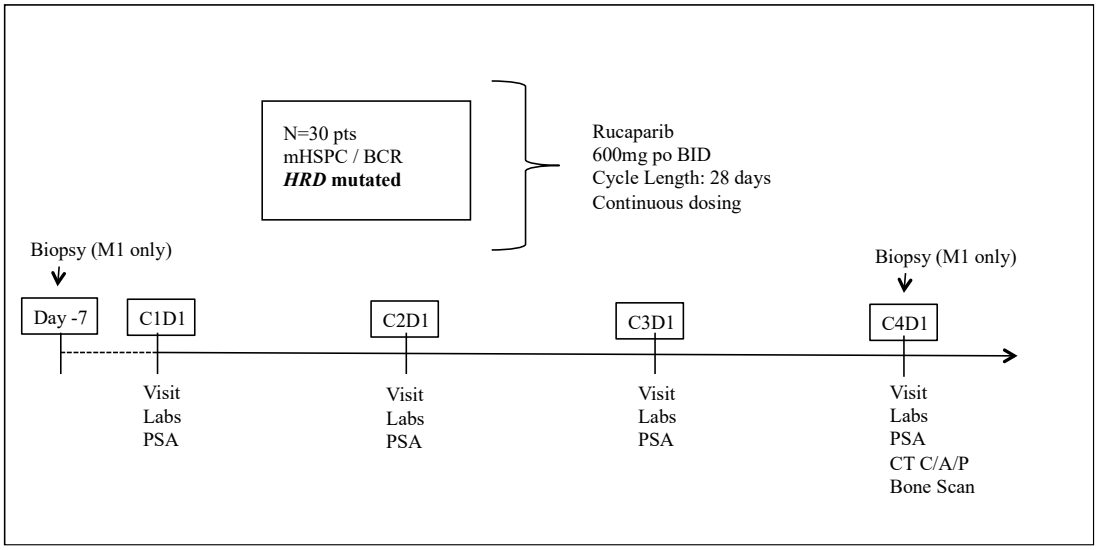
Study design

The study is an open-label single arm Phase II trial. Eligible patients are those with metastatic hormone-sensitive prostate cancer (mHSPC) or high-risk biochemically recurrent prostate cancer (BCR). All patients must have a documented germline or somatic mutation in a homologous recombination DNA-repair gene (BRCA1, BRCA2, ATM, CHEK2, NBN, BRIP1, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM). Germline genetic testing and molecular sequencing as a screening for eligibility will not be offered. A mandatory tumor biopsy will be performed prior to the start of therapy in all patients with metastatic disease (if tumor material is not successfully obtained at the time of biopsy, then archival material will be sought). A second, OPTIONAL tumor biopsy will take place after three months of therapy.

After enrollment, patients will be treated with rucaparib at the established dose of **600mg by mouth twice daily**. Patients will be followed monthly with clinic visits, safety labs (including CBC w/diff, Comp), PSA, and toxicity assessments. Treatment [with a minimum drug exposure of 12 weeks] will be continued until PSA progression (PCGW3 criteria) or clinical/radiographic progression (whichever comes first), or until unmanageable toxicity requiring drug cessation. Patients who remain on treatment

for >12 months can begin to have their clinic visits, safety labs (including CBC w/diff, Comp), PSA, and toxicity assessments every 3 months.

A trial schema for study treatment appears below:



Criteria for evaluation

Primary Endpoint

- PSA_{50} response rate, defined as a decline in PSA to ≥50% of baseline level, confirmed with a second measurement at least 4 weeks later (PCWG3).

Secondary Endpoints

- Safety/Tolerability, defined as incidence of CTCAE v5.0 grade ≥3 toxicities experienced by patients on the trial.
- PSA progression-free survival, defined as a time from initiation on rucaparib therapy until PSA increase of 25%, confirmed with another measurement at least 4 weeks later (PCWG3).
- Radiographic progression–free survival (PCWG3): time to radiographic or clinical progression or death, whichever comes first. Based on RECIST version

1.1 and PCWG3 definitions including: Progression of soft tissue lesions according to RECIST 1.1; Progression of bone lesions detected with bone scan according to PCWG3 criteria; Radiologically-confirmed spinal cord compression or pathological fracture due to malignant progression, or other clinical event deemed to be cancer-related

- Objective response rate, defined as the proportion of patients with measureable disease achieving a complete/partial response in target lesions (RECIST 1.1).

Exploratory Endpoints

- PSA_{50} response, defined as decline in PSA to ≥50% of baseline level, confirmed with a second measurement at least 4 weeks later, in patients with and without a loss-of-function mutation or total allelic loss of second (somatic) gene allele (i.e. biallelic inactivation) (In patients who undergo biopsy or with archival tissue available).
- To associate PSA response to rucaparib with changes in gamma-H2AX, RAD51, 53BP1 formation in tumor tissue compared to baseline (In M1 patients who undergo biopsy).
- To associate mRNA expression array signature with PSA response (In M1 patients only who undergo biopsy).
- To associate PSA response to rucaparib with baseline PARP-1 and PARP-2 protein and mRNA expression levels in baseline tumor biopsy specimens or archived tissue.
- To associate the incidence of reversion mutations with clinical progression.

<u>Exploratory Analyses</u>
Estimate the percentage of patients with a loss-of-function mutation or total allelic loss of second (somatic) gene allele (i.e. biallelic inactivation):
The DNA mutations present in the tumor will be identified through Foundation Medicine sequencing. Patients with biallelic inactivation in an HRD gene(BRCA1, BRCA2, ATM, CHEK2, NBN, BRIP1, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM) will be considered biomarker positive. For biomarker positive and biomarker negative subjects, we will calculate PSA_{50} response rates with confidence intervals for hypothesis generation.

mRNA expression profile signature (positive and negative) and PSA_{50} response rates:
Subjects will have pretreatment tumor (or archived tissue) tested with mRNA expression profiling and scored for likelihood for response to rucaparib per the Decipher GRID platform (GenomeDx). For subjects considered to have a positive mRNA expression signature based upon a binary score assigned via the GenomeDx proprietary algorithm, a PSA_{50} response rate will be calculated. Similarly, a calculation will be performed for subjects considered to have a negative sRNA expression signature.

PARP-1, PARP-2, γH2AX, RAD51, 53BP1 mRNA/protein levels:
In patients that have biopsy-able disease, subjects will have pretreatment and on-treatment tumor biopsy specimens analyzed. IHC and RNA in situ hybridization staining

PARP-1 and PARP-2 will be performed on the pretreatment samples and scored on scale of 0 (none) to 3 (intense staining), and the results will be associated with responses for both proteins, separately, using descriptive statistics and Fisher's Exact Tests. Immunofluorescence will be used to quantify the median intensity of each gH2AX, RAD51m and 53BP1 foci per cell as well determine the median number of foci per cell on the pretreatment biopsies. Using analytical microscopy, Drs. Meeker and Heaphy have developed imaging software, which can isolate single nuclei and quantify both the intensity and number of immunofluorescent foci per nucleus (i.e. per cell). Using FFPE tissue obtained at biopsy, we will examine the change in DNA damage foci number and intensity (reported as median percent change) induced by PARPi in PSA_{50} responders versus non-responders using a T-test.

Reversion Mutations:
Subjects will have circulating tumor DNA (ctDNA) examined by FoundationACT testing before starting treatment and at clinical progression while on rucaparib. We will report the incidence and describe the observed reversion mutation, a known mechanism of resistance to PARP inhibition.

Statistical method

Primary Analysis
The primary endpoint of this study is PSA_{50} response, defined as a decrease in the PSA to ≥50% less than the baseline PSA upon enrollment in the trial. The decrease must be confirmed by a second measurement at least 4 weeks apart. For purposes of meeting the primary endpoint, patients will be considered to have done so if they have a PSA_{50} response only while on therapy with rucaparib. PSA values will be measured monthly during the trial. All patients who take at least one dose of rucaparib will be considered evaluable for the primary endpoint. If patients do not have follow-up PSAs after initiation rucaparib therapy due to stopping therapy for toxicity or withdrawing consent, then they will be replaced.

Secondary Analysis
Safety:
Patients will be assessed for toxicities at each clinical evaluation. Toxicities will graded according to CTCAE v5.0 standardized grading scales. The incidence of grade 3-5 toxicities will be reported. Patients will be assessed for toxicity as long as they are taking rucaparib, and patients will continue to be followed if rucaparib is discontinued for toxicity until the toxicities improve to grade 1 or resolve. Toxicities will be reported as a tabulated table by type and grade.

PSA progression-free survival (PSA-PFS):
A standard definition of PSA progression per PCWG3 will be used. PSA-PFS will be defined as an increase in 25% over a nadir value, confirmed by a follow-up PSA at least 4 weeks later. If patients are removed from study prior to PSA progression, then they will be censored at that time. We will use the Kaplan-Meier method to estimate the median PSA-PFS.

Radiographic progression-free survival (PFS):
Progression-free survival will be measured from the time of first dose to objective clinical or radiographic tumor progression as defined by PCWG3 for progressive disease

or death, and summarized using a Kaplan-Meier curve. Progression will be assigned to the earliest observed time. Patients whose disease has not progressed at follow-up will be censored at the date when the last tumor assessment determined a lack of progression. We will use the Kaplan-Meier method to estimate the median PFS.

Objective response rate:
The objective response rate is defined as the percentage of patients with measurable disease at baseline who achieve an objective response by RECIST1.1 criteria (i.e. Complete response or Partial Response) to rucaparib. We will estimate the objective response rate, along with the exact 95% confidence interval, for the population of patients.

Sample size/Power calculation:
The sample size is calculated to detect an improved PSA_{50} response rate from 50% to 75%. An optimal Simon two stage design is planned. A total of 12 patients will be entered in the first stage and the data analyzed for futility 12 weeks after the last patient begins rucaparib treatment. If 6 or fewer subjects have a PSA response, the study will be terminated and we will conclude the regimen is ineffective. If ≥7 subjects respond, then an additional 16 patients will be studied, for a total of 28 patients. If a total of 17 or fewer subjects respond in stage one and two combined, we consider this regimen ineffective. If a total of 18 or more respond, we conclude the regimen is promising and warrants further study. The maximum sample size will be increased to 30 patients to account for possible dropouts. The total number of patients allowed with a non-*BRCA1* or -*BRCA2* mutations will be capped at 10. This will ensure that at least 20 men will be enrolled with *BRCA1/BRCA2* mutations.

This design provides 90% power to detect an absolute 25% increase in PSA response rate with a one-sided type I error of 0.1. The probability of early stopping is 0.61 under the null hypothesis that the PSA response rate is 50%.

Safety analysis

Standard safety summaries will be provided for treatment exposure, patient disposition, adverse events leading to discontinuation, serious adverse events, and all events resulting in death, including those up to 30 days after treatment discontinuation. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance.

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1. INTRODUCTION

1.1 Disease Background

Prostate cancer is the most commonly diagnosed non-cutaneous malignancy in men, with an estimated 180,000 cases annually in the United States (2). It is the second most common cause of cancer mortality in the United States as well, with over 26,000 deaths in 2016 (2). The discrepancy between the incidence and mortality numbers demonstrate its potential curability if treated while disease is local, as well as the non-lethal nature of some cancers, even if not treated definitively. While many men are cured of their disease, many others will unfortunately progress to incurable and lethal metastatic disease.

1.1.1 Clinical States of Prostate Cancer

The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states (Fig. 1). These states are defined by the extent of disease and status of responsiveness to hormonal therapy. Therapies have been developed for specific states, as each state presents unique risks to the patient and different responsiveness of the disease to therapy.

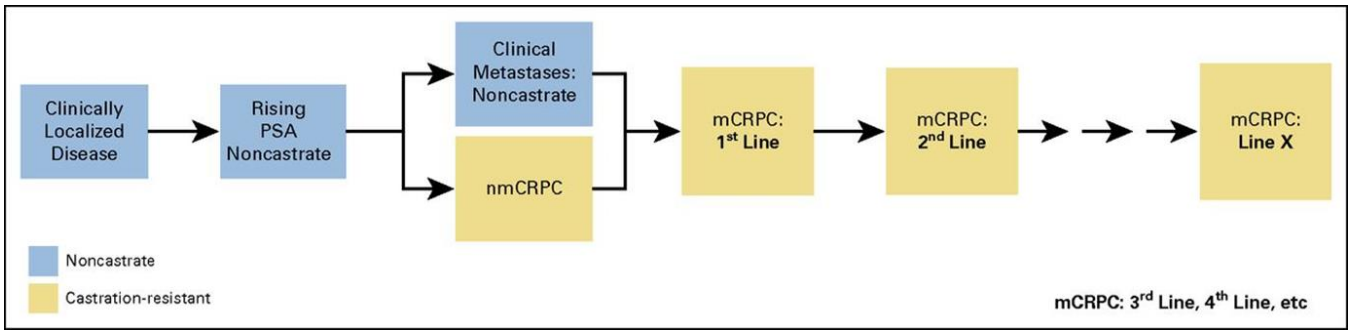

Figure 1 Clinical states of prostate cancer (3)

1.1.2 Metastatic Non-Castrate Disease State

Patients may develop metastatic prostate cancer following a recurrence after local therapy or present with M1 disease as the first diagnoses of prostate cancer. Continuous androgen deprivation therapy (ADT) is initiated for the treatment of metastatic hormone sensitive prostate cancer (mHSPC). In recent years, the addition of docetaxel to ADT in mHSPC patients with high volume disease has been shown to improve overall survival.(4,5) In addition, suppressing adrenal androgen synthesis via abiraterone acetate also improved survival when combined with ADT. However, many men find it difficult to tolerate treatment-related toxicities, including sexual impotency, decreased libido, hot flashes, and weight gain. For instance, in the STAMPEDE trial, 99% of patients on the ADT only arm experienced any Grade 1-5 adverse event (32% of patients experienced a Grade 3-5 adverse event).(4) These symptoms can persist with the development of castration resistance.

Treatment with non-AR targeted agents, such as PARPi, may avoid or delay the toxicities of hormonal therapy.

1.2 Treatment Background

1.2.1 Description and mechanism of action

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) functions in the DNA repair pathway, specifically by serving in base excision repair of DNA single strand breaks. Inhibition of PARP results in inability for cells to repair single strand breaks. Cells normally would employ the error-free homologous recombination pathway to repair such defects. However, in tumors that harbor defects in these DNA repair genes (such as BRCA1/2), the strand breaks lead to chromosomal instability and eventually cell death (6).

Rucaparib (CO-338) is a small molecule inhibitor of PARP being developed for the treatment of ovarian cancer and other solid tumor malignancies associated with homologous recombination deficiency (HRD). Rucaparib has been shown to potently inhibit PARP-1, PARP-2, and PARP-3 and has demonstrated activity in a background of breast cancer gene 1 and 2 (*BRCA1* and *BRCA2*) mutations in both clinical and nonclinical studies.

1.2.2 Nonclinical activity

Investigators should be familiar with the current rucaparib (CO-338) Investigator Brochure (IB).

Pharmacology

Rucaparib is a potent, oral small molecule inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3, which play critical roles in DNA repair. Rucaparib has shown to have *in vitro* and *in vivo* anti-tumor activity in *BRCA1* and *BRCA2* homozygous mutant cell lines. These findings provide a rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary (germline) and acquired (somatic) deficiencies of *BRCA1* and/or *BRCA2*.

Safety pharmacology studies showed that any adverse effects of rucaparib on cardiovascular or central nervous systems occurred at doses that were either 5-fold (motor activity in rats) or 10-fold (*in vitro* hERG assay) higher than the clinical dose of 600 mg twice daily (BID). There were no adverse cardiovascular effects observed in dogs. Effects on the respiratory system were evaluated within repeat-dose toxicity studies in dogs and showed no effects on vital signs or respiration rate.

Pharmacokinetics, Metabolism, and Drug-Drug Interaction Potential

Rucaparib pharmacokinetics (PK) and metabolism, and potential factors affecting these parameters were evaluated *in vitro* and in animals. A single oral dose of rucaparib in mice, rats, and dogs demonstrated a time to maximum plasma concentration (T_{max}) of 2 to 8 hours and an absolute oral bioavailability (F) of 17% to 75%. Toxicokinetic evaluations from 1- and 3-month repeat-dose toxicity studies in rats and dogs, and a dose-range-finding embryo-fetal development study in pregnant rats, showed dose-dependent increases in exposure and no marked sex-related differences or significant accumulation after repeat oral administration.

In vitro plasma protein binding studies in mouse, rat, and dog plasma showed moderate binding and ranged from 49.5% to 66.8%. Plasma protein binding in humans was 70.2% at clinically observed plasma rucaparib concentrations.

Following a single oral dose of [^{14}C] rucaparib in male and female Sprague-Dawley rats, rucaparib-derived radioactivity was well distributed into tissues with concentrations higher than that in blood at all monitored time points. The tissues with the highest radioactive concentrations were cecum, kidney medulla, adrenal gland medulla, stomach, liver, and small intestine. Concentrations in most tissues were below or near the lower limit of quantification by 7 days postdose, except for liver, kidney (cortex and medulla in male, medulla in female), testis, uterus, ovary, and adrenal gland (cortex in male and cortex and medulla in female).

Following a single oral dose of [^{14}C] rucaparib in male pigmented Long-Evans rats, the rucaparib-derived radioactivity was well distributed into tissues. The radioactivity distribution pattern in pigmented and albino rats was qualitatively similar, with the exception of the uveal pigment of the eyes and the pigmented skin where a higher concentration of radioactivity was observed, suggesting an association of radioactive drug-related material with melanin. At 7 days and 50 days after dosing, radioactivity was still detectable in the pigmented skin and uveal pigment of the eyes, respectively.

Rucaparib is not extensively metabolized in vitro. In vitro recombinant CYP phenotyping results indicated that CYP2D6, and to a lesser extent, CYP1A2 and CYP3A4, have the ability to metabolize rucaparib.

Following oral administration of [^{14}C] rucaparib camsylate to male and female intact Sprague-Dawley rats, 93.0% to 94.7% of the dose was recovered in feces and 5.7% to 7.3% of the dose was recovered in urine. Following oral administration of [^{14}C] rucaparib camsylate to beagle dogs, approximately 89% of the dose was recovered by 168 hr postdose. Fecal excretion was the major elimination route, with the mean dose recovery of 81% and 77% in males and females, respectively, and approximately 6% in urine in both males and females.

In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UGT1A1. Rucaparib induced CYP1A2, and down regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures.

Two in vitro studies using human liver microsomes and specific P450 probe substrates were conducted to evaluate the ability of rucaparib to inhibit 8 CYP isoforms (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Based on the more conservative potency observed in the two studies, and in order of decreasing potency, rucaparib reversibly inhibited CYP1A2 (IC_{50} = 3.55 μM), CYP2C19 (IC_{50} = 5.42 μM), CYP2C9 (IC_{50} = 12.9 μM), CYP3A (IC_{50} = 17.2 to 22.9 μM), CYP2C8 (K_i = 16.7 μM), and CYP2D6 (IC_{50} = 41.6 μM).

The direct inhibition potential of rucaparib on recombinantly expressed uridinediphosphoate-glucuronosyletransferase (UGT) 1A1 and UGT2B7 was evaluated. Rucaparib inhibited UGT1A1 with an IC_{50} of 31.9 μM; no inhibition of UGT2B7 was observed (IC50>100 μM).

Rucaparib is a substrate for both P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP) and has the potential to inhibit P-gp and BCRP in the gut.

Rucaparib is a potent inhibitor of multidrug and toxin extrusion transporter (MATE) 1 and MATE2-K, and a moderate inhibitor of organic cation transporter (OCT) 1. Inhibition of MATE1, MATE2-K, and OCT2 has been reported to mediate renal excretion of creatinine in humans.(7,8) Given that the steady-state total C_{max} of rucaparib at 600 mg BID was 13- and 43-fold above IC_{50} value of MATE1 and MATE2-K, respectively, MATE1 and MATE2-K inhibition is considered a plausible mechanistic explanation for the mild to moderate creatinine elevations observed with rucaparib treatment.

The effect of rucaparib co-administration on the PK of sensitive substrates of CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp is currently being assessed in a cocktail-based drug-drug interaction study in patients. The specific probe substrates being assessed are caffeine (CYP1A2), S-warfarin (CYP2C9), omeprazole (CYP2C19), midazolam (CYP3A4), and digoxin (P-gp).

Toxicology

Rucaparib was evaluated in single- and repeat-dose studies (up to 13 weeks) in both rats and dogs. Target organs included the hematopoietic system and gastrointestinal tract. No cardiovascular findings were noted in any of the oral toxicity studies.

In vitro genetic toxicology assays demonstrated rucaparib to be clastogenic. Bacterial mutagenicity data for rucaparib were clearly negative in 4 microbial tester strains both with and without metabolic activation and equivocal in a fifth tester strain (TA98) in the absence of metabolic activation.

In the non-GLP dose range finding, embryo-fetal development study in rat, rucaparib caused maternal toxicity at doses ≥ 500 mg/kg/day. Rucaparib was also found to be a selective developmental toxicant in that it was embryotoxic at all doses.

Rucaparib was not phototoxic when administered to Long Evans pigmented rats orally at doses up to 750 mg/kg/dose, followed by a single exposure to solar-simulated ultraviolet radiation.

1.2.3 Preclinical studies

The anti-tumor activity of rucaparib at doses of 2, 5, 15, 50, and 150 mg/kg BID was evaluated in the orthotopic BRCA1 mutant MDA-MB-436 TNBC xenograft model (Figure 2). Rucaparib was generally well-tolerated; however, in the 150 mg/kg BID group, treatment-related mortality was observed in 1 animal, and 3 animals had a dosing interruption of 2 to 6 days due to body weight loss. Based on these observations, additional nutrient supplement was provided to all groups, and rucaparib was generally well-tolerated at all dose levels for the remainder of the study. Rucaparib administration resulted in dose-dependent and statistically significant reduction in mean tumor volumes on the last day of dosing (Day 28) in all rucaparib treated groups, with > 100% tumor growth inhibition (TGI) observed in animals treated with 50 and 150 mg/kg BID. The tumors were monitored for 11 days after dosing was terminated (Day 39), and dose- dependent and statistically significant TGI was also observed in all rucaparib treated groups.

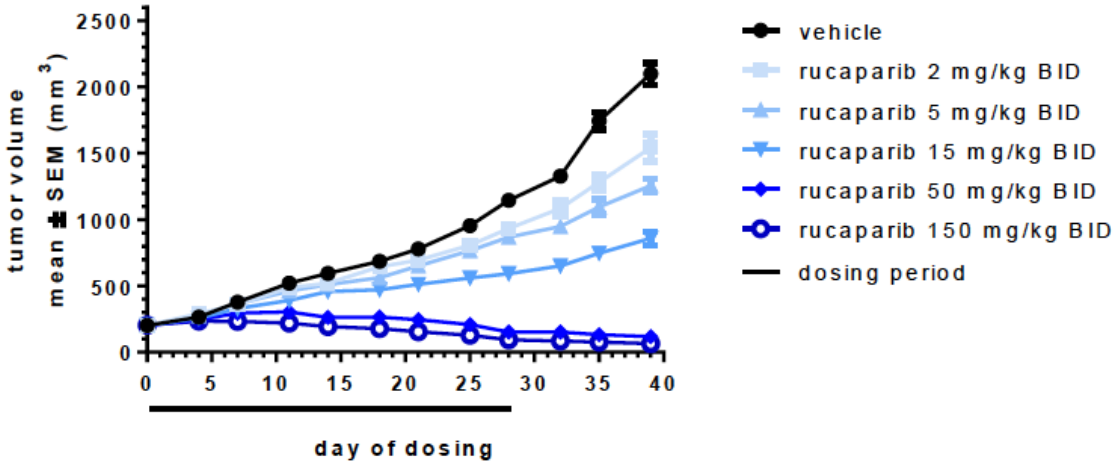

Figure 2 – Efficacy of Single Agent Rucaparib in the MDA-MB-436 (BRCA1 Mutant) Orthotopic Xenograft Model

In vivo studies were conducted to evaluate the anti-tumor effects of rucaparib as a single agent in the BRCA2 mutant HBCx-17 and BRCA wild-type HBCx-6 TNBC PDX models. Both models have mutated TP53. Rucaparib was administered at doses of 50 mg/kg QD, 150 mg/kg QD, and 150 mg/kg BID for 24 and 28 days in the HBCx-17 and HBCx-6 models, respectively. Minimal body weight loss was observed in all rucaparib-treated groups. Rucaparib treatment at all doses evaluated resulted in significant reduction in tumor growth, with mean tumor/control (T/C) volumes ranging from 7.0% to 15.2% and 0.6% to 14.7% in the HBCx-17 and HBCx-6 models, respectively. In both studies, tumors were monitored for 13 to 15 days after rucaparib dosing was discontinued. In the HBCx-17 model, 50% of the mice treated with 150 mg/kg BID rucaparib had a PR or CR, whereas in the HBCx-6 model 100% of the mice treated with 150 mg/kg QD or 300 mg/kg BID rucaparib had a PR or CR.

The efficacy of 150 mg/kg BID rucaparib was evaluated in the PAXF 1876, PAXF 2005, and PAXF 2094 pancreatic PDX models that have deleterious BRCA2 frame shift mutations. The median body weight loss in rucaparib treated groups in the 3 studies ranged from 2.5% to 9% as compared to 0% to 5.8% in the groups receiving the vehicle control. On Day 28 of dosing, rucaparib showed differential sensitivity in the 3 models, with a T/C of 4.5%, 26.1%, and 55.6% for the PAXF 2005, PAXF 2094, and PAXF 1876 models, respectively.

1.2.4 Clinical studies

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).

1.2.5 Clinical safety summary

Treatment-related adverse events (AEs; all grades) reported in ≥15% of patients treated with 600 mg BID rucaparib include gastrointestinal and related symptoms (nausea, vomiting, dysgeusia, and abdominal pain), anemia, asthenia/fatigue, neutropenia, thrombocytopenia, and headache. Elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels were also reported. Elevations of ALT/AST occurred early (within first 2-4 weeks of treatment), were generally mild to moderate (Grades 1-2), not accompanied by any significant changes in bilirubin levels, often transient, and resolved to within normal ranges or stabilized. As has been observed with rucaparib and other PARP inhibitors, myelosuppression may be delayed and observed after a period of continuous dosing. All treatment-related AEs were successfully managed with concomitant medication and treatment interruption and/or dose reduction, or supportive care (in the case of myelosuppression AEs).

Extensive centrally reviewed electrocardiogram (ECG) monitoring was conducted in the Phase 1 portion of Study CO-338-010 and results are available for 55 of 56 treated patients. No patient had a QTcF measurement ≥ 500 msec and only 1 patient had a QTcF measurement ≥ 480 msec. This measurement occurred in a patient receiving 480 mg BID rucaparib and concomitant administration of citalopram, a medication with known potential to cause QT prolongation. This patient continued to receive rucaparib monotherapy at a dose of 480 mg BID with no further QTcF measurement ≥ 480 msec. Only 1 patient had a QTc increase from baseline > 60 msec. This patient had a history of QT prolongation prior to study entry and received 1 dose of rucaparib before discontinuing from the study due to eligibility violation. Overall, rucaparib in doses up to 840 mg BID exhibited a mean change of QTcF from baseline of 11.3 msec at the maximum concentration (5565 ng/mL) observed in the study. At a dose of 600 mg BID, the mean values for change of

QTcF in Cycle 1 ranged from 5.0 to 14.0 msec. Overall, the alteration of the mechanism of repolarization was minimal. There were no AEs suggestive of cardiac arrhythmia (eg, presyncope, syncope, sudden death) in any patient.

1.3 Rationale

1.3.1 Rationale for conducting the study

Much of the early work studying mechanism of action and efficacy of PARPi has been done in ovarian and breast cancer due to the well-characterized incidence of BRCA1/2 mutations in these cancers. However, somatic mutations in DNA-repair genes have been identified in both primary(9) and metastatic castration-resistant prostate cancer (mCRPC)(10), with prevalence rates of approximately 5-10% in localized prostate cancer and 20-25% in metastatic castration-resistant prostate cancer (mCRPC).

These findings served as the rationale to test PARPi (olaparib) in heavily pre-treated mCRPC (TOPARP-A trial, Mateo et al., NEJM 2015).(1) Although the presence of a DNA-repair defect in the tumor was not an eligibility requirement, the response rate to olaparib was 33% in the unselected population (16 of 49; 95% CI 20-48%), including a PSA decline of over 50% (PSA_{50}) in 10/49 patients. The trial did identify somatic and germline mutations in DNA-repair genes, and the presence of a DNA-repair defect correlated with improved response rates (88% vs. 6%) as well as improved progression-free (9.8 vs. 2.7 months) and overall (13.8 vs. 7.5 months) survival compared to DNA-repair proficient cancers. Notably, all 7 patients with a BRCA2 mutation achieved a PSA_{50} response and 4/5 patients with an ATM mutation had a clinical response to olaparib. The most pronounced responses were observed in those patients with germline, inactivating mutations in BRCA2, most of which also had somatic loss-of-heterozygosity of the second allele in the tumor. Several studies are now ongoing to confirm PARPi as a potential treatment strategy for mCRPC either as a single agent (NCT01682772) or in combination with next-generation hormonal therapies (NCT01576172, NCT02500901). The FDA recently announced breakthrough designation for olaparib in patients with mCRPC refractory to novel hormonal therapy, with germline or somatic mutations in BRCA1/2 or ATM.

With respect to germline mutations, a recent study found that the incidence of inherited DNA-repair gene alterations in metastatic prostate cancer to be significantly higher (11.8%) than in both men with localized prostate cancer (4.6%) and in the general population at large (2.7%).(11) Specifically, mutations in 7 genes (ATM, BRCA1, BRCA2, CHEK2, PALB2, RAD51D, GEN1) were significantly enriched in patients with metastatic prostate cancer compared to the general population. These findings suggest that a subset of men are more likely to develop metastatic prostate cancer (i.e. those with germline mutations in DNA-repair genes) and may potentially benefit from PARPi therapy.

The clinical activity of PARPi in patients with DNA-repair mutations and metastatic prostate cancer has now been established. We hypothesize that targeted therapy with PARPi should be sufficient to induce a clinical response irrespective of hormonal (castration-sensitive or castration-resistant) or metastatic (M1 or M0) status. Our hypothesis is based largely on the data from Mateo et al showing a clinical response rate of 88% in a heavily pre-treated population of mCRPC patients with a DNA repair mutation, with the most pronounced responses being in men with germline inactivation. For men with either BCR or mHSPC, this trial would also provide an alternative to ADT. Identification of a non-hormonal based therapy is warranted as ADT is associated with a shorter time to castration resistance in men harboring a germline DNA repair mutation versus those with intact DNA repair.(12)

However, given that primary ADT (in mHSPC and in certain instances of high-risk BCR) is a standard first-line therapy, all patients on trial must be **ineligible for or decline** standard-of-care hormonal treatment. For patients with mHSPC who do not respond to PARPi, we will build safety rules into the trial design to take patients off study at first signs of progression. Primary ADT would still remain a treatment option upon progression.

1.3.2 Rationale for dosage selection

Rucaparib will be administered at a dose of 600mg by mouth twice daily in tablet formulation. This is the FDA-approved dose of rucaparib described in the USPI.

1.3.3 Rationale for correlative studies

1.3.3.1 Genetic mutation analysis in tumor

We hypothesize that inactivation or loss of the second allele in the gene of interest (i.e. homologous recombination gene with germline mutation) is required for response to PARPi. Tumors will be analyzed using the FoundationOne platform by Foundation Medicine (Cambridge, MA). This test sequences provides mutation analysis in 315 selected genes and rearrangement analysis in 28 genes. The genes include those commonly mutated (*BRCA2*, *ATM, BRCA1*, etc.). The analysis provides a depth of coverage of 500X, and is reported by variant analysis with regard to likely pathogenicity. By cataloging the mutations present in the primary tumors for subjects in the study, correlative analysis associating response with specific mutations can be performed. The testing will be inclusive of a sub-panel of genes of particular interest (*BRCA1, BRCA2, ATM, CHEK2, NBN, BRIP1, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, and FANCM*). We will also collect and examine ctDNA before treatment and at progression. Reversion mutations are a known mechanism of resistance to PARP inhibitors, which may give insight into the etiology of clinical progression while on rucaparin in this clinical setting.

1.3.3.2 mRNA expression array analysis in tumor

An alternative possibility for tumor sensitivity to rucaparib is through epigenetic gene expression changes that may not be identified through genetic mutation analysis alone. In conjunction with the DNA mutation testing planned to be performed through Foundation Medicine, subjects will have tissue tested for RNA expression arrays for associating response to rucaparib. For this assay, samples will be tested by GenomeDx (San Diego, CA) using the Decipher GRID microarray platform. The gene expression profile will be inclusive of a metastasis signature and PARP-sensitivity signature. The metastatic signature has been validated in a cohort of patients with high risks for recurrence after primary prostate cancer therapy (13,14), as well as in a cohort of patients undergoing salvage radiation therapy after biochemical recurrence of prostate cancer (15). A post-hoc analysis will be performed to evaluate these signatures, and further determine a gene expression profile that predicts response to rucaparib.

1.3.3.3 PARP-1, PARP-2, γH2AX, RAD51, 53BP1 mRNA/ protein levels in tumor

Beyond the underlying genetic mutations in DNA repair genes and the associated RNA expression profiles, we are exploring whether baseline assessment of the PARP-1 and PARP-2 enzyme protein levels by immunohistochemistry and mRNA by

RNA in situ hybridization is predictive of response. γH2AX, RAD51, and 53BP1 are proteins that serve as a marker for double strand DNA breaks. PARP-1 is the primary molecular target for rucaparib.

2. OBJECTIVES

2.1 Primary Objective

The primary objective is to estimate the PSA response rate (PSA_{50}) to rucaparib in homologous repair-deficient patients with either metastatic hormone sensitive prostate cancer (mHSPC) or high-risk biochemical recurrence. This will serve as an initial exploration of rucaparib's activity in these disease states.

2.2 Secondary Objectives

- Safety/Tolerability, defined as incidence of CTCAE v5.0 grade ≥3 toxicities experienced by patients on the trial.
- PSA progression-free survival, defined as a time from initiation on rucaparib therapy until PSA increase of 25%, confirmed with another measurement at least 4 weeks later (PCWG3).
- Progression-free survival: time to radiographic or clinical progression or death, whichever comes first. Based on RECIST version 1.1 and PCWG3 definitions including: 1. Progression of soft tissue lesions according to RECIST 1.1; 2. Progression of bony lesions detected by bone scan according to PCWG3 criteria; 2. Radiographically-confirmed spinal cord compression or pathological fracture due to malignant progression, or other clinical event deemed to be cancer-related.
- Objective response rate, defined as the proportion of patients with measurable disease at baseline, achieving a complete/partial response in target lesions (RECIST 1.1).

2.3 Correlative/Exploratory/Tertiary Objectives

- To measure the quantitative change in gamma-H2AX, RAD51, 53BP1 formation in tumor tissue following treatment with rucaparib (only in patients undergoing biopsy).
- To develop an mRNA expression signature associated with response to rucaparib.
- To estimate the percentage of patients with a loss-of-function mutation or total allelic loss of second (somatic) gene allele (i.e. biallelic inactivation).
- To investigate any association between PARP-1 and PARP-2 protein and mRNA expression levels in tumor with response to rucaparib.
- To investigate any association between acquired reversion mutations with clinical progression on rucaparib.

3. PATIENT SELECTION

3.1 Target Population

The target population is men with hormone sensitive prostate cancer, either biochemically recurrent or metastatic. All patients must have an mutation in a homologous recombination DNA repair gene (*BRCA1, BRCA2, ATM, CHEK2, NBN,* BRIP1, *RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM*).

3.2 Expected Enrollment

A total of 30 patients will be included in this study. Of these, we will include up to a maximum of 10 patients with non-*BRCA1* or -*BRCA2* mutations in this study. This will ensure a minimum of 20 men with *BRCA1/BRCA2* mutations. The first patients are expected to be enrolled in May 2018. Accrual is expected to be completed in 24 months once the protocol has been approved by the IRB at each participating institution.

3.3 Inclusion Criteria

To be included in this study, patients should meet all of the following criteria:

- Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information.

  NOTE: HIPAA authorization may be either included in the informed consent or obtained separately.

- Males aged 18 years of age and above
- Histological or cytologic proof of adenocarcinoma of the prostate
- Pathogenic mutation in one or more homologous recombination DNA-repair genes (*BRCA1, BRCA2, ATM, CHEK2, NBN,* BRIP1, *RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM*) as documented by a clinical CLIA-grade, saliva, tissue or blood-based (i.e leukocyte DNA) genetic or molecular test (including but not limited to Invitae, Foundation One, Color Genomics, etc). Germline and/or molecular testing will not be offered as an eligibility screen.
- All patients must be ineligible for or have declined androgen deprivation therapy (ADT)-based systemic treatment, if indicated
- Absolute PSA ≥2.0 ng/ml at screening.
- Either (1) Metastatic disease as defined for one or more bone metastases confirmed by bone scintigraphy or radiographic soft tissue metastasis by CT and/or bone scan, performed within 8 weeks.. Or (2) biochemically recurrence disease as defined by a PSA >0.2 ng/ml post prostatectomy or a PSA rise of 2ng/ml or more from the nadir after radiation therapy.
- Serum testosterone ≥ 100 ng/dl.
- Participants must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
  - Hemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
  - Platelet count ≥ 100 x 10^9/L
  - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
  - Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) < 3.0 x institutional upper limit of normal

Note: Patients with elevations in bilirubin, AST, or ALT should be thoroughly evaluated for the etiology of this abnormality prior to entry and patients with evidence of viral infection should be excluded.

- Participants must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥51 mL/min:

  Estimated creatinine clearance = $\frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$

  Note: Patients with creatinine clearance between 51- 80 mL/min either at trial enrolment or during the course of the trial should be monitored every 2 weeks for laboratory assessment and toxicity evaluation.

- ECOG Performance Status ≤2(Appendix A: Performance Status Criteria)
- Participants must have a life expectancy ≥ 12 months.
- Male participants and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination [see appendix E for acceptable methods], throughout the period of taking study treatment and for 6 months after last dose of study drug to prevent pregnancy in a partner.

3.4 Exclusion Criteria

Patients that meet any of the criteria listed below will not be eligible for study entry:

- Current active second malignancy (history of non-melanoma skin cancers and superficial bladder cancers are allowed)
- Prior ADT in the past 6 months. Prior ADT in context of neoadjuvant/adjuvant primary is allowed; prior ADT for biochemical recurrence is also allowed, as long as no ADT has been administered in past 6 months and testosterone has recovered (>100 ng/dl). The total duration of prior ADT should not exceed 24 months.
- Prior treatment with anti-androgens (e.g., bicalutamide, nilutamide, enzalutamide, apalutamide) or androgen synthesis inhibitors (e.g., abiraterone, orteronel) at therapeutic dosing for more than one month within the past 6 months is not permitted. If used for less than one month, the subject may be enrolled. The use of 5-alpha reductase inhibitor therapy (e.g., finasteride, dutasteride) is allowed, as long as the subject has been on a steady dose of the medication for the past 6 months and has tolerated it satisfactorily.
- Presence of visceral (i.e. lung or liver) metastases >3cm in long-axis dimension.
- Pain due to bone metastases requiring narcotic analgesics.
- Prior treatment with intravenous chemotherapy.
- Use of any prohibited concomitant medications (Appendix B: Medications With the Potential for Drug-Drug Interactions) within the prior 2 weeks.
- Involvement in the planning and/or conduct of the study (applies to both Clovis Oncology staff and/or staff at the study site)
- Previous enrollment in the present study

- Participation in another clinical study with an investigational product during the last 1 month.
- Any previous treatment with a PARP inhibitor, including rucaparib.
- Resting ECG with QTc > 480 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome
- Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.
- Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.
- Major surgery within 2 weeks of starting study treatment, and patients must have recovered from any effects of any major surgery.
- Poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 6 months) myocardial infarction, uncontrolled major seizure disorder, extensive interstitial bilateral lung disease, or any psychiatric disorder that prohibits obtaining informed consent.
- Unable to swallow orally administered medication or gastrointestinal disorders likely to interfere with absorption of the study medication.
- Immunocompromised patients, e.g., patients who are known to be serologically positive for HIV. Known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids
- Known hypersensitivity to rucaparib or any of the excipients of the product.
- Whole blood transfusions in the last 30 days prior to entry to the study.

4. PATIENT REGISTRATION AND ENROLLMENT PLAN

4.1 Registration Procedure

After eligibility screening and confirmation that a patient is eligible, patients who are selected to participate will be registered with the Lead Center Johns Hopkins, with their local study site/institution. A record of patients who fail to meet entry criteria (i.e., screen failures) will be maintained. Patient registration must be complete before beginning any treatment or study activities. A complete, signed study consent and HIPAA consent are required for registration.

4.1.1 Registration at Johns Hopkins

Confirm eligibility as defined in ***Section 3. Patient Selection***.

Obtain informed consent, by following procedures in ***Section 11.3 Written Informed Consent***.

Patient will be entered into CRMS system and enrolled in trial.

4.1.2 Multicenter/Participating site registration

Central registration for this study will take place at Johns Hopkins.

Patient registration at each study site/institution will be conducted according to the institution's established policies. Before registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form and a research authorization/HIPAA form. Patients must be registered with their local site/institution and also with the sponsor or Lead Site before beginning any treatment or study activities.

5. TREATMENT/INTERVENTION PLAN

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Table 1.

	Pre-study	Study Period				
		On Treatment Assessments (Every 28 days)[i]				Off Treatment / Follow-up
	Day -7[a, h] (±7days)	C1D1[h] (±3 d)	C2D1[h] (±3 d)	C3D1[h] (±3 d)	CnD1[h] (±3 d)	Every 28 days[d, h] (±3 d)
Informed consent	X					
Demographics	X					
Medical history	X					
EKG	X					
Focused Medical history		X	X	X	X	X
Physical exam	X	X	X	X	X	X
Vital signs (P, BP, RR, T)	X	X	X	X	X	X
Height	X					
Weight	X	X	X	X	X	X
Performance status	X		X	X	X	X
Toxicity assessment	X		X	X	X	X
Concomitant meds	X	X	X	X	X	X
Metastatic tumor biopsy	X[e]				(X)[e]	
ctDNA (10ml)		X[g]				X[g]
Radiologic tests[b]	X				X[b]	X[b]
Laboratory tests[c]	X	X[f]	X	X	X	X
Rucaparib		X	X	X	X	
Adverse events			X	X	X	X

Table 1 Study Calendar

Abbreviations: CBC, complete blood count; CT, computerized tomography; MRI, magnetic resonance imaging; PSA, prostate-specific antigen

[a] Informed consent and radiologic assessments should be obtained within 8 weeks of study start date. EKG should be obtained within 28 days of study start date.

[b] Radiographic evaluations (CT A/P and NM Bone Scan) every 3 months (if metastatic disease) or every 6 months (for BCR) while enrolled in the study). They are needed within 8 weeks of screening; if previously performed then they are to be performed at screening. CT A/P and NM Bone Scan are to be performed at off-treatment visit if they have not been performed in the prior month.

[c] CBC w/diff, Complete Metabolic Panel, PSA, lipid panel at each visit. Testosterone, PT/INR, PTT, and Urinalysis at screening visit only and should be obtained within 28 days of study start date.

[d] Subjects will be followed after completion of rucaparib therapy monthly until toxicities resolve to grade 0-1. No post treatment follow up visit needed otherwise.

[e] Only for patients with metastatic disease: MANDATORY soft tissue Core tumor biopsy performed pretreatment (Day -7 +/- 7 days), bone biopsies are optional at pretreatment. OPTIONAL soft tissue and bone tumor biopsy on C4D1 (+/- 7 days)

[f] C1D1 routine labs (CBC w/diff, Comprehensive Metabolic Panel, PSA, lipid panel) are only required if >7 days since screening labs.

[g] ctDNA will be collected once at before starting treatment and once at the time of progression.

[h] In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for inperson clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

I Patients who remain on treatment for >12 months can begin to have their clinic visits, safety labs (including CBC w/diff, Comp), PSA, and toxicity assessments every 3 months.

5.1 Screening/Pretreatment Assessment (Day -7 ± 7 days)

Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy. After this explanation, patients should be asked to sign and date a Notice of Privacy Practice research authorization/HIPAA form and an IRB-approved statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50).

The screening visit will determine patient eligibility according to the inclusion and exclusion criteria (sections 3.3 Inclusion Criteria & Exclusion Criteria). The following assessments will be performed at this visit:

- obtain informed consent and research authorization
- record demographics (including age) and medical history (including prior treatment for prostate carcinoma)
- conduct physical exam (including vital signs, height/weight)
- obtain histologic and radiologic confirmation of disease. If radiographic studies have not been performed in prior 4 weeks, they must be obtained as part of screening
- obtain history regarding prior treatment history for prostate cancer (including history of ADT, history of radiation therapy or other local therapy).
- perform laboratory tests (Complete blood count w/Diff, PSA, Comprehensive metabolic panel, urinalysis, PT/INR, PTT, testosterone, lipid panel).
- assess performance status (ECOG). (Appendix A)
- Perform 12-lead EKG. ECGs are required within 14 days prior to starting study treatment and when clinically indicated.
    - Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.
    - ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.
- determine suitability for rucaparib.
- Confirm/schedule CT guided biopsy of a metastatic site of disease if applicable (i.e. soft tissue, lymph node, bone) – further described in section 5.1.1
- Confirmation of a pathogenic mutation in a homologous recombination DNA repair gene of interest , as documented by a CLIA-grade, saliva, tissue or blood based test ,(*BRCA1, BRCA2, ATM, CHEK2, NBN,* BRIP1, *RAD50, RAD51C, RAD51D,*

PALB2, *MRE11*, *FANCA*, *FANCB*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *FANCM*) is necessary prior to proceeding with enrollment.

- discuss concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)

Relevant information should be documented. The institutional registration should be finalized, and appropriate documents (i.e. signed informed consent, research authorization/HIPAA form, and supporting source documentation for eligibility questions) faxed or emailed to the lead site/sponsor.

5.1.1 Surgical Procedures

A core needle biopsy of a metastatic site of disease, in those patients with metastatic disease, (soft tissue, lymph node, or bone) will be performed before C1D1 of treatment (Day -7 +/- 7 days). Patients will be referred to the Johns Hopkins Biopsy Service for an image guided core biopsy. At least 4 standard core biopsies should be obtained from a metastatic site (soft tissue, lymph node, or bone). *Fine needle aspiration is unlikely to yield adequate tumor tissue for molecular analysis, and should only be attempted when core biopsy is not feasible.* A unique identifier code system, in which no names and other personal healthy information will be used to identify the samples, will be used to assign a subject number to each of the biopsy samples. Each specimen of collected tissue will be submitted as formalin-fixed paraffin-embedded (FFPE) tissue according to standard procedures. To minimize tissue autolysis, a dedicated tissue technician will be called/paged to the biopsy room to initiate processing steps including FFPE preparation, which should be done within 30 minutes of biopsy collection. All samples will be evaluated for adequacy and assessment of tumor –to-normal ratio by the urologic pathologist on the study (Dr. Tamara Lotan). FFPE specimens will be processed according to the standard FFPE procedures in the Pathology department.

<u>Special considerations for optional bone biopsies</u>

In patients with metastatic bone lesions only, the following guidelines should be considered when obtaining a bone biopsy.(16) These guidelines have been established by a Johns Hopkins musculoskeletal pathologist with over 30 years of experience interpreting bone biopsies.

- Bone biopsies should preferably be obtained using CT guidance.
- Osteolytic lesions should be targeted preferentially over osteoblastic lesions.
- Metastases in the pelvic bones and long bones (e.g. femur, humerus) should be targeted preferentially over vertebral or rib metastases.
- At least 4 cores from different zones of the lesions should be performed.
- Bone biopsies should not be decalcified, due to degradation of nucleic acids during the decalcification process.

5.1.1.1 Potential biopsy complications

Potential complications include: infection, bleeding, and pain at the biopsy site.

5.2 Treatment/Intervention Period (Day 1 of each 28 day cycle +/- 3 days, ongoing)
Patients will be seen on D1 of each cycle of rucaparib (consisting of 28 days, +/- 3 days). The following assessments will be performed at each visit:

- conduct physical exam (including vital signs, weight)
- obtain any medical history changes from prior assessment
- assess performance status (ECOG). (Appendix A)
- review concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)
- Patients who remain on treatment for >12 months can begin to have their clinic visits, safety labs (including CBC w/diff, Comp), PSA, and toxicity assessments every 3 months.

5.2.1 Clinical and laboratory assessments
On Day 1 of each cycle, patients will have a non-fasting blood drawn for the following values: Repeat labs are not needed on C1D1 as long as visit is within 7 days of screening values.

- CBC
- Comprehensive chemistry panel
- PSA
- Lipid panel
- ctDNA blood collection (10ml) (C1D1 only)

Every 3 cycles for patients with metastatic disease or every 6 cycles for patients with BCR, patients will have radiographic studies:

- CT Abdomen and Pelvis with contrast
- NM Bone scan

Laboratory Safety Assessments:

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available, will check % differentials. Coagulation [activated partial thromboplastin time (APTT) and international normalized ratio (INR)] will be performed at baseline and if clinically indicated.

Biochemistry assessments for safety (sodium, potassium, calcium, glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin.•

Urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix F 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions

5.2.2 Surgical Procedures

A core needle biopsy will be performed on C4D1 +/- 7 days at the same site of metastatic disease previously biopsied at screening for patients with metastatic disease. This biopsy is optional. Further description of this biopsy can be found in section 5.1.1.

5.2.3 Safety assessments

Adverse events (AEs) will be monitored at each scheduled visit and throughout the study. Toxicity will be assessed using the most recent National Cancer Institute (NCI) guidance: the most recent version of Common Terminology Criteria for Adverse Events (CTCAE).

5.3 Treatment-Limiting Adverse Event

A treatment-limiting adverse event is any AE related to protocol therapy experienced during the study resulting in treatment termination. Such events include dose adjustments for each drug (i.e., increases, decreases, delaying, or omitting therapy) related to the AE after therapy has been initiated or AEs because of other therapies, such as surgery and radiation therapy.

5.4 Dosing and Dose Modifications

5.4.1 Dosing

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 and 86° F)

Patients will take 600 mg rucaparib orally twice a day (BID), as close as possible to 12 hours apart and preferably at the same times every day, with water starting on Day 1. Rucaparib tablets must be swallowed whole and may be taken with or without food. 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. If vomiting occurs shortly after the rucaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted.

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.

5.4.2 Dose Modifications

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 6. The most recent NCI CTCAE will be used to grade adverse events.

At each study visit for the duration of their participation in the study, patients will be evaluated for adverse events (all grades), serious adverse events (SAEs), and adverse events that require study drug interruption or discontinuation. Patients discontinued from the treatment phase of the study for any reason will be evaluated approximately 30 days after the last dose of the study drug.

5.4.2.1 Dose Modifications for Toxicities

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions.

Patients who require an interruption in rucaparib for >2 weeks due to toxicity must discontinue study drug unless discussed with Protocol Chair.

Adverse events possibly related to study drug must be resolved to grade 1 or baseline prior to resumption of dosing.

Study treatment can be dose reduced to 500 mg twice daily as a first step, to 400 mg twice daily as a second step and 300mg twice daily as a third step. If the reduced dose of 300 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted.

5.4.2.1.1 Management of hematological toxicity

Management of anemia

Table 2 Management of anaemia

Haemoglobin	Action to be taken
Hb < 10 ***but*** **≥ 8 g/dl (CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue rucaparib with supportive treatment (e.g. transfusion) *or* interrupt dose for a maximum of 2 weeks. If repeat Hb**< 10** ***but*** **≥ 8 g/dl**, dose interrupt (for max of 2 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to **500 mg twice daily** as a first step and to **400 mg twice daily** as a second step may be considered.
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt rucaparib for a maximum of 2 weeks until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to dose should be reduced to 500 mg twice daily as first step. If the reduced dose of 500 mg twice daily is not tolerable, further dose reduction to 400mg BID as a second step may be considered.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions.

Management of neutropenia, leukopenia and thrombocytopenia

Table 3 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 2 weeks; appropriate supportive treatment and causality investigation

Toxicity	Study treatment dose adjustment
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 2 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce rucaparib to **500 mg twice daily** as a first step and **400 mg twice daily** as a second step Discontinue therapy in cases of febrile neutropenia and thrombocytopenia associated with haemorrhage.

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for PEGylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Management of prolonged hematological toxicities while on study treatment

Discontinue rucaparib if a patient develops prolonged hematological toxicity such as:

≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence

≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)

≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Adverse events possibly must be resolved to grade 1 or baseline prior to resumption of dosing.

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 2 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to Clovis Oncology. Rucaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

Bone marrow or blood cytogenetic analysis

Bone marrow or blood cytogenetic analysis may be performed according to standard hematological practice for patients with prolonged hematological toxicities. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to Clovis Oncology for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

5.4.2.1.2 Management of non-hematological toxicity

Dose interruptions are allowed as required, for a maximum of 2 weeks. Patients who require an interruption in rucaparib for >2 weeks due to toxicity must discontinue study drug. Where toxicity reoccurs following re-challenge with study treatment, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 500 mg bid as a first step , to 400 mg bid as a second step and 300mg bid as a third step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

Adverse events possibly related to study drug must be resolved to grade 1 or baseline prior to resumption of dosing.

Management of nausea and vomiting

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines.

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines or dexamethasone.

Management of AST/ALT 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: Patients should stop taking rucaparib until values have returned to Grade 2 or better, then resume rucaparib with a dose reduction to 500mg BID. Monitor liver function tests weekly for 3 weeks after rucaparib has been restarted. If a Grade 4 ALT/AST elevation is again observed at 500mg BID, Patients should stop taking rucaparib until values have returned to Grade 2 or better, then resume rucaparib with a dose reduction to 400mg BID. Dose reductions to 300mg BID will be allowed.

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

- Monitor liver function tests weekly until resolution to ≤ Grade 2.

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

- If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before rucaparib can be resumed, either at the at a reduced dose (500mg BID (if currently taking 600mg BID), 400mg BID (if currently taking 500mg BID), 300mg BID (if currently taking 400mg BID).

Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with Principle Investigator.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to a planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

5.5 End of Treatment/Treatment Discontinuation Visit 28 days after last dose +/- 3 days)

- Conduct physical exam (including vital signs, height/weight)
- perform laboratory tests: Complete blood count w/Diff, PSA, Comprehensive metabolic panel
- ctDNA blood collection (10ml)
- assess performance status (ECOG). (Appendix A)
- review concurrent medications
- assess AEs
- if patient is discontinuing participation in study, perform radiographic tests: CT A/P and NM Bone Scan (if these have not been performed in the prior 3 months)

5.6 Follow-up (At least every 28 days while active AEs)

Patients will be followed every 28 days beyond the end of treatment visit if they have withdrawn from study because of AEs. Patients withdrawn from the study because of AEs will be followed until the adverse event has either resolved or stabilized. Reasons for premature withdrawal should be determined and noted. To be performed at each visit will be:

- conduct physical exam (including vital signs, height/weight)

- perform laboratory tests (CBC w/diff, Comprehensive metabolic panel) only as indicated by AEs requiring follow-up
- assess performance status (ECOG). (Appendix A)
- review concurrent medications
- reassess AEs.
- When patient will discontinuing participation in study, perform radiographic tests: CT A/P and NM Bone Scan (if these have not been performed in the prior 3 months)

5.7 Correlative/Special Studies

5.8.1. DNA sequencing
FFPE biopsy tissue will be sent to Foundation Medicine for next generation sequencing, based upon their commercially available platform.

5.8.2. mRNA expression profiling
A sample of FFPE biopsy tissue will be sent to GenomeDx for RNA expression profiling.

5.8.3. PARP-1, PARP-2, γH2AX, RAD51, 53BP1 mRNA/ Protein Analysis
A sample of biopsy will be sent to the Lotan laboratory for analysis.

5.8 Concomitant Medications

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies must be documented on the case report form (CRF).

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.

CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on results of in vitro CYP interaction studies, caution should be used for concomitant medications with narrow therapeutic windows that are substrates of CYP2C19, CYP2C9, and/or CYP3A. Selection of an alternative concomitant medication is recommended.

Examples of CYP Substrates with Narrow Therapeutic Range

CYP Enzyme	Substrates with Narrow Therapeutic Range [a]
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 (eg, Torsades de Pointes).

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.

Anti-emetics/Anti-diarrheals

If a patient develops nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs and appropriate treatment of the event given.

Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment.

Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of survival.

5.8.1 Prohibited before enrollment and during administration of study treatment
Medications that are prohibited during study treatment and in the prior 6 months prior to enrollments: LHRH agonist / antagonist therapy, androgen receptor antagonists, and androgen synthesis inhibitors. 5-alpha reductase inhibitors are allowed if subject has been taking stable dose of medication for prior 6 months.

5.9 Contraception

Patients with partners of child bearing potential, who are sexually active, must agree to the use of two highly effective forms of contraception throughout period of taking study treatment and for 3 months after last dose of study drug.

For details refer to Appendix E Acceptable Birth Control Methods.

6. THERAPEUTIC/DIAGNOSTIC AGENT(S)/MODALITY(-IES)

6.1 Description of Treatments

The drug to be tested in this clinical protocol is rucaparib (IND #). Rucaparib will be supplied by Clovis Oncology.

6.2 Pharmacokinetics

Dose proportional PK were observed up to 600 mg BID. The mean T_{max} and mean $T_{1/2}$ were approximately 4 hours and 17 hours, respectively. Oral administration of 600 mg rucaparib with a high-fat meal resulted in a moderate increase of C_{max} and AUC of rucaparib compared with that under fasted conditions. The increases in rucaparib exposures were not considered clinically significant, thus rucaparib can be taken with or without food.

6.3 Dosage Selected, Preparation, and Schedule of Administration

Rucaparib will be dosed based upon guidelines in Section 5. Treatment will be administered on an outpatient basis. Rucaparib is dosed twice daily. Patients will be asked to keep a drug diary and present bottles for assessment at each assessment.

6.3.1 Supply, storage requirements, and special handling

6.3.1.1 Supply and packaging

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

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

6.3.1.3 Labeling
Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

6.4 Removing Patients from the Protocol

In the absence of treatment delays because of adverse events, treatment will continue for until one of the following criteria applies:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Severe non-compliance with the study protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)
- Potential Hy's Law cases (AST or ALT ≥3x ULN and TBL ≥2xULN with no other reason)
- PSA doubling from baseline value, confirmed by a second value at least 4 weeks apart, with a minimum time since initiation of therapy of 12 weeks.
- Disease progression by symptomatic or radiographic assessment. Patient requiring palliative radiation therapy will be considered to have disease progression and removed from the study.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the patient to be retreated.
- Adverse events requiring cessation of rucaparib, with inability to restart therapy within 14 days.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator

Because an excessive rate of withdrawals can render the study uninterpretable, unnecessary withdrawal of patients should be avoided. When a patient discontinues treatment early, the investigator should make every effort to contact the patient and to perform a final evaluation. The reason(s) for withdrawal should be recorded.

7. ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

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

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a non-leading question (eg, "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE). Symptoms reported spontaneously by the patient during the physical examination would also qualify as an AE (and hence documented on the AE eCRF, not on the physical examination eCRF, which is reserved for physical signs or findings).

7.1.2 Serious Adverse Event (SAE)

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

- Results in death. Any event resulting in death during the reporting period (from date of first dose of study drug through 28 days after last dose) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing that results in death must also be reported as an SAE.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity
- Results in a congenital anomaly or birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

7.1.2.1 *Events or Outcomes Not Qualifying as Serious Adverse Events*

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

- Pre-planned or elective hospitalization including social and/ or convenience situations (eg, respite care)
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward)
- Overdose of either Clovis study drug or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a nonserious AE on the appropriate eCRF page
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTCAE Grade 5 (fatal outcome) indicated.

7.1.3 Medical significance

An event that is not fatal or life-threatening and that does not necessitate hospitalization may be considered serious if, in the opinion of the investigator, it jeopardizes the patient's status and might lead to medical or surgical intervention to prevent any of the outcomes described in section 7.1.2. Such medically significant events could include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

7.1.4 *Adverse Events of Special Interest (AESI)*

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

Details on the sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to the sponsor expeditiously.

7.1.5 Progression of malignancy

Progression of a patient's malignancy should not be considered an AE or SAE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. If disease progression results in death or hospitalization while on study or within 28 days of the last dose, progressive disease will be considered an SAE.

7.1.6 Life-threatening events

A life-threatening event is any AE that places the patient at immediate risk of death from the reaction as it occurs. It is not a reaction that had it occurred in a more severe form, might have caused death.

7.1.7 Hospitalization or prolongation of hospitalization

Hospitalization encompasses any inpatient admission (even for less than 24 hours) resulting from a precipitating, treatment-emergent adverse event. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered AEs (e.g. admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

7.1.8 Significant disability

Disability is a substantial disruption of the patient's ability to conduct normal life functions.

7.1.9 Pregnancy

Male participants should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

All outcomes of pregnancy should be reported to Clovis Oncology.

7.1.10 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

Death that is clearly the result of disease progression should be reported to the study monitor at the next monitoring visit, be documented, and reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours**. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should be reported as a SAE., but followup should be done to determine the cause of death. If a cause of death is determined, the event term of "death" must be updated at that time. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to Clovis Oncology within the usual timeframes.

The most recent version of the NCI CTCAE v.5.0 handbook will be used for adverse event descriptions and grading.

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 28 days after the last dose of study drug. Any SAEs, AESIs, and treatment-related Grade 3/4 AEs must be followed until resolution or stabilization, or until lost to follow-up. After the 28-day window, treatment-related SAEs and all AESIs, irrespective of causality, need to be reported.

7.2 Expectedness

Adverse events can be considered, "expected," or, "unexpected."

7.2.1 Expected Adverse Events

Expected adverse events are those that have been previously identified as resulting from administration of the agent. An adverse event can be considered expected when it appears in the same nature severity and specificity as what is in the current adverse event list of the Investigator's Brochure (Reference Safety Information [RSI] section).

7.2.2 Unexpected Adverse Events

An adverse event can be considered unexpected when the nature, intensity or frequency of which is not consistent with the current adverse event list of the Investigator's Brochure, contact the lead site, principal investigator or sponsor to confirm unexpected adverse events when necessary.

7.3 Recording and Grading

7.3.1 Recording

All observed or volunteered adverse events, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be documented.

A clinically significant change in a physical examination finding or an abnormal test result (i.e., laboratory, x-ray, EKG) should be recorded as an AE, if it:

- is associated with accompanying symptoms
- is suggestive of organ toxicity
- requires additional diagnostic testing or medical or surgical intervention
- leads to a change in study dosing or discontinuation from the study
- is considered clinically significant by the investigator.

An abnormal test result that is subsequently determined to be in error does not require recording as an adverse event, even if it originally met one or more of the above criteria.

7.3.2 Grading severity

All adverse events will be graded for intensity on a scale of 0 to 5. Severity grades will be recorded and based on the most recent version of the NCI CTCAE v.5.0 handbook.

7.3.3 Attributing causality

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge with the study drug (Table 4).

Table 4 *Relationship of Adverse Event to Study Drug*

Not Related To Study Drug	• An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.) • It does not follow a reasonable temporal sequence from administration of the study drug. • It does not follow a known pattern of response to study drug • It does not reappear or worsen when study drug is restarted. • An alternative explanation is likely, but not clearly identifiable.

Related to Study Drug	• An AE that is difficult to assign to alternative causes. • It follows a strong or reasonable temporal sequence from administration of study drug. • It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. • It follows a known response pattern to study drug • It is confirmed with a positive rechallenge or supporting laboratory data.

7.4 Reporting Adverse Events

7.4.1 Reporting serious adverse events

All SAEs and AESIs, regardless of relationship to study drug, must be reported to the lead site within 48 business 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 28-day specified window, only SAEs considered to be treatment-related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report.

The Clovis or the Sponsor-Investigator's study-specific Serious Adverse Event (SAE)/Adverse Events of Special Interest (AESI) Report Form must be used for reporting SAEs and AESIs. The contact information for reporting of SAEs and AESIs can be found on the SAE/AESI Reporting Form and Pregnancy Report Forms.

The Sponsor-Investigator is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the U.S. Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32 ; to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA); to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other applicable regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), Clovis or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

The Sponsor-Investigator will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

7.4.2 Reporting SAEs at multi-site/participating institutions

SAEs should be reported to the lead site.

8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

8.1 Outcome Assessment

All baseline evaluations will be performed as closely as possible to the beginning of treatment (within 7 days). For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

Note: Any bone lesions, however, that are identified on the baseline CT or MRI studies and judged as providing meaningful information about nontarget disease status on the basis of their size or other features should be considered for inclusion in the follow-up assessments of nontarget lesions by the same imaging modality.

- Conventional CT, Bone Scan

  CT Chest, abdomen, pelvis and Bone scans will be used to measure tumor response as a secondary endpoint per RECIST 1.1 criteria (metastatic disease only).

- Tumor markers

  PSA measurements will be used to assess the primary endpoint

8.1.1 Primary endpoint

The primary endpoint is defined as a PSA_{50} response, defined as a decline in PSA to ≥50% of baseline level, confirmed with a second measurement at least 4 weeks later.

8.1.2 Secondary endpoints

8.1.2.1. Safety: this endpoint is defined as incidence of grade 3-5 toxicities based upon CTCAE v5.0 standard grading scales.

8.1.2.2. PSA Progression-Free Survival (PFS): PSA progression (PSA progression-free survival; PSA–PFS) will be defined per PCWG3 guidelines

For those subjects showing an initial decline in PSA from baseline, is defined as an increase in PSA that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend).

For those subjects with no decline in PSA from baseline, is defined as an increase in PSA that is ≥25% and ≥2 ng/mL after 12 weeks.

8.1.2.3. Radiographic Progression–free survival: time to radiographic or clinical progression or death, whichever comes first. Based on RECIST version 1.1 and PCWG3 definitions including: Progression of soft tissue lesions according to RECIST 1.1; Progression of bone lesions detected with bone scan according to PCWG3 criteria; Radiologically-confirmed spinal cord compression or pathological fracture due to malignant progression, or other clinical event deemed to be cancer-related.

8.1.2.4 Objective response rate (metastatic disease only): defined as the proportion of patients achieving a complete/partial response in target lesions (RECIST

1.1)

8.2 Therapeutic Response

Response and progression will be evaluated in this study using a combination of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee(17) and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG3).(18)

Patients will need to be reevaluated for response every cycle according to the guidelines below.

8.2.1 PSA

Perform PSA testing at a minimum of 1-week intervals with the threshold PSA level at 2.0 ng/mL. To report PSA-based outcomes, PCWG3 recommends that the percent of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient using a waterfall plot. PSA measurements obtained during the first 12 weeks should not be used as the sole criterion for clinical decision making.

8.2.2 Measurable disease

According to RECIST 1.1, measurable disease is defined as at least 1 lesion > 10mm in its longest diameter as measured with conventional techniques (i.e., CT with slice cut of 5mm, MRI). All tumor measurements will be taken using a ruler or calipers and recorded in millimeters (or decimal fractions of centimeters). To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

8.2.3 Nonmeasurable disease

Following RECIST, all other lesions (or sites of disease) will be considered nonmeasurable disease. This includes small lesions (longest diameter < 10 mm using spiral CT scan) lymph nodes (shortest diameter $\geq$10mm to <15mm) and any of the following:

- bone lesions
- ascites
- pleural or pericardial effusion
- lymphangitis cutis or pulmonis
- abdominal masses that are not confirmed and followed by imaging techniques
- cystic lesions
- lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

Note: If only a single, asymptomatic bone lesion is present at baseline, and will be irradiated, the metastatic nature of this lesion must be confirmed by x-ray, CT, or MRI.

8.2.4 Target (nodal and visceral) lesions

Following RECIST, progression in a nodal or visceral site (i.e., liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately.

All measurable lesions (up to a maximum of 2 lesions per organ and 5 lesions in total) will be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected on the basis of size (i.e., the largest area) and suitability for accurate, repeated measurements (either by imaging techniques or clinically). The sum of the longest diameter (LD) of all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Because small lymph nodes are difficult to measure accurately and may not be malignant, to be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

8.2.5 Bone lesions

When the bone scan is the sole indicator of progression, disease progression in bone is defined as 2 or more new lesions seen on bone scan compared with a prior scan for used trial entry. In situations where scan findings suggest a flare reaction or where new lesion(s) may represent trauma, confirm these results with other imaging modalities (eg, MRI or fine-cut CT). If many new areas of uptake are observed, confirmation is generally not necessary.

8.2.6 Nontarget lesions

All other lesions (or sites of disease) will be identified as nontarget lesions and recorded at baseline. Nontarget lesions will include measurable lesions that exceed the maximum number per organ (2) or total of all involved organs (5), as well as nonmeasurable lesions. The presence or absence of these lesions will be recorded on the CRF and should be evaluated at the same assessment time points as all target lesions.

8.2.7 New lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).

8.3 Response Criteria for Primary and Secondary Endpoints

8.3.1. Measurable soft-tissue lesions

When evaluating soft-tissue lesions, the definitions in Table 5 apply.

Table 5 RECIST1.1 response criteria for target lesions

Response	Evaluation of Soft-Tissue Lesions
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

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

Changes in nodal and visceral sites should be recorded and reported separately, and lymph nodes in the pelvis must measure at least 1.5 cm in shortest diameter to be considered target lesions. Complete elimination of disease at a particular site should be recorded separately. Any favorable change should be confirmed using a second follow-up scan.

8.3.2 PSA

For each patient, use a waterfall plot to report the percent change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment. We will also report the proportion of patients to achieve a 50% of greater decrease in PSA from baseline (i.e. PSA_{50} response rate)

8.3.3 Bone

Record post-treatment changes as either “no new lesions” or “new lesions.”

In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later. In the rare case where visible lesions disappear, this too should be confirmed.

8.3.4 Nontarget lesions

When assessing nontarget lesions, the definitions in Table 6 will apply.

Table 6 RECIST1.1 response criteria for nontarget lesions

Response	Evaluation of Nontarget Lesions
Complete response (CR)	the disappearance of all nontarget lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10mm short axis)
Non-CR/non-PD	the persistence of one or more nontarget lesions and/or maintenance of tumor marker levels above the normal limits
Progressive disease (PD)	the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions

8.4 Criteria for Progressive Disease.

8.4.1. Measurable soft-tissue lesions

When evaluating soft-tissue lesions, the definitions in Table 5 apply:

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

Progression in a nodal or visceral site should be defined using RECIST1.1 (Table 5).

8.4.2 PSA

Per the PCWG3, PSA progression is defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second value obtained 3 or more weeks later. Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

8.4.3 Bone

Progressing disease on bone scan is considered when at least 2 new lesions are observed. Yet, progression remains unconfirmed unless at least 2 *additional* new lesions appear at a subsequent time point.

Unless clinically indicated, there is no need to perform a follow-up bone scan before 12 weeks of treatment. To define disease progression requires a confirmatory scan (which shows additional new lesions compared with the first follow-up scan) performed 6 or more weeks later. When further progression is documented on the confirmatory scan, the date of progression recorded for the trial is the date of the first scan that shows the change.

8.4.4 Nontarget lesions

When assessing nontarget lesions, the definitions in Table 6 apply.

9. DATA REPORTING AND REGULATORY REQUIREMENTS

Multicenter Guidelines

The Protocol Chair

The Protocol Chair, Dr. Mark Markowski is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data from all sites

Lead Center

The Lead Center (Johns Hopkins) is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration
- Collecting and compiling data from each site
- Establishing procedures for documentation, reporting and submitting of AE's and SAE's to the Protocol Chair and all other applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating PCCTC Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Lead Center
- Registering all patients with the Lead Center by submitting patient registration form, and signed informed consent promptly
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the Lead Center
- Collecting and submitting data according to the schedule specified by the protocol

9.1 Data Entry

Data collected during this study will be entered into a secure database. Staff at Johns Hopkins will be responsible for the initial study configuration and setup in the CRMS database and for any future changes.

9.1.1 Case report forms completion

Case report forms will be generated by the coordinating center for the collection of all study data. Investigators will be responsible for ensuring that the CRFs are kept up-to-date.

The paper Eligibility Checklist CRF must be completed using black ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction.

eCRFs will be completed within 2 weeks of the patient coming to the clinic and all relevant supporting documentation such as scans, progress notes, nursing notes, blood work, pathology reports, etc., will be submitted via email to the Study Manager for remote monitoring approximately every 4-6 weeks when requested. All patient names or other identifying information will be removed prior to being sent to the Coordinating Center (SKCCC) or non- redacted source documents can be sent via a password -protected/ secured document transfer based on each institution's guidelines.

Authorized representatives of the Coordinating Center (SKCCC) may visit the satellite sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

9.1.2 Source documents

Study personnel will record clinical data in each patient's source documents (i.e., the patient's medical record). Source documentation will be made available to support the patient research record. Study monitors will review entries on the CRFs at regular intervals, comparing the content with source documents.

9.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents, study-related documents, and the CRFs. Because the length of time required for retaining records depends upon a number of regulatory and legal factors, documents should be stored until the investigator is notified that the documents may be destroyed. In this study, records are to be retained and securely stored for a minimum of 5 years after the completion of all study activities.

9.2 Data Management

9.2.1 Lead research program coordinators

A Lead research program coordinator at the coordinating center will be assigned to the study. A Lead Research Program Coordinator will manage the study activities at each of the participating sites. The responsibilities of the Lead Research Program Coordinator include project compliance, data collection, data entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol team.

9.3 Clinical Trial Agreement

This trial is being conducted under one or more clinical trial agreements that contain, among other terms, the publication policy, indemnity agreements, and financial arrangements for the study.

9.4 Study Monitoring

Study calls between sites will be held every 3 months to discuss accrual goals and AE/toxicity data. Interim analysis will be performed as described in Section 10.

10. STATISTICAL CONSIDERATIONS

The primary endpoint will be the proportion of subjects who achieve a PSA response, defined as a 50% or greater decline in PSA from baseline, confirmed on a subsequent

measurement at least 3 weeks apart. The treatment regimen would be considered of insufficient activity for further study in this population if the PSA response rate is 50% or less. The sample size is calculated to detect an improved PSA response rate from 50% to 75%. An optimal Simon two stage design is planned. A total of 12 patients will be entered in the first stage with a planned analysis for futility performed 12 weeks after the last patient began rucaparib. The number of patients allowed with a non-BRCA1, -BRCA2, or –ATM mutation in stage 1 will be capped at 3. If 6 or fewer subjects have a PSA response, the study will be terminated and we will conclude the regimen is ineffective. If ≥7 subjects respond, then an additional 16 patients will be studied, for a total of 28 patients. If a total of 17 or fewer subjects respond in stage one and two combined, we consider this regimen ineffective. If a total of 18 or more respond, we conclude the regimen is promising and warrants further study. The maximum sample size will be increased to 30 patients to account for possible dropouts. The total number of patients (stage 1 and 2) allowed with a non-BRCA1/ -BRCA2 mutation will be capped at 10; this will ensure that at least 20 men will be enrolled with germline BRCA1/BRCA2mutations.

This design provides 90% power to detect an absolute 25% increase in PSA response rate with a one-sided type I error of 0.1. The probability of early stopping is 0.61 under the null hypothesis that the PSA Response Rate is 50%.

10.1 Study Endpoints

10.1.1 Analysis of the primary endpoint

The primary endpoint of this study is PSA_{50} response, defined as a decrease in the PSA to 50% less than the baseline PSA upon enrollment in the trial. The decrease must be confirmed by a second measurement at least 4 weeks apart. For purposes of meeting the primary endpoint, patients will be considered to have done so if they have a PSA_{50} response only while on therapy with rucaparib. PSA values will be measured each cycle during the trial. All patients who are administered at least one dose of rucaparib will be considered evaluable for the primary endpoint. If patients do not have follow-up PSAs after initiation rucaparib therapy due to stopping therapy for toxicity or withdrawing consent, for example, then they will be replaced.

We will estimate the PSA_{50} response rate, along with the exact 95% confidence interval, for the population of patients.

10.1.2 Analysis of secondary endpoints

10.1.2.1. Safety

Patients will be assessed for toxicities at each clinical evaluation. Toxicities will graded according to CTCAE v5.0 standardized grading scales. The incidence of grade 3-5 toxicities will be reported. Patients will be assessed for toxicity as long as they are taking rucaparib, and patients will continue to be followed if rucaparib is discontinued for toxicity until the toxicities improve to grade 1 or resolve

Toxicities will be reported as a tabulated table by type and grade.

10.1.2.2. PSA progression-free survival (PFS)

A standard definition of PSA progression per PCWG3 will be used. PSA PFS will be defined as an increase in 25% over a nadir value, confirmed by a follow-up PSA at least 4 weeks apart. If patients are removed from study prior to PSA progression, then they will be censored at that time.

We will use the Kaplan-Meier method to estimate the median PSA PFS.

10.1.2.3. Radiographic progression-free survival (rPFS)

Progression-free survival will be measured from the time of first dose to objective tumor progression as defined by RECIST 1.1 for progressive disease or death and summarized using a Kaplan-Meier curve. Progression will be assigned to the earliest observed time. Patients whose disease has not progressed at follow-up will be censored at the date when the last tumor assessment determined a lack of progression.

We will use the Kaplan-Meier method to estimate the median PFS.

10.1.2.4 Objective response rate

The objective response rate is defined as the percentage of patients with measureable disease who achieve an objective response by RECIST1.1 criteria (i.e. Complete response or Partial Response) to rucaparib.

We will estimate the objective response rate, along with the exact 95% confidence interval, for the population of patients.

10.1.3 Analysis of exploratory endpoints

10.1.3.1. Estimate the percentage of patients with a loss-of-function mutation or total allelic loss of second (somatic) gene allele (i.e. biallelic inactivation):

The DNA mutations present in the tumor will be identified through Foundation Medicine sequencing. Patients with a somatic alteration including: protein truncating mutations, splice site mutations, homozygous deletions, large protein truncating rearrangements, and deleterious missense alterations in the pre-specified gene list (*BRCA1, BRCA2, ATM, CHEK2, NBN,* BRIP1, *RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM*) will be considered biomarker positive. For biomarker positive and biomarker negative subjects, we will calculate PSA50 response rates with confidence intervals for hypothesis generation.

10.1.3.2 mRNA expression profile signature positive and negative PSA_{50} response calculations:

Similarly to above, subjects will have tumor tested with RNA expression profiling and scored for likelihood for response to rucaparib per the Decipher GRID platform (GenomeDx). For subjects considered to have a positive RNA expression signature based upon a binary score assigned via the GenomeDx proprietary algorithm, a PSA_{50} response rate will be calculated. Similarly, a calculation will be performed for subjects considered to have a negative RNA expression signature.

10.1.3.3 PARP-1, PARP-2, γH2AX, RAD51, 53BP1 mRNA/protein levels:

Subjects will have pretreatment and on-treatment tumor specimens analyzed. IHC and RNA in situ hybridization staining PARP-1 and PARP-2 will be performed on the pretreatment samples and scored on scale of 0 (none) to 3 (intense staining), and the results will be associated with responses for both proteins, separately, using descriptive statistics and Fisher's Exact Tests. Immunofluorescence will be used to quantify the median intensity of each γH2AX, RAD51 and 53BP1 foci per cell as well determine the median number of foci per cell on the pretreatment biopsies. Using analytical microscopy, Drs. Meeker and Heaphy have developed imaging software, which can isolate single nuclei and quantify both the intensity and number of immunofluorescent foci per nucleus (i.e. per cell). Using FFPE tissue obtained at biopsy, we will examine the change in DNA damage foci number and intensity (reported as median percent change) induced by PARPi in PSA50 responders versus non-responders using a T-test.

10.1.3.4 *Reversion Mutations:*
Subjects will have ctDNA examined by FoundationACT testing before starting treatment and at clinical progression while on rucaparib. We will report the incidence and describe the observed reversion mutation, a known mechanism of resistance to PARP inhibition.

10.2 Analysis Populations

10.2.1 Intent-to-treat/Response-to-treatment/Evaluable population
All patients who meet eligibility criteria and receive at least 1 dose of rucaparib will be included in the main analysis of the response rate, even if there are major protocol deviations (eg, incorrect treatment schedule or drug administration). Each patient will be assigned to one of the following categories:

Table 7 Categories for Response to Treatment

Category	Response
1	Complete response
2	Partial response
3	Stable disease
4	Progressive disease
5	Early death from malignant disease
6	Early death from toxicity
7	Early death from other causes
9	Unknown (not assessable/insufficient data)

NOTE: By arbitrary convention, category 9 designates unknown status in a clinical database. Patients in response categories 4 to 9 will be considered to have treatment failure (disease progression).

Conclusions are to be based on the population of all eligible patients. Subanalyses

may be performed on various subsets of patients, such as those with no major protocol deviations or those who continued in the study for the entire treatment period (i.e., did not withdraw prematurely). Subanalysis will not serve as the basis for drawing conclusions concerning treatment efficacy.

10.2.2 Safety population

All patients enrolled in the study will be included in the safety analysis population and considered evaluable for toxicity and safety from the time of their first dose. Demographic and baseline characteristics for the safety population will be summarized by number and percent for categorical data (eg, sex, race/ethnicity) and by descriptive statistics for continuous data (eg, weight, vital signs, EKG readings, disease status).

10.3 Safety Analysis

10.3.1 Evaluation of adverse events

Treatment-emergent adverse events will be translated from investigator terms to MedDRA v20.1 terminology and summarized (number and percentage of patients) for all patients who receive at least 1 dose. Adverse event summaries will be organized by body system, frequency of occurrence, intensity (i.e., severity grade), and causality or attribution. Patients who experience an adverse event more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity.

10.3.2 Evaluation of serious adverse events and premature withdrawals

Adverse events deemed serious and those resulting in treatment withdrawal or death will be summarized separately. Narrative paragraphs will be generated to describe the circumstances surrounding each SAE and death.

10.3.3 Evaluation of laboratory parameters and assays

Selected clinical laboratory parameters will be summarized and clinically significant changes from baseline will be discussed.

10.3.4 Extent of exposure

Treatment exposure will be summarized for all patients, including dose administration, number of cycles, dose modifications or delays, and duration of therapy.

11. PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonization, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

11.2 Protocol Amendments

Before starting the study, the protocol must be approved by each institution's IRB or Independent Ethics Committee (IEC). Amendments to the protocol may be made only with consent of the lead site/sponsor and principal investigator and are subject to IRB approval before instituting.

11.3 Written Informed Consent

Before obtaining consent, members of the study team will review the rationale for the treatment program with the patient. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an adverse event occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the patient.

Patients will be required to sign and date (in triplicate) a statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study. The original signed document will become part of the patient's medical record, a copy will be forwarded to the lead site/sponsor pursuant to sponsor registration and a copy will be sent home with each patient.

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible for the protocol
- the right of the patient to accept or refuse treatment and to withdraw from participation in this study
- Text regarding the consortium and the coordinating center should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (eg, "Prostate Cancer Clinical Trial Consortium, Coordinating Center at Memorial Sloan-Kettering Cancer Center, New York, NY")

11.4 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the patient's medical records, and each patient will receive a copy of the signed documents. The use and disclosure of protected health information will be limited to the individuals described in the research authorization form. The research authorization form must be completed by the principal investigator and approved by the IRB.

11.5 Terminating or Modifying the Study

Adverse event and laboratory data from this trial will be assessed by the medical monitor (Dr. Mark Markowski) on an ongoing basis. At least quarterly, data from the clinical database will be reviewed. The results of this review will be shared with all investigators either in writing or as part of a teleconference. SAEs will be reviewed as they are reported

to the lead site/sponsor, and the medical monitor will make an assessment regarding the safety of continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the principal investigator be that the study should be terminated, the study will be closed to further accrual. Patients who are receiving rucaparib will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**%**	**Description**
0	Normal activity. Fully active, able to continue all predisease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity, minor signs or symptoms of disease
1	Symptoms, but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair > 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled, cannot carry on any self-care, totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX B: MEDICATIONS WITH THE POTENTIAL FOR DRUG-DRUG INTERACTIONS

CYP Enzyme	Substrates with Narrow Therapeutic Range
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

APPENDIX C: LABORATORY MANUAL

Pathology will be reviewed and processed centrally at Johns Hopkins. Biopsy specimens will be handled and sampled in a uniform fashion.

The lead pathologist at Johns Hopkins, Dr. Tamara Lotan, will perform the central review and prepare tissue for correlative analysis.

All slides listed below should be sent to Dr. Tamara Lotan's lab for central handling at:

Department of Pathology
1550 Orleans St.
Cancer Research Building II, Room 343
Baltimore, MD 21231

- 10 unstained slides and 1 H&E slide representative of tumor will be prepared and send to Foundation Medicine for FoundationOne testing. Tumor will be placed in the FoundationOne specimen kit and mailed to:
  Foundation Medicine, Inc.
  7010 Kit Creek Road
  Morrisville, NC 27560
  Phone: 888.988.3639

- 10 unstained slides representative of tumor will be prepared and send to the Lotan Laboratory for PARP-1, PARP-2, gamma-H2AX, 53BP1, and RAD51 analysis.

- 10 unstained slides will be stored at 4deg C until placement in cooler shipping box with ice packs and mailed to:
  GenomeDx Biosciences Laboratory
  10355 Science Center Drive
  Suite 240
  San Diego, CA 92121

- 5 unstained slides representative of tumor will be prepared and banked, for those subjects consenting to optional tissue banking for future research.

- ctDNA specimens will be analyzed by FoundationACT. Lab kits will be provided by Johns Hopkins study team.

For Subjects with metastatic bone disease only

Subjects who decline the bone biopsy are asked permission to obtain 30-35 unstained slides from their prior prostatectomy. If agreed, the unstained slides received will be apportioned in the same manner above.

APPENDIX D: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

17-AAG	17-allylamino-17-demethoxygeldanamycin
17-DMAG	17-dimethylaminoethylamino-17-demethoxygeldanamycin
2-MPPA	2-(3-mercaptopropyl) Pentanedioic acid
AdEERS	Adverse Event Expedited Reporting System
ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
AGA	androgenetic alopecia
AI	accumulation index
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
APTT	activated partial thromboplastin time
AR	androgen receptor
ASAEL	Agent Specific Adverse Event List
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
AUMC(INF)	area under the moment concentration time curve extrapolated to infinity
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
%BE	percent biliary excretion
bid	bis in die (twice a day)
BLQ	below limit of quantification
BMI	body mass index
BP	blood pressure
BSA	Body Surface Area
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
caBIG	Cancer Biomedical Informatics Grid

CAEPR	Comprehensive Adverse Event and Potential Risks
CALGB	Cancer and Leukemia Group B
CBC	complete blood count
CCC	Clinical Consortium Committee
CCD	Central Consortium Database
CDE	common data element
CDUS	Clinical Data Update System
CFR	Code of Federal Regulations
CI	confidence interval
Cl-	chloride
Clcr	creatinine clearance
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F	apparent total body clearance
Cm	centimeter
Cmax	maximum plasma concentration
Cmin	trough observed concentration
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CNS	central nervous system
CR	complete response
CRC	Clinical Research Center
CRDB	Clinical Research Database
CRF	case report form
CRMIS	Clinical Research Management Information System
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Monitoring Service
CTO	Clinical Trials Office
CV	coefficient of variation
CYP	cytochrome p-450
DCTD	Division of Cancer Treatment and Diagnosis
DEV	deviation from the nominal value
%DEV	percent deviation
dL	deciliter
DHEA	dehydroepiandrosterone

DHEA-S	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
DLT	dose-limiting toxicity
DSM	data and safety monitoring
EA	extent of absorption
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEG	electroencephalogram
EKG	electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
ESF	eligibility screening form
ESR	expedited safety report
F	bioavailability
FDA	Food and Drug Administration
FDG-PET	2-[18F]fluoro-2-deoxyglucose positron emitting tomography
FDHT	18-fluoro-dehydrotestosterone
%FE	percent fecal excretion
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GAPDH	glyseraldehayde-3-phophate dehydrogenase
GC	gas chromatography
GCP	good clinical practice
GCPII	glutamate carboxypeptidase II enzyme
GFR	glomerular filtration rate
GnRH	gonadotropin-releasing hormone
HAT	histone acetyltransferases
HCO3-	bicarbonate
HDAC	histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL7	American National Standards Institute's Health Level Seven
HPF	high power field
HPLC	high-performance liquid chromatography
HR	heart rate
HRPC	hormone-refractory prostate cancer
HRT	hormone replacement therapy
HSP90	heat-shock protein 90

ICD	International Classification of Diseases
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunochemical
IM	intramuscular
IMSL	International Mathematical Statistical Library
IND	investigational new drug
INR	international normalized ratio
IP	intraperitoneal
IRB	Institutional Review Board
ITT	intent-to-treat population
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K+	potassium
K3EDTA	potassium ethylenediaminetetraacetic acid
KLK1	kallikrein 1
LBD	ligand-binding domain
LC	liquid chromatography
LCM	laser capture microdissection
LC-MS	liquid chromatography/mass spectrometry
LD	longest diameter
LDH	lactate dehydrogenase
LLQ	lower limit of quantitation
ln	natural logarithm
LOCF	last observation carried forward
LOI	letter of intent
LPF	low power field
MAD	maximum administered dose
MDS	myelodysplasia
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
MRT	mean residence time
MRT(INF)	mean residence time adjusted for infusion time
MRT(PO)	mean residence time following oral administration
MRT(SS)	mean residence time at steady-state
MSKCC	Memorial Sloan-Kettering Cancer Center
MS	mass spectrometry

MTD	maximum tolerated dose
N	number of subjects or observations
NA	not applicable
N/A	not available
NBN	National Biospecimen Network
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NOS	not otherwise specified
NSAID	nonsteroidal anti-inflammatory drug
NTX	N-telopeptide cross-link
NVB	neurovascular bundle
OCR	Office of Clinical Research at MSKCC
PCCTC	Prostate Cancer Clinical Trials Consortium
PCRP	Department of Defense Prostate Cancer Research Program
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PIN	prostatic intraepithelial neoplasia
PK	pharmacokinetics
PMB	Pharmaceutical Management Branch
PO	per os (by mouth)
PR	partial response
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time
PSMA	prostate specific membrane antigen
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
qd	quaque die (every day)
qRT-PCR	quantitative reverse transcription-polymerase chain reaction
QOL	quality of life
RBC	red blood cell
RC	Research Council
RDBMS	Relational Database Management System
RDRC	Radioactive Drug Research Committee
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy

RPC	eResearch Program Coordinator
RSA	Research Study Assistant
RSD	relative standard deviation
%RSD	percent relative standard deviation
SAE	serious adverse event
SAHA	suberoylanilide hydroxamic acid
SC	subcutaneous
SD	standard deviation
SD	stable disease
Seq	sequence
SHBG	sex hormone binding globulin
SKI	Sloan-Kettering Institute for Cancer Research
SMD	stable metabolic disease
SOP	Standard Operating Procedures
SPORE	Specialized Programs of Research Excellence
STAR	Symptom Tracking and Reporting
SUV	standardized uptake value
t	temperature
t1/2	terminal half-life
T	time
TAUC(TAU)	trapezoidal area under the concentration-time curve in one dosing interval
TAUC(0-T)	trapezoidal area under the concentration-time curve from time zero to the time of the last quantifiable concentration
TDP	time to disease progression
TGP	prostate-specific transglutaminase
tid	ter in die (3 times a day)
TMA	tissue microarray
Tmax	time of maximum observed concentration
TMPRSS2	transmembrane protease, serine 2
TNM	tissue, lymph node, metastases
TX	treatment
ULN	upper limit of normal
ULQ	upper limit of quantitation
UR	urinary recovery
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady-state
WBC	white blood cell
WHO	World Health Organization

APPENDIX E. ACCEPTABLE BIRTH CONTROL METHODS

Rucaparib is regarded as a compound with medium/high fetal risk. Subjects with partners of childbearing potential, who are sexually active, must agree to the use of TWO highly effective forms of contraception (defined as a method that can achieve a failure rate of <1% per year when used consistently and correctly) in combination [as listed below], throughout the period of taking study treatment and for at least 4 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Highly Effective Non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose. Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

Highly Effective hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (eg., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom.

APPENDIX F. ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN – HY'S LAW

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study. The Investigator participates, together with Clovis Oncology clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP). The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

- Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

- AST or ALT ≥ 3x ULN and TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

Potential Hy's Law Criteria not met
If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met
If the patient does meet PHL criteria the Investigator will:

- Notify the Clovis Oncology representative who will then inform the central Study Team.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:
- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met. No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. Clovis Oncology and the Principal Investigator will also be involved in this review together with other subject matter experts as appropriate. According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the Clovis Oncology standard processes

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to Clovis Oncology standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence. The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease?

  - If No: follow the process described in Section 4 of this Appendix

  - If Yes: Determine if there has been a significant change in the patient's condition# compared with when PHL criteria were previously met
    - If there is no significant change no action is required
    - If there is a significant change follow the process described in Section 4 of this Appendix

      # A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

7. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf