Official Title	PLATI-PARP: A Phase 2 Study of Induction Docetaxel and Carboplatin followed by Maintenance Rucaparib in Treatment of Patients with Metastatic Castration Resistant Prostate Cancer with Homologous Recombination DNA Repair Deficiency
NCT Number	NCT03442556
Document Type	Study Protocol and Statistical Analysis Plan
Document Date	01/20/2022

IRO received 12/29/21

CLINICAL STUDY PROTOCOL

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Study Number:	338-IIT-071
Cancer Consortium Protocol Number:	9841
Study Phase:	2
Product Name:	Docetaxel, Carboplatin, and Rucaparib
Indication:	Treatment of metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency
Study Sites:	University of Washington, Seattle Cancer Care Alliance
Principal Investigator:	Heather H. Cheng, M.D., Ph.D.

FHCRC IRB Approval
01 20 2022
Document Released Date

PROTOCOL SYNOPSIS

Primary, Secondary, and Exploratory Objectives and Endpoints	
STUDY OBJECTIVES	**STUDY ENDPOINTS**
Primary Objective: 1. To determine radiographic progression free survival with 4 cycles of docetaxel with carboplatin followed by maintenance rucaparib in the treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency.	Primary Endpoint: 1. Radiographic progression free survival (modified RECIST 1.1/PCWG3, Appendix 3).
Secondary Objectives: 1. To assess maximal PSA response to induction docetaxel and carboplatin 2. To assess PSA response to switch maintenance with rucaparib 3. To assess PSA response duration with docetaxel and carboplatin followed by switch maintenance with rucaparib 4. To assess time to PSA progression with docetaxel and carboplatin followed by switch maintenance with rucaparib 5. To assess overall response of measurable disease Exploratory Objectives: 1. To correlate the presence of a DNA repair pathway mutations in cell free DNA and circulating tumor cells (CTC) with the mutations in tumor biopsy 2. To correlate differential responses to treatment based on the specific HR DNA repair mutation 3. To compare responses in patients who carry germline vs somatic-only HR alterations. 4. To assess mechanisms of resistance to rucaparib	Secondary Endpoints: 1. PSA nadir after induction, rate of PSA_{50}, rate of PSA_{90} 2. PSA nadir after maintenance, rate of PSA_{50}, rate of PSA_{90} 3. PSA response duration 4. Time to PSA progression (PCWG3) 5. ORR of measurable disease (PCWG3) Exploratory Endpoints: 1. Levels and detection of HR DNA repair pathway mutations in ctDNA and CTCs found in tumor biopsy 2. ORR in relation to specific HR DNA repair pathway mutation 3. ORR separately in germline mutation carriers and patients with somatic-only mutation 4. Assess HR DNA repair gene from biospecimens collected at progression.

METHODS:

This is a phase II study of induction docetaxel and carboplatin followed by maintenance rucaparib in patients whose tumors demonstrate evidence of homologous recombination deficiency (HRD), including inactivation of *BRCA2, BRCA1, ATM* and other genes involved in HR repair processes. Patients will be treated with docetaxel (60 mg/m^2) and carboplatin (AUC 5) every 21 days for 4 cycles followed by maintenance therapy with rucaparib 600 mg twice daily (BID) until progression or unacceptable toxicity. Progression will be determined by Modified RECIST 1.1[1] and Prostate Cancer Working Group 3 (PCWG3) criteria[2] (Appendix 3).

Number of Patients: 20

Inclusion Criteria:

Patients meeting the following inclusion criteria will be eligible to participate in this study:

1. Signed informed consent form (ICF) providing agreement to adhere to the dosing schedule, report for all trial visits and authorization, use and release of health and research trial information
2. Male age ≥ 18 years
3. Histologically or cytologically confirmed adenocarcinoma of the prostate (excluding predominant small cell histology)
4. Ongoing gonadal androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) analogues, antagonists or orchiectomy. Patients who have not had an orchiectomy must be maintained on effective GnRH analogue/antagonist therapy
5. Castration resistant prostate cancer as defined by serum testosterone < 50 ng/ml AND PSA level of at least 2 ng/ml that has risen on at least 2 successive occasions at least 1 week apart.
6. Presence of metastatic disease on bone or CT scan
    A. Evaluable disease progression by modified RECIST 1.1 (Response Evaluation Criteria in Solid Tumors)
    B. Bone disease on bone scan
7. Prior therapy with sipuleucel-T, abiraterone, enzalutamide, docetaxel and/or cabazitaxel. There is no limit to the number of prior treatment regimens in the *castration resistant* setting, so long as prior therapy did not include platinum chemotherapy or a PARP inhibitor. Prior platinum chemotherapy in the *hormone sensitive* setting is permitted, so long as it has been at least 6 months since last dose.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1
9. Life expectancy ≥12 weeks.
10. No prior malignancy is allowed except:
    A. Adequately treated basal cell or squamous cell skin cancer or
    B. In situ carcinoma of any site or

C. Other adequately treated malignancy for which the patient has been disease-free for at least one year (any prior chemotherapy is allowed).

11. Documented evidence of at least ONE or MORE of the following:

A. Pathogenic mutation or inactivating alteration of a gene involved in homologous recombination repair in the tumor, listed in Appendix II. Note, that if this alteration is identified in a ctDNA assay, the variant-allele fraction must be >20% to indicate relevance to predominant tumor clone.

B. Mutation in one or more other genes involved in homologous DNA recombination repair in the tumor (beyond those in Appendix II) may be included at investigator's discretion.

C. Homologous recombination repair deficiency by genomic signature in the tumor by BROCA-HR, Foundation One or equivalent assay.

D. Presence of pathogenic or likely pathogenic germline mutation/variant in BRCA2, BRCA1, ATM or PALB2. (Note: germline mutations in other HR genes will be considered at investigator's discretion).

12. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of first dose of study drug:

A. Bone Marrow Function

a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L

b. Platelets $> 100 \times 10^9$/L

c. Hemoglobin ≥ 9 g/dL

B. Hepatic Function

a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ ULN; if liver metastases, then $\leq 5 \times$ ULN

b. Bilirubin $\leq 1.5 \times$ ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)

C. Renal Function

a. Serum creatinine $\leq 1.5 \times$ ULN or estimated glomerular filtration rate (GFR)

b. ≥ 45 mL/min using the Cockcroft Gault formula

Exclusion Criteria:

Patients meeting any of the following exclusion criteria are NOT eligible:

1. Currently receiving active therapy for other neoplastic disorders.

2. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.

3. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, active or symptomatic viral hepatitis or chronic liver disease

4. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart

Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of <35 % at baseline

5. Treatment with an investigational therapeutic drug within 30 days of first dose of study drug.
6. Prior therapy with a PARP inhibitor (e.g., olaparib, talazoparib, veliparib, niraparib, rucaparib).
7. Prior therapy with a platinum chemotherapy (e.g. cisplatin, carboplatin, oxaliplatin) in the castration resistant setting. (Prior platinum chemotherapy in the hormone sensitive setting is permitted, so long as time since last dose is at least 6 months or greater).
8. Active, ongoing toxicity (CTCAE grade 2 or higher) from prior therapy.
9. Presence of dementia, psychiatric illness, and/or social situations limiting compliance with study requirements or understanding and/or giving of informed consent.
10. Pre-existing duodenal stent and/ or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib.
11. Any condition(s), medical or otherwise, which, in the opinion of the investigators, would jeopardize either the patient or the integrity of the data obtained.

STATISTICAL METHODS:

Historical comparisons of median PFS for second line therapy after enzalutamide, abiraterone or docetaxel are 18-24 weeks (Mezynski et al, Schweizer et al). Primary comparison for this study will be to the median PFS of 39 weeks with the PARP inhibitor olaparib alone (Mateo et al., NEJM 2015). Assuming a proportional hazard of progression among patients accrued for this study, we anticipate that N=20 patients will provide approximately 90% power to determine whether the proposed treatment lowers the risk of progression if the hazard ratio is 0.5, implying a median PFS of 78 weeks, based on a 1-sided 1-sample log-rank test with alpha=10%. This design anticipates that patients will be accrued uniformly over the initial 52 weeks, a maximum of 1 patient will be lost to follow-up, and the analysis will occur 4 years after all patients are accrued. If the hazard ratio for PFS is instead 0.58, this design still provides approximately 80% power to determine whether the proposed treatment is more favorable. In all analyses of PFS and secondary endpoints, we will evaluate robustness of conclusions to possibly non-ignorable missing data using best/worst case scenario analyses.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

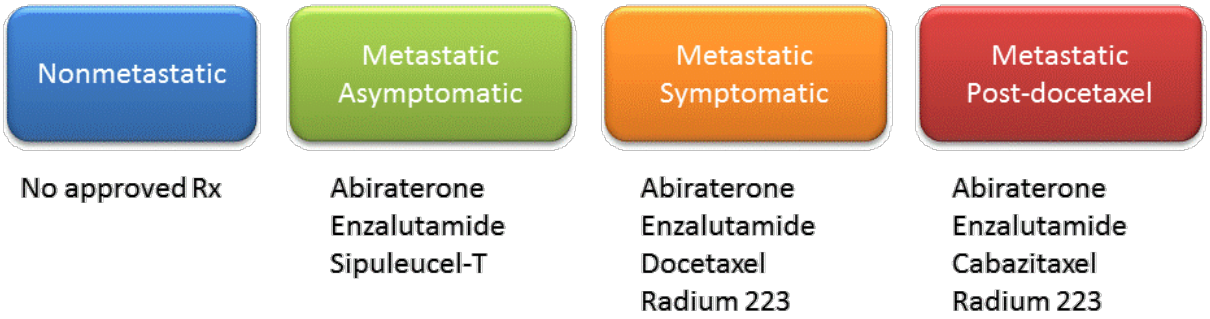
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BUN	Blood urea nitrogen
C	Celsius
CBC	Complete blood count
CR	Complete response
ctDNA	Circulating tumor DNA
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Circulating Tumor Cells
ECG	Electrocardiogram
F	Fahrenheit
FDA	Food and Drug Administration
GCSF	Granulocyte stimulating factor
GLP	Good Laboratory Practice
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
INR	International normalized ratio
IRB	Institutional Review Board
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LN	Lymph node
MRI	Magnetic resonance imaging
PD	Progressive disease

PCWG3	Prostate Cancer Working Group 3
PFS	Progression free survival
PR	Partial response
PT	Prothrombin time
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SUSAR	Suspected unexpected adverse event reaction
ULN	Upper limit of normal
WBC	White blood cell (count)

INTRODUCTION

1.1 Therapy for metastatic, castration resistant prostate cancer (CRPC)

Prostate cancer is the most common cancer among men, with approximately 220,000 new cases per year in the United States alone. Roughly 10-20% of patients present with metastatic disease, and 40% of patients relapse after surgery or radiation therapy for presumed localized disease. As a rule, androgen-deprivation therapy for advanced prostate cancer is initially effective, however, almost all tumors eventually become castration resistant after a median of 18-24 months. The current FDA-approved therapies for metastatic castration resistant prostate cancer (mCRPC) include: docetaxel (Taxotere), sipuleucel-T (Provenge), abiraterone (Zytiga), enzalutamide (Xtandi), cabazitaxel (Jevtana) and radium 223 (Xofigo). Despite the many treatment options for men with mCRPC, a major challenge is the identification of subsets of patients with distinct cancer biology that may particularly benefit from targeted "precision" treatment.



In current clinical practice, the vast majority of patients receive either abiraterone or enzalutamide, and often radium-223, prior to docetaxel in the mCRPC setting.

The second generation androgen receptor pathway-targeting agents abiraterone and enzalutamide are FDA-approved prior to docetaxel in patients with mCRPC. No prospective studies have been performed with docetaxel after either agent, and these are unlikely to be carried out given the cost and lack of industry sponsor. Single institution series suggest prior abiraterone and/or enzalutamide reduces PSA response rates and progression free survival (PFS) to docetaxel in the second line and cabazitaxel in the second and third line in men with mCRPC, representing a clinical need for more effective and durable treatment options, particularly in the era of the promise of precision treatments.

Regimen	Indication	PSA50	PFS	OS	Reference
Docetaxel after Abi	mCRPC	26%	4.6 mos	12.5 mos	Mezynski, et al
Docetaxel after Abi	mCRPC	38%	4.4 mos	NA	Schweizer, et al
Cabazitaxel after Abi and/or Enza	mCRPC	39%	4.6 mos	15.8 mos	Pezaro, et al

1.2 Homologous recombination DNA damage repair pathway genes in CRPC

Recent efforts to perform molecular profiling of metastatic, castration resistant prostate cancer have revealed approximately 20-33% of CRPC metastatic tumors contain inactivation of *BRCA1, BRCA2 or ATM*, likely resulting in homologous recombination deficiency (HRD)[3,4]. In approximately half of these cases, inactivation results from heterozygous copy loss in combination with a germline mutation, with the other half exhibiting mechanisms of biallelic inactivation loss. The majority of mutations identified thus far are in the *BRCA2* gene, but mutations have also been identified in *BRCA1, ATM*, and other homologous recombination repair pathway genes. Thus, the 20-33% of patients with mCRPC whose tumors harbor biallelic inactivation of *BRCA1/2, ATM* and other DNA repair genes may be a subset with increased sensitivity to DNA-damaging agents such as platinum and PARP inhibitors, as has been observed in other HRD malignancies such as ovarian cancer.

1.3 Response to platinum and PARP inhibitors in CRPC with homologous recombination DNA repair inactivation

The Phase II TOPARP-A study showed that 33% (16/49) of men with mCRPC and tumor material available for evaluation had evidence of inactivation of DNA repair genes, including *BRCA1/2, ATM, CHEK2* and others[4]. Of this group with evidence of DNA repair inactivation in their tumors, 88% (14/16) patients had a response to the PARPi olaparib. In addition, a recent case series using targeted next generation tumor sequencing to understand the molecular features of exceptional response to platinum chemotherapy demonstrated that all 3 of the 3 patients had biallelic inactivation of *BRCA2*[5]. Other studies have reevaluated response to platinum in mCRPC in the context of HR DNA repair deficiency (Pomerantz et al, personal communication). The connection between inactivation of homologous recombination DNA repair genes and response to platinum and PARP inhibitors is not new, but rather the discovery of high prevalence of these mutations in mCRPC and the early results suggesting that HR-DNA repair defects may serve as predictive biomarkers for platinum and PARP inhibitor therapy.

These early findings in the prostate cancer setting are reminiscent of earlier observations in breast and ovarian cancer, where HR-DNA deficiency is better studied. For example, a study of 390 ovarian cancer tumors analyzed by massively parallel sequencing identified germline and somatic mutations in *BRCA1, BRCA2 and ATM*, as well as 10 other homologous recombination genes (*BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C and RAD51D*) were associated with platinum response and survival[6,7]. Hence, the current study is designed to determine if better clinical response (as measured by radiographic progression free survival) can be achieved through induction docetaxel/carboplatin followed by maintenance rucaparib.

If this study successfully demonstrates an improvement in radiographic progression free survival with the combination of docetaxel and carboplatin followed by rucaparib maintenance in men with mCRPC and HR-DNA repair deficiency, the results could lead to changes in practice. In addition, follow-up studies would be warranted to further refine the findings and applications. For example, investigations of whether frontline use of this regimen in men mCRPC and HR

DNA repair deficiency could offer benefit over the oral hormonal agents in the mCRPC setting, as well as studying this combination in the metastatic hormone sensitive setting and earlier disease states.

This correlative biospecimens from this study will also allow further investigation into better understanding the mutations that may confer sensitivity or resistance to this treatment strategy.

1.4 Docetaxel, carboplatin and rucaparib

Docetaxel (Taxotere) and carboplatin (Paraplatin) are synthetic antineoplastic agents extensively used in the treatment of solid tumors.

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

Clovis Oncology, Inc. (Clovis) is developing rucaparib for oral administration in patients with a cancer associated with evidence of HRD, i.e., presence of a germline or somatic alteration in *BRCA1/2* or other HR gene and/or a high level of genome wide loss of heterozygosity (LOH) in the tumor. The therapeutic rationale for PARP inhibition with rucaparib in the presence of HRD is induction of synthetic lethality.

<u>Docetaxel and carboplatin toxicities</u>

Toxicity of docetaxel includes:

- Allergic Reaction: Hypotension, urticaria, and severe hypersensitivity have been reported. Premedication with dexamethasone is required.
- Hematologic: The dose limiting toxicity of Docetaxel is neutropenia with 75.4% of patients with normal liver function (transaminases ≤1.5 times ULN, alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN) having grade 4 neutropenia when docetaxel is used as a single agent at a dose of 100mg/m^2. Docetaxel has also been associated with acute myeloid leukemia or myelodysplasia (<1%)
- Neurologic: neuropathy is reported in over 10% of patients
- Dermatologic: Alopecia (56% to 76%), dermatological reaction (20% to 48%; severe: ≤5%), nail disease (11% to 41%)
- Endocrine & metabolic: Fluid retention (13% to 60%; severe: 7% to 9%; dose dependent)
- Gastrointestinal: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)
- Hepatic: Increased serum transaminases (4% to 19%). If bilirubin > ULN, or if AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN docetaxel should not be administered.
- Neuromuscular & skeletal: Weakness, myalgia and arthralgia are reported in greater than 10% of patients.

- Ophthalmic: Epiphora (associated with canalicular stenosis ≤1% with every 3-week administration)

Toxicity of carboplatin includes:

- Endocrine & metabolic: Hyponatremia (29% to 47%), hypomagnesemia (29% to 43%), hypocalcemia (22% to 31%), hypokalemia (20% to 28%)
- Gastrointestinal: Vomiting (65% to 81%), abdominal pain (17%), nausea without vomiting (10% to 15%), diarrhea (6%), constipation (6%)
- Hematologic & oncologic: Bone marrow depression (dose related and dose limiting; nadir at ~21 days with single-agent therapy), anemia (grades 3/4: 71%), leukopenia (grades 3/4: 15% to 26%), neutropenia (grades 3/4: 16% to 21%), thrombocytopenia (grades 3/4: 25% to 35%)
- Hepatic (5-29%)
- Cardiovascular (23%)
- Hypersensitivity: Hypersensitivity (2% to 16%)
- Renal: Abnormal renal function tests (6-14%)
- Central nervous system: Peripheral neuropathy (4% to 6%), neurotoxicity (5%), ototoxicity and sensory abnormalities (1%)
- Dermatologic: Alopecia (43%)
- Respiratory (12%)
- Mucositis (6%)

Toxicity of docetaxel in combination with carboplatin includes:

	Grade 3	Grade 4
Anemia	6%	0
Neutropenia	56%	6%
Thrombocytopenia	6%	0
Febrile neutropenia	3%	0
Infection	6%	0
Hyperglycemia	6%	0
Pain	6%	0
Renal insufficiency	3%	0

Rucaparib

1.4.1.1 Summary of Nonclinical Experience with Rucaparib

Refer to the Rucaparib IB for detailed nonclinical data.

Nonclinical studies have shown that rucaparib is a potent and selective inhibitor of PARP-1, PARP-2, and PARP-3. Rucaparib demonstrated robust and durable in vitro and in vivo efficacy in multiple *BRCA1* or *BRCA2* mutant cell lines and xenograft models. Rucaparib was also active in a *BRCA* wild-type model, consistent with in vitro data suggesting that rucaparib is active in cells with other deficits in HR through synthetic lethality. Safety pharmacology studies suggest

that when given orally, rucaparib poses a low risk for causing neurobehavioral and cardiac effects in patients.

The absorption, distribution, metabolism, excretion, and pharmacokinetic (PK) drug interaction potential of rucaparib were characterized in nonclinical studies. Rucaparib showed species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) substrate, rucaparib showed minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. In vitro data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and, to a lesser extent, CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. In vivo metabolite profiling in rats, dogs, and humans showed that a carboxylic acid metabolite (M324) is a common major metabolite in all three species. A Phase II N-methylated metabolite of M324 (M338) was only observed in patients. Rucaparib was mainly excreted in feces in rats and dogs. In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, and CYP3A, and to a less extent CYP2C8, CYP2D6, and UGT1A1. Rucaparib induced CYP1A2 and downregulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion (MATE) 1 and MATE2-K, a moderate inhibitor of organic cation transporter 1, and also has the potential to inhibit P-gp and BCRP in the gut.

The oral toxicity of rucaparib was evaluated in a total of 12 studies, including 10 studies in rats and dogs by single and repeated oral dose administration for up to 91 days of daily treatment. In summary, toxicity involved the hematopoietic, lymphopoietic, and gastrointestinal tract systems. In general, the toxicities induced in rats and dogs reversed after a 4-week recovery period, and no additional targets were identified in animals following prolonged oral dosing. As anticipated based on the mechanism of action, rucaparib was clastogenic in an in vitro chromosomal aberration assay in culture human lymphocytes suggesting potential genotoxicity in humans. Although no rucaparib-related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility. Overall, the results from nonclinical studies are consistent with the anticipated mechanism of action and pharmacological effects of PARP inhibition.

1.4.1.2 Summary of Clinical Experience with Rucaparib

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

Four studies (A4991002, A4991005, A4991014, and CO-338-023 [RUCAPANC]) with rucaparib have been completed and 4 studies (CO-338-010, CO-338-014 [ARIEL3], CO-338-017 [ARIEL2], and CO-338-044) are ongoing.

The clinical studies are described briefly below and additional information is provided in the rucaparib Investigator's Brochure (IB).

Completed Studies

A4991002 was a Phase 1 open-label, dose-escalation study of IV rucaparib in combination with temozolomide (TMZ) in 32 patients with advanced solid tumors or malignant melanoma. A4991005 was a Phase 2, open-label study of IV rucaparib in combination with TMZ in 46 patients with metastatic melanoma. The results from these studies are available in manuscript form.[8,9] Clinical data indicate that rucaparib exposures were similar between extensive metabolizers and poor metabolizers of CYP2D6.

A4991014 was a Phase 1, open-label, dose-escalation study of IV and oral rucaparib administered with different chemotherapeutic agents in 85 patients (33 patients dosed orally) with advanced solid tumors. Rucaparib PK parameters following a single 30 minute IV infusion (12 to 40 mg) and oral dose (12 to 360 mg) showed dose-proportional increases in exposure and dose-independent half-life ($T_{1/2}$) of approximately 17 hours after IV or oral dosing. Oral bioavailability was 36%.

Study CO-338-010

Study CO-338-010 is a 3-part, open-label, Phase 1/2 study of oral rucaparib monotherapy administered daily in continuous 21-day cycles. Part 1 (Phase 1) evaluated PK and safety of escalating doses of rucaparib in patients with solid tumors dose (N = 56; enrollment complete) and identified 600 mg BID as the recommended starting for Phase 2 based on safety, PK, and the clinical activity profile. Part 2 (Phase 2) is evaluating the efficacy and safety of rucaparib in patients with relapsed, high-grade ovarian cancer associated with a *BRCA* mutation. Part 2A enrolled platinum-sensitive patients (ie, disease progression occurred at least 6 months after last dose of platinum was administered) with a *gBRCA1/2* mutation who had received 2 to 4 prior treatment regimens (N = 42, enrollment complete). Part 2B is enrolling patients with a *gBRCA1/2* or *sBRCA1/2* mutation who received at least 3 prior chemotherapy regimens (N = 40 planned). Part 3 enrolled patients with relapsed solid tumor and a *BRCA* mutation to characterize the PK, food-effect, and safety of a higher dose strength tablet (enrollment completed).

Dose levels of 40 to 500 mg QD and 240 to 840 mg BID rucaparib were evaluated in the 56 patients enrolled in Part 1. A dose-limiting toxicity (DLT) of National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0 (v4.03)[10] Grade 3 nausea was observed in 1 of the 6 patients at 360 mg BID rucaparib in Cycle 1. No DLTs were observed at any other dose level in Cycle 1. However, similar to other PARP inhibitors, non-DLT myelosuppression was observed beyond Cycle 1.

Dose proportional and time-independent PK were observed at studied dose levels. 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. In pooled plasma samples from 3 patients who received 600 mg rucaparib BID, rucaparib, an oxidation and deamination product (M324), and a subsequent N-methylated metabolite (M338) were

tentatively identified as major circulating moieties. M324 was a major metabolite in rats and dogs, but M338 was not observed in animals. This is to be further evaluated in a [^{14}C]rucaparib study in patients.

Efficacy data from Part 1 showed Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 responses in patients with *gBRCA* mutant ovarian cancer, breast cancer, and pancreatic cancer. The disease control rate (complete response [CR], partial response [PR], or stable disease [SD] > 12 weeks) at doses ≥ 360 mg BID in evaluable ovarian cancer patients was 92% (11/12). Responses were durable across tumor types.

In Part 2A, the latest efficacy data indicate that rucaparib provides significant clinical benefit to patients with a *gBRCA1/2* mutation. Of the 42 patients treated, 25 patients (60%) achieved a confirmed complete or partial response according to RECIST Version 1.1 and the median duration of response (DOR) was 7.8 months (95% Confidence Interval [CI] 5.6, 10.5). (Clovis, data on file)

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.

Study CO-338-017 (ARIEL2)

ARIEL2 is a 2-part, single-arm, open-label Phase 2 study in patients with relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer. The primary purpose of this study is to define a tumor-based molecular signature of HRD in ovarian cancer that correlates with response

to rucaparib and enables selection of appropriate ovarian cancer patients for treatment with rucaparib. Tumor HRD status is assessed using next generation sequencing, with an algorithm for HRD status based on the presence of a *BRCA1/2* mutation (germline or somatic) and/or degree of tumor genome-wide loss of heterozygosity (genomic LOH), a phenotypic consequence of HRD. Patients are prospectively classified into 1 of 3 subgroups: tumor BRCA mutant (tBRCA^{mut}), tumor BRCA wild-type with high genomic LOH (*BRCA^{wt}*/LOH^{high}; also referred to as BRCA-like), and tumor BRCA^{wt} with low genomic LOH (*BRCA^{wt}*/LOH^{low}; also referred to as biomarker negative).

Part 1 enrolled ovarian cancer patients with relapsed, platinum-sensitive disease who had received ≥1 prior platinum-based regimen (N = 204; enrollment complete). Enrollment of patients known to harbor a *gBRCA1/2* mutation was capped in order to maximize the ability to assess rucaparib activity in the *BRCA^{wt}* patient population. A total of 17 patients known to harbor a germline *BRCA1/2* mutation were enrolled. Another 23 patients were identified as having a *BRCA1/2* mutation (3 germline, 20 somatic) based on analysis of their tumor.

Efficacy data indicate a RECIST ORR in *BRCA1/2^{mut}* tumor-evaluable patients of 80.0% (32/40 patients), median DOR of 11.2 months (95% CI: 7.4, 13.7), and median PFS of 12.8 months (95% CI: 9.0, 14.7)[7]. The objective response rate was similar in patients with a germline (85.0%; 17/20) or somatic *BRCA1/2* mutations (75.0%; 15/20). Clinical activity was also observed in patients with a BRCA-like molecular signature as assessed by genome-wide loss of heterozygosity (genomic LOH). A RECIST ORR of 28.0% (23/82 patients), median DOR of 11.0 months (95% CI: 7.6, 20.6), and median PFS of 5.7 months (95% CI: 5.3, 7.6) was observed in patients with a BRCA-like tumor (*BRCA^{wt}* with high genomic LOH) versus a RECIST ORR of 10.0% (7/70 patients), median DOR of 5.8 months (95% CI: 4.6, 8.5), and median PFS of 5.2 months (95% CI: 3.6, 5.5) in patients with a *BRCA^{wt}*/low genomic LOH tumor. (Clovis, data on file)

A BRCA-like molecular signature was observed in approximately 55% of patients with a *BRCA*^{wt} tumor, indicating there is a significant population of ovarian cancer patients beyond those who have a *BRCA1/2* mutation who may benefit from rucaparib treatment. Importantly, approximately 30% of BRCA^{wt} patients noted as having low genomic LOH in an archival tumor sample had high genomic LOH in their pre-treatment screening biopsy, indicating that a recent tumor sample is preferred to assess BRCA-like status in order to identify patients most likely to benefit from rucaparib treatment.

An exploratory objective in ARIEL2 was to assess rucaparib efficacy in tumors with an alteration in a HR gene other than *BRCA1/2*. The overall frequency of non-BRCA1/2 HR gene mutations was low (11%, 22/204 tumor samples) and the presence of a mutation did not always correlate with LOH, with the exception of tumors with a *RAD51C* or *RAD51D* mutation, which consistently exhibited high genomic LOH. RECIST and/or cancer antigen-125 (CA-125) responses were observed in patients with a *RAD51C* (75%, 3/4), *ATM* (50%, 1/2), *ATR* (100%, 1/1), *BRIP1* (50%, 1/2), *NBN* (100%, 2/2), and *RAD51D* (50%, 1/2) mutation. (Clovis, data on file)

ARIEL2 Part 2 has enrolled advanced ovarian cancer patients (N=287) who have received at least 3 prior chemotherapy regimens in order to refine the BRCA-like molecular signature (ie, genomic LOH) and assess its predictive utility in a more heavily pre-treated patient population.

Similar to the safety profile in Study CO-338-010 Part 2A, the most frequent (reported in ≥ 15% of patients) treatment-related AEs (all grades) included gastrointestinal-related toxicities (nausea, constipation, vomiting, and diarrhea), asthenia/fatigue, elevations in ALT/AST, anemia/decreased hemoglobin, dysgeusia, and decreased appetite.

Study CO-338-014 (ARIEL3)

ARIEL3 is a double-blind, placebo-controlled, Phase 3 study of rucaparib as switch maintenance treatment in patients with relapsed, platinum-sensitive, high-grade ovarian, fallopian tube or primary peritoneal cancer who achieve a response to platinum-based chemotherapy (N = 564 enrollment complete). The primary endpoint is PFS in HRD within subgroups as determined by next generation sequencing analysis of archival tumor tissue using an optimized algorithm from Study CO-338-017 (ARIEL2)[7].

Study CO-338-023 (RUCAPANC)

Study CO-338-023 (RUCAPANC) is a single-arm, open-label Phase 2 study of rucaparib treatment in patients with previously treated locally advanced or metastatic pancreatic ductal adenocarcinoma and a known deleterious *BRCA* mutation. The primary endpoint is efficacy as measured by objective response rate (ORR). Of the 19 patients evaluable for response, 2 achieved a confirmed PR and 1 achieved a confirmed CR. These patients all received only 1 prior line of therapy. The overall safety profile was similar to that observed in ovarian cancer patients.

1.4.1.3 Toxicity of rucaparib

Toxicity of rucaparib includes:

- Gastrointestinal: diarrhea (Grade 3 or 4: 1.4%), dyspepsia (Grade 3 or 4: 0.3%), nausea (Grade 3 or 4 (4.7%), vomiting (Grade 3 or 4: 4.1%), abdominal pain (0.3%), constipation (1.6%)
- Dermatologic: photosensitivity reaction (0.2%)
- Hematologic & oncologic: anemia/decreased hemoglobin (Grade 3 or 4: 22.0%), neutropenia/decreased ANC (Grade 3 or 4: 7.3%), febrile neutropenia (Grade 3 or 4: 1.4%), leukopenia (Grade 3 or 4: 0.5%), thrombocytopenia (Grade 3 or 4: 5.7%), lymphocytopenia (0.5%)
- Constitutional: asthenia/fatigue (Grade 3 or 4: 9.7%), pyrexia (Grade 3 or 4: 0.1%), anorexia (Grade 3 or 4: 2.4%), dizziness (Grade 3 or 4: 0.2%)
- Liver: increased ALT/AST (Grade 3 or 4: 14.1%)
- Metabolic: lipid/cholesterol abnormalities (Grade 3 or 4: 0.5%), hyperphosphatemia(Grade 3 or 4: 1.2%)
- Kidney: creatinine abnormalities (Grade 3 or 4: 0.4%)
- Respiratory: dyspnea (0.9%), upper respiratory tract infection (all below grade 3: 9.8%)
- Nervous system disorders: Dysgeusia (Grade 3 or 4: 0.1%), Insomnia (all below grade 3: 12.1%)

- Acute myeloid leukemia or myelodysplastic syndrome (<0.6%)

Docetaxel, Carboplatin and Rucaparib Supplier

Commercial supplies of docetaxel and carboplatin will be used. Rucaparib will be provided by Clovis Oncology, Inc.

1.5 Rationale for study design

There is biologic rationale and early evidence of treatment efficacy of the combination of docetaxel and carboplatin for men with metastatic castration resistant prostate cancer with mutations in genes involved in homologous recombination DNA repair gene such as *BRCA2*, *BRCA1, ATM* and others[4,5]. Even in the setting of outstanding therapeutic response, the continued use of docetaxel/carboplatin eventually leaves patients with cumulative and dose-limiting toxicities such as fatigue and myelosuppression and result in decreased quality of life.

Rucaparib is being developed as an antineoplastic agent by Clovis. Nonclinical evaluation has demonstrated exquisite sensitivity of *BRCA1* and *BRCA2* homozygous mutant cell lines to rucaparib, which is attributed to PARP inhibition alone, and provides a rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary (germline) and acquired (somatic) deficiencies of *BRCA1* and *BRCA2*. Clinical data indicate that patients with prostate cancer and a gBRCA or sBRCA mutation benefit from treatment with a PARP inhibitor, and that this benefit may extend to patients with other HRD alterations (Mateo, et al 2015). This supports the investigation of PARP inhibitors such as rucaparib in a broader group of tumors with HRD, such as the subset of mCRPC patients with HRD.

Switching to maintenance oral rucaparib is appealing given its synthetic lethal mechanism of action against HRD tumors as well as potential for continued disease control with fewer toxicities. The hypothesis is that the radiographic progression free survival of the combination of docetaxel with carboplatin followed by maintenance rucaparib will be longer than the reported rPFS of olaparib alone.

2 STUDY OBJECTIVES

2.1 Primary Objective

To determine radiographic progression free survival with 4 cycles of docetaxel with carboplatin followed by maintenance rucaparib in the treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency.

2.2 Secondary Objectives

- To assess maximal PSA response to induction docetaxel and carboplatin
- To assess PSA response to switch maintenance with rucaparib
- To assess PSA response duration to docetaxel and carboplatin followed by switch

maintenance with rucaparib

- To assess time to PSA progression with docetaxel and carboplatin followed by switch maintenance with rucaparib
- To assess response of measurable disease

2.3 Exploratory Objectives

- To correlate the presence of a DNA repair pathway mutations in cell free DNA and circulating tumor cells (CTC) with the mutations in tumor biopsy
- To correlate differential responses to treatment based on the underlying HR defect
- To compare responses in patients who carry germline vs somatic-only HR alterations.
- To assess mechanisms of resistance to rucaparib

Primary, Secondary, and Exploratory Objectives and Endpoints

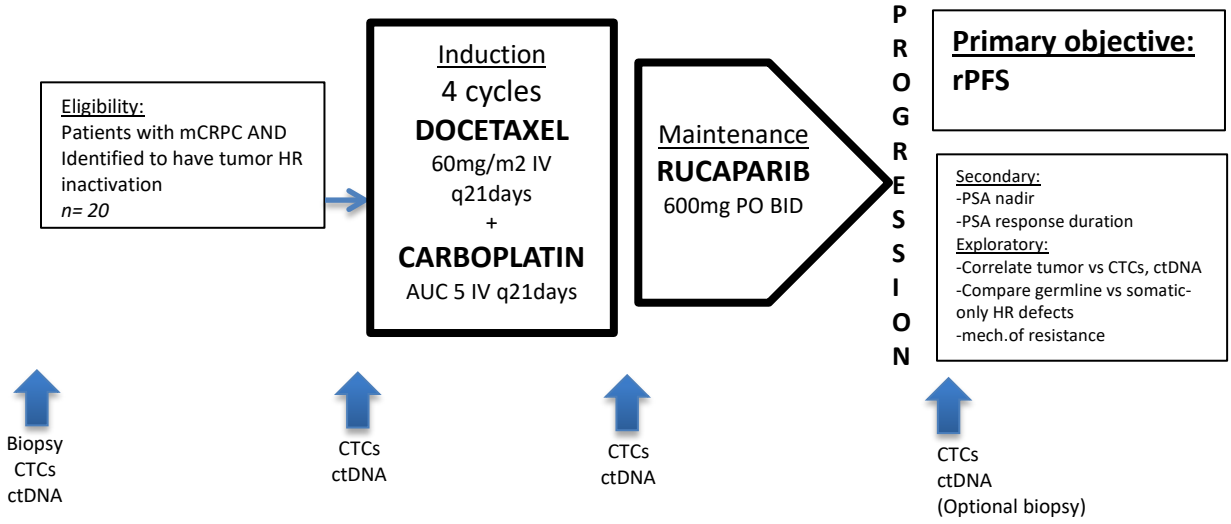
STUDY OBJECTIVES	STUDY ENDPOINTS
Primary Objective: To determine radiographic progression free survival with 4 cycles of docetaxel with carboplatin followed by maintenance rucaparib in the treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency.	Primary Endpoint: Radiographic progression free survival (RECIST 1.1, Appendix 3).
Secondary Objectives: 1. To assess maximal PSA response to induction docetaxel and carboplatin 2. To assess PSA response to switch maintenance with rucaparib 3. To assess PSA response duration with docetaxel and carboplatin followed by switch maintenance with rucaparib 4. To assess time to PSA progression with docetaxel and carboplatin followed by switch maintenance with rucaparib 5. To assess overall response of measurable disease	Secondary Endpoints: 1. PSA nadir after induction, rate of PSA_{50}, rate of PSA_{90} 2. PSA nadir after maintenance, rate of PSA_{50}, rate of PSA_{90} 3. PSA response duration 4. Time to PSA progression (PCWG3) 5. ORR of measurable disease (PCWG3)

Exploratory Objectives: 1. To correlate the presence of a DNA repair pathway mutations in cell free DNA and circulating tumor cells (CTC) with the mutations in tumor biopsy 2. To correlate differential responses to treatment based on the specific HR DNA repair mutation 3. To compare responses in patients who carry germline vs somatic-only HR alterations. 4. To assess mechanisms of resistance to rucaparib	Exploratory Endpoints: 1. Levels and detection of HR DNA repair pathway mutations in ctDNA and CTCs found in tumor biopsy 2. ORR in relation to specific HR DNA repair pathway mutation 3. ORR separately in germline mutation carriers and patients with somatic-only mutation 4. Assess HR DNA repair gene from biospecimens collected at progression.

3 INVESTIGATIONAL PLAN

3.1 Overall study design and plan

This is an open-label study with a single phase II component.



Patients will remain on treatment until any of the following occur:

- unacceptable toxicity
- documented progression by radiographic imaging
- unequivocal clinical progression
- investigator believes it is in best interest of the subject to discontinue study drug
- initiation of any subsequent prostate cancer treatment or procedure not specified in the treatment phase of the protocol (i.e. palliative radiation not allowed)
- withdrawal of consent for continued treatment

RECIST 1.1: (See Appendix).

Baseline CT or MRI of the abdomen/pelvis and chest film or chest CT will be performed during screening and following the induction cycles of docetaxel with carboplatin, up to 7 days before starting Rucaparib and then every 3 cycles during the rucaparib phase (up to 7 days prior to Day 1 of the applicable cycles), or as clinically indicated.

Bone Scan: Baseline bone scan will be performed during screening and following completion of induction cycles (+ up to 14 days) of docetaxel with carboplatin, up to 7 days before starting Rucaparib and then every 3 cycles during the rucaparib phase (up to 7 days prior to Day 1 of the applicable cycles), or as clinically indicated.

4 STUDY POPULATION SELECTION

4.1 Study Population

Study subjects will be recruited from the Seattle Cancer Care Alliance (SCCA) and University of Washington (UW), which are separate sites within the same practice and share a single IRB.

Eligible patients will be identified by their medical oncologist, who will discuss the study with the patient. If a patient is interested in participating, he will be appropriately counseled and informed consent will be obtained by one of the investigators. A total of 20 subjects will be enrolled in the study.

4.2 Inclusion Criteria

Patients meeting the following inclusion criteria will be eligible to participate in this study:

1. Signed informed consent form (ICF) providing agreement to adhere to the dosing schedule, report for all trial visits and authorization, use and release of health and research trial information
2. Male age $\geq$ 18 years
3. Histologically or cytologically confirmed adenocarcinoma of the prostate (excluding predominant small cell histology)
4. Ongoing gonadal androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) analogues, antagonists or orchiectomy. Patients who have not had an orchiectomy must be maintained on effective GnRH analogue/antagonist therapy
5. Castration resistant prostate cancer as defined by serum testosterone < 50 ng/ml and PSA level of at least 2 ng/ml that has risen on at least 2 successive occasions at least 1 week apart.
6. Presence of metastatic disease on bone or CT scan
    A. Evaluable disease progression by modified RECIST 1.1 (Response Evaluation Criteria in Solid Tumors)
    B. Bone disease on bone scan

7. Prior therapy with sipuleucel-T, abiraterone, enzalutamide, docetaxel, and/or cabazitaxel. There is no limit to the number of prior treatment regimens in the *castration resistant* setting, so long as prior therapy does not include platinum chemotherapy or a PARP inhibitor. Prior platinum chemotherapy in the *hormone sensitive* setting is permitted, so long as it has been at least 6 months since last dose.

8. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1
9. Life expectancy ≥12 weeks.
10. No prior malignancy is allowed except:
    A. Adequately treated basal cell or squamous cell skin cancer or
    B. In situ carcinoma of any site or
    C. Other adequately treated malignancy for which the patient has been disease-free for at least one year (any prior chemotherapy is allowed).
11. **Documented evidence of at least ONE or MORE of the following:**
    A. Pathogenic mutation or inactivating alteration of a gene involved in homologous recombination repair in the tumor, listed in Appendix II. Note, that if this alteration is identified in a ctDNA assay, the variant-allele fraction must be >20% to indicate relevance to predominant tumor clone.
    B. Mutation in one or more other genes involved in homologous DNA recombination repair in the tumor (beyond those in Appendix II) may be included at investigator's discretion.
    C. Homologous recombination repair deficiency by genomic signature in the tumor by BROCA-HR, Foundation One or equivalent assay.
    D. Presence of pathogenic or likely pathogenic germline mutation/variant in *BRCA2, BRCA1, ATM or PALB2*. (Note: germline mutations in other HR genes will be considered at investigator's discretion).
12. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of first dose of study drug:
    A. Bone Marrow Function
        a) Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
        b) Platelets > 100 x 10^9/L
        c) Hemoglobin ≥ 9 g/dL
    B. Hepatic Function
        a) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN; if liver metastases, then ≤ 5 × ULN
        b) Bilirubin ≤ 1.5 × ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)
    C. Renal Function
        a) Serum creatinine ≤ 1.5 × ULN or estimated glomerular filtration rate (GFR)
        b) ≥ 45 mL/min using the Cockcroft Gault formula

4.3 Exclusion Criteria

Patients meeting any of the following exclusion criteria will be excluded from the study:

1. Currently receiving active therapy for other neoplastic disorders.
2. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
3. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, active or symptomatic viral hepatitis or chronic liver disease
4. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of <35 % at baseline
5. Treatment with an investigational therapeutic drug within 30 days of Cycle 1.
6. Prior therapy with a PARP inhibitor (e.g., olaparib, talazoparib, veliparib, niraparib, rucaparib).
7. Prior therapy with a platinum chemotherapy (e.g. cisplatin, carboplatin, oxaliplatin) in the castration resistant setting. (Prior platinum chemotherapy in the hormone sensitive setting is permitted, so long as time since last dose is 6 months or greater).
8. Active, ongoing toxicity (CTCAE grade 2 or higher) from prior therapy.
9. Presence of dementia, psychiatric illness, and/or social situations limiting compliance with study requirements or understanding and/or giving of informed consent.
10. Pre-existing duodenal stent and/ or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib.
11. Any condition(s), medical or otherwise, which, in the opinion of the investigators, would jeopardize either the patient or the integrity of the data obtained.

5 STUDY TREATMENT(S)

5.1 Treatments Administered

<u>Docetaxel with carboplatin</u>

Please refer to the docetaxel and carboplatin package inserts for complete preparation and administration. Docetaxel and carboplatin should be administered intravenously per institutional protocol.

Docetaxel 60 mg/m^2 will be administered on Day 1 of each 21-day cycle for 4 cycles.

Carboplatin AUC 5 will be administered on Day 1 of each 21-day cycle for 4 cycles.

Rucaparib

Rucaparib 600 mg PO BID will be administered continuously as monotherapy daily on days 1-28 of each 28 day cycle.

Anti-Emetics

Dose modifications for nausea and vomiting should not be made until patients are on adequate doses of antiemetics. Docetaxel and carboplatin are classified as moderately emetogenic chemotherapeutic agents, with a frequency of emesis of 30-60%. Institutional guidelines for moderately emetogenic chemotherapy should be followed.

Prior and Concomitant Therapy

Hematopoetic 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]
CYP 1A2	Tizanidine, theophiline
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.[11 Data Analysis, Implications for Dosing, and Labeling Recommendations February 2012. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf.)]

[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.

Other Concomitant Medications

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

In vitro data showed that rucaparib is an inhibitor of P-gp and thus patients taking digoxin, a P-gp substrate, should have their digoxin levels monitored regularly via standard clinical practice. Caution should also be exercised for concomitant use of certain statin drugs (eg, rosuvastatin and fluvastatin) due to potential increase in exposure from inhibition of BCRP and CYP2C9.[12] Caution should also be exercised for concomitant use of metformin due to potential decrease in effective dose from transporter mediated interaction.

The concurrent administration of other anticancer therapy, including cytotoxic or immunotherapy, is prohibited therapy. Use of other investigational drug or device therapy for any reason is prohibited. The decision to administer a prohibited drug/treatment will be made by the investigator based on the consideration of the safety of study participant.

Dose modification criteria for docetaxel and carboplatin

5.1.1.1 Modifications of docetaxel and carboplatin for hematologic toxicity

On day 1 of a cycle	**Dose**
ANC ≥1.5 x10^9 cells /L and platelet count ≥100 x 10^9 /L	100%
ANC <1.5 x10^9 cells /L and platelet count <100 x 10^9 /L	Delay docetaxel and carboplatin. Repeat CBC weekly. If ANC resolves to ≥1.5 x10^9 cells /L AND platelet count to ≥100 x 10^9/L, resume docetaxel and carboplatin at 100% of starting dose If holding for ANC or platelets is required for a second cycle, decrease docetaxel to approximately 80% for subsequent cycles If treatment is delayed by more than 4 weeks, the patient should be removed from chemotherapy treatment.

At any time during a cycle	
Grade 3 febrile neutropenia (defined as an ANC <1.0 x 10^9 cells/L) and a single Temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour)	Delay treatment until improvement of symptoms and resolution of the ANC to ≥1.5 x10^9 cells /L and platelet count to ≥100 x 10^9/L.
Documented infection with Grade 3 neutropenia (defined as an ANC <1.0 x 10^9 cells/L)	Decrease BOTH docetaxel and carboplatin to approximately 80% for all subsequent cycles.
Grade 4 neutropenia (defined as an ANC <0.5 x 10^9 cells/L lasting more than 5 days	With recurrence of any of these toxicities, consider removal from chemotherapy

5.1.1.2 Modifications of docetaxel and carboplatin for hepatic toxicity

AST/ALT >2 x ULN **with AP>ULN** and bilirubin WNL: delay treatment until recovery.

5.1.1.3 Modifications of docetaxel and carboplatin for gastrointestinal toxicity

For Grade 4 nausea and vomiting **despite maximal antiemetic therapy**, delay docetaxel and carboplatin until symptoms have resolved to ≤Grade 2. When symptoms have resolved to ≤Grade 2, continue docetaxel and carboplatin at 100% of the current dose. If Grade 4 nausea and vomiting recur despite maximal antiemetic therapy, the patient should be removed from chemotherapy.

Dose modification criteria for rucaparib

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

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

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

Dose reduction steps are presented in Table 1.

Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 is permitted, upon the investigator's discretion.

5.1.1.4 Management of Rucaparib Treatment-Emergent ALT/AST Elevations

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

2. Grade 3 ALT/AST elevations should be managed as follows:
    a. Monitor liver function tests weekly until resolution to ≤ Grade 2.
    b. Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN, alkaline phosphatase is < 3 x ULN, and there are no other signs of liver dysfunction.

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

Table 1. Dose Reduction Steps

Starting Dose	**600 mg BID**
Dose Level -1	500 mg BID
Dose Level -2	400 mg BID
Dose Level -3*	300 mg BID
*Consult with medical monitor before reducing to this dose	

5.1.1.5 Criteria for rucaparib retreatment

A new cycle of treatment may begin if:

1. ANC ≥ 1.0 x 10^9/L
2. Platelet count ≥ 100 x 10^9/L
3. Non-hematologic toxicities have returned to baseline or ≤ CTCAE Grade 1 severity (or, at the investigator's discretion, ≤ CTCAE Grade 2 severity if not considered a safety risk for the patient). Grade 3 or Grade 4 ALT/AST elevations should be managed as described above.

5.1.1.6 Patients or partners of patients of reproductive potential

Patients whose female partners of childbearing potential must not be considering getting pregnant during the study.

Men of reproductive potential who join this study and their opposite sex partner must agree to use one or more forms of effective and acceptable birth control from the time this form is signed **until at least 6 months after the last dose** of docetaxel with carboplatin followed by rucaparib. The following are allowable only:

- Ongoing use of progesterone-only injectable or implantable contraceptives (eg, Depo Provera, Implanon, Nexplanon)
- Placement of an intrauterine device or intrauterine system
- Bilateral tubal occlusion
- Male sterilization, with appropriate post-vasectomy documentation of absence of sperm in ejaculate
- True, complete (as opposed to periodic) abstinence.

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

Men who join this study must also agree to use a condom during sex with a partner to avoid the possibility of exposure of the partner to rucaparib. Men who join this study must not make semen donations for 4 months following the last dose of rucaparib.

5.2 Supply, Packaging and Storage

Docetaxel and carboplatin supply, packaging, storage

Docetaxel and carboplatin are stored and administered per institutional protocol.

Rucaparib packaging and labeling

All tablets are provided in high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers in ambient storage with no special storage conditions. Patients will be dispensed one or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28 days treatment per cycle, including a small overage. Study drug containers containing rucaparib tablets will be labeled according to national regulations for investigational products.

Description of rucaparib

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 – blue, round, embossed with C2 250 mg - white, diamond, embossed with C25 300 mg – yellow, oval, embossed with C3
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 28 tablets
Storage Conditions:	Ambient, with no special storage conditions

Rucaparib tablets should be taken with 8 oz (240 mL) of water. Tablets can be taken on an empty stomach or with food. Tablets should be swallowed whole without crushing or chewing. Patients should take rucaparib doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (ie, does not take it within 4 hours of the scheduled time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up.

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.

6 STUDY PROCEDURES

6.1 Informed Consent

Written Informed Consent and Authorization must be obtained from the patient in accordance with local practice and regulations. The study will be discussed with the patient, and a patient wishing to participate must give written informed consent and Authorization for Use and Release of Health and Research Study Information prior to any study-related procedures or change in treatment.

A signed, Institutional Review Board/Ethics Committee (IRB) approved, informed consent must be obtained from patients before any study specific procedures can occur. Confirmation of the patient's informed consent and the informed consent process must also be documented in the patient's medical record.

A copy of the fully signed informed consents will be given to the patient.

6.2 Medical History

Medical history, such as previous treatments, procedures, and conditions will be collected during the screening period.

6.3 Physical Examination

Physical examination includes HEENT (head, eyes, ears, nose, and throat), chest, cardiac, abdominal, extremities, neurologic, and lymph node examinations.

Vital signs include blood pressure, heart rate and temperature within 2 days from the day of treatment. Weight will be recorded at every chemotherapy visit. Height will be recorded at initial clinic visit only.

6.4 Laboratory Tests

Clinical Safety Laboratory Tests

Clinical safety laboratory tests will be assessed as UWMC/SCCA standard of practice. At a minimum, a complete blood count (CBC) and complete serum chemistry will be performed within 3 days of the first day of each cycle and thereafter as clinically indicated.

Clinical safety labs will include the following:

Table 2. List of Clinical Safety Laboratory Tests

Hematology:	**Serum Chemistry:**
Hematocrit (Hct)	Albumin (ALB)
Hemoglobin (Hgb)	Blood urea nitrogen (BUN)
Platelet count	Calcium (Ca)
Red blood cell (RBC) count	Carbon dioxide (CO_2)
White blood cell (WBC) count with differential	Chloride (Cl)
	Creatinine
Liver Function:	Glucose
Alanine aminotransferase (ALT; SGPT)	Potassium (K)
Aspartate aminotransferase (AST; SGOT)	Sodium (Na)
Alkaline phosphatase (ALK-P)	Magnesium (Mg) (During induction cycles or as clinically indicated)
Total bilirubin	Phosphate (P) (During induction cycles or as clinically indicated)
	***Additional laboratory tests:**
	Prothrombin Time (PT/INR) test for patients who are taking Coumadin while on study.

Research Samples

6.4.1.1 Biomarker Analysis – Blood

Blood samples will be collected from all patients entered in the study at the time points indicated in Appendix 1. Biomarker studies may include CTC analysis and the purification of cell-free DNA for analysis by next generation sequencing to identify mutations in genes associated with response or resistance to rucaparib. The biomarker studies will be based on the results of the study, as well as available material and assay platforms. See Lab Manual for additional details.

6.4.1.2 Biomarker Analysis – Tumor Tissue

Archival, screening, and progression tissue biopsies may be collected from patients entered in the study. Biomarker studies may include the purification and sequencing of genomic DNA to identify mutations in genes or other genomic features (e.g. loss of heterozygosity) associated with response or resistance to rucaparib. The biomarker studies will be based on the results of the study, as well as available tissue specimens and assay platforms. See Lab Manual for additional details.

Optional metastatic tumor biopsy will be obtained prior to Day 1 of the Induction cycle. Sites where prior radiation has been administered for metastatic disease will be avoided. Soft tissue sites are preferred over bone sites. Participants will be offered the option of a second biopsy at the time of progression. If they consent, all attempts will be made to biopsy the same lesion as was sampled for the first biopsy. See Lab Manual for details on specimen handling.

Sample Collection, Storage, and Shipping

The Seattle Cancer Care Alliance and University of Washington clinical laboratories will analyze all hematology, blood chemistry samples collected for the study. Samples will be analyzed at a facility meeting Good Laboratory Practice (GLP) requirements and/or using methods documented in a methods validation report.

7 STUDY ACTIVITIES

7.1 Study Visit Overview

1. Expected toxicities, potential risks, and dose modifications are described in Section 5 (Risks and Precautions and Dose Reductions).
2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

7.2 Screening Period

Screening procedures to be completed within 30 days prior to the start of study treatment,

1. Informed consent
2. Medical history and demographics
3. Concurrent illness
4. Physical examination, including weight and height
5. Vital signs including blood pressure, heart rate, temperature.
6. Assessment of ECOG Performance Status
7. Clinical laboratory tests:
    a. CBC (WBC with differential count, RBC, hemoglobin, hematocrit, platelets)
    b. Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin),
    c. Serum chemistries (albumin, sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium)
    d. PSA
    e. PT/INR (if on warfarin)
8. Research blood collection (see 6.4.1.1 and Lab Manual)
9. Bone scan
10. CT or MRI of the abdomen/pelvis
11. Chest film or chest CT if indicated
12. Concomitant medications: obtain a complete and thorough listing of all prescription and nonprescription (over the counter) medications currently taken including pain medications.
13. Obtain documentation of the tumor sequencing report (UW Oncoplex, Foundation One, etc) wherein HR mutation is reported AND/OR the tumor HR mutational signature report for investigator to review for documentation of eligibility.
14. Optional: obtain fresh or archival tumor tissue (see 6.4.1.2).

7.3 Treatment Period

Note: Visits have a +/- 4-day window, but all required procedures must be complete before study drug administration.

Induction phase, Day 1 of every cycle for Cycles 1-4 (Docetaxel and Carboplatin)

On Day 1 (up to - 4 days) of each cycle the following procedures will occur:

1. Vital signs (blood pressure, heart rate, temperature and weight)
2. CBC (WBC with differential count, RBC, hemoglobin, hematocrit, platelets)
3. Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin)
4. Serum chemistries (albumin, sodium, potassium, chloride, carbon dioxide, creatinine, BUN, calcium, glucose)
5. Serum PSA
6. Research blood draw (see Appendix 1)
7. CT or MRI of the abdomen/pelvis and Chest film or chest CT will be performed within -7 days of starting the maintenance phase and every 3rd cycle on Rucaparib, or as clinically indicated.
8. Bone scan - if bone lesions are present at baseline, then bone scans will be performed within -7 days of starting the maintenance phase and every 3rd cycle on Rucaparib or as clinically indicated, whichever occurs first.

Note: If there is clear evidence of clinical or radiographic progression during the Induction Phase of Docetaxel and Carboplatin, patient may proceed to the Maintenance Rucaparib phase. PSA progression alone will not be sufficient to proceed to Maintenance.

Maintenance phase, Cycle 5 Day 1, and Day 1 of every cycle thereafter (Rucaparib)

The following procedures/assessments will be completed for all patients within 4 days before initiation of treatment on Cycle 5 Day 1 and study drug administration on Day 1 of each cycle thereafter.

- Physical examination;
- Weight;
- Vital Signs;
- 12-lead ECG (at cycle 5 and every 3rd cycle thereafter)
- Concomitant medications and procedures;
- Disease/ tumor assessment (using the same methodology as was used at screening [eg, CT scan, bone scan]) at the start of treatment on Day 1 of Cycle 5 (within 7 days before is permitted), and thereafter every 3rd cycle (within 7 days before is permitted), or as clinically indicated.
- ECOG performance status;
- Clinical safety laboratory tests (see Table 2)
- AE monitoring; and
- Study drug administration
- Research blood draw (see Appendix 1)

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

7.4 Criteria for Evaluation of Antitumor effects

- The percentage of patients achieving ≥50% reduction in PSA according to PCWG3 criteria.
- The percentage of patients achieving ≥90% reduction in PSA according to the PCWG3 criteria.
- The percentage of patients achieving ≥30% reduction in measurable disease by modified RECIST 1.1.
- Median time to tumor progression by PCWG3 criteria

7.5 Criteria for Discontinuation of Study

- The patient develops an unacceptable toxicity
- Disease progression per PCWG3 criteria
- The patient develops a concurrent illness that is a contraindication to receiving further treatment.
- The patient elects to discontinue treatment or withdraws consent.
- At the discretion of the Investigator.

7.6 Withdrawal from Study

The investigator may withdraw a patient from any phase of the study for any of the following reasons.

1. Patient meets criteria for discontinuation of treatment.
2. Patient receives prohibited medications. I.e., concurrent administration of other anticancer therapy, immunotherapy or investigational drug therapy given for any reason during study treatment Phase.
3. Patient withdraws consent. In this event, the reason(s) for withdrawal must be documented and clarification if withdrawal of consent includes follow-up phase for progression data collection.

If a subject terminates the study early, an End of Treatment visit will be performed.

8 ADVERSE EVENT REPORTING AND MANAGEMENT

8.1 *Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest*

8.2 Grading of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, Version 4.03 grading scale (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).[10]

Severity is not the same as Serious.

- For AEs not covered by NCI CTCAE, the severity will be characterized according to the 'general guidelines' available to assess AEs into Grades 1-5 published in CTCAE 4.03.

8.3 Causal Relationship of Adverse Events to Study Drugs

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

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

8.4 Outcome and Action Taken

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

Action Taken with Study Drug (note all that apply)

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

Outcome

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

8.5 Follow up of Adverse Events, Serious Adverse Events and Adverse Events of Special Interest

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

8.6 Reporting Serious Adverse Events and Adverse Events of Special Interest

All SAEs and AESIs, regardless of relationship to study drug, must be reported to Clovis Oncology **within 24 hours** of knowledge of the event, during the study through 28 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 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.

8.7 *Reporting to IRB*

Serious adverse events and protocol problems (e.g. protocol deviations, non-adherence) will be reported in compliance with FHCRC/University of Washington Cancer Consortium Institutional Review Board. Reports of SAEs should be signed and dated by the principal

investigator. In the absence of the PI, reports should be signed and dated by the individual reporting the event. If s/he is not medically licensed, the report should also be signed by a licensed medical practitioner, preferably a sub-investigator for this protocol. The PI will review and sign the report at the next opportunity.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the End of Study Case Report Form as well as all SAE/SUSAR reports.

9 PLANNED STATISTICAL METHODS

9.1 Determination of Sample Size

Historical comparisons of median PFS for second line therapy after enzalutamide, abiraterone or docetaxel are 18-24 weeks (Mezynski et al, Schweizer et al). Primary comparison for this study will be to the median PFS of 39 weeks with the PARP inhibitor olaparib alone (Mateo et al., NEJM 2015). Assuming a proportional hazard of progression among patients accrued for this study, we anticipate that N=20 patients will provide approximately 90% power to determine whether the proposed treatment lowers the risk of progression if the hazard ratio is 0.5, implying a median PFS of 78 weeks, based on a 1-sided 1-sample log-rank test with alpha=10%. This design anticipates that patients will be accrued uniformly over the initial 52 weeks, a maximum of 1 patient will be lost to follow-up, and the analysis will occur 4 years after all patients are accrued. If the hazard ratio for PFS is instead 0.58, this design still provides approximately 80% power to determine whether the proposed treatment is more favorable. In all analyses of PFS and secondary endpoints, we will evaluate robustness of conclusions to possibly non-ignorable missing data using best/worst case scenario analyses.

9.2 Analysis Populations

The following analysis populations are defined for the study:

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

Efficacy Population – The efficacy population will consist of all patients evaluable for response by RECIST Version 1.1[1]/PCWG3 criteria[2] (Appendix 3).

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

9.3 Demographics and Baseline Characteristics

All demographic (eg, age, race, and ethnicity as allowed by local regulations) and baseline characteristics will be summarized for the safety population.

The following baseline variables will be summarized with frequency tabulations:

- Age, race, height and weight, ECOG performance status
- Clinical stage, PSA at diagnosis
- Primary treatment (radical prostatectomy or radiation)
- Prior therapies: sipuleucel-T, abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223
- Number of prior therapies for castration resistant prostate cancer

The following BRCA/ATM/other HR gene mutation characteristics will also be summarized:

- BRCA/ATM/other HR gene mutation status (germline or somatic)

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

9.4 Efficacy Analyses

Primary Efficacy Analysis

Radiologic PFS (rPFS) is defined as the time from first dose of docetaxel/carboplatin to the date of first objective evidence of radiographic progression (soft tissue or bone lesion) or death due to any cause, whichever occurs first. Radiographic disease progression includes confirmed bone disease progression and soft tissue disease progression adjudicated by investigator assessment using the RECIST 1.1/PCWG3 criteria (Appendix 3).

Secondary Efficacy Analysis

PSA_{50}: confirmed PSA decrease from baseline of ≥ 50% decrease assessed by a local laboratory
PSA_{90}: confirmed PSA decrease from baseline of ≥ 90% decrease assessed by a local laboratory
PSA nadir: Lowest post baseline PSA

Time to PSA progression (PCWG3): Time to PSA progression is defined as the time from first dose of docetaxel/carboplatin to the date that a ≥ 25% increase and absolute increase of ≥ 2 ng/mL above the nadir (or baseline value for patients who did not have a decline in PSA) in PSA was measured. The increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later.

PSA-response duration: duration of confirmed response is defined as the time from the date that a response (PSA decrease ≥ 50%) is first reported to the time that PSA progression is first documented

ORR of measurable disease (PCWG3): radiologic ORR (CR or PR per modified RECIST Version 1.1 criteria and no bone progression per PCWG3 prior to a CR or PR) by investigator assessment in patients with measurable visceral and/or nodal disease at baseline per IRR (Cohort A). An analysis of radiologic ORR by the investigator will also be conducted as supportive to the primary endpoint.

9.5 Safety Analyses

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

Data from ALL patients who receive at least 1 dose of study treatment will be included (and reported individually and together as induction phase, maintenance phase) will be included in the safety analyses. AEs, clinical laboratory results, vital signs, ECG results, ECOG performance status, body weight, and concomitant medications/ procedures will be tabulated and summarized.

Adverse Events
AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE Version 4.03 or later. Only treatment-emergent adverse events (TEAEs) will be collected: TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until the date of the last study drug dose plus 28 days.

The number and percentage of patients who experienced TEAEs for each system organ class (SOC) and preferred term will be presented. Multiple instances of the TEAE in each SOC and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least 1 TEAE will also be summarized.

Separate tables will be presented as follows:
• CTCAE grade 3 or greater TEAEs
• Treatment-related TEAEs
• TEAEs with an outcome of death
• TEAEs leading to discontinuation of study medication
• TEAEs resulting in interruption/delay of study medication
• TEAEs resulting in dose reduction of study medication

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

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

Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will generally be presented in SI units. The on-treatment period will be defined as the time from the first dose of study drug to 28 days after

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

The summary of laboratory data will include shift tables based on CTCAE for shifts in grade from baseline to maximum, minimum and last value during the on-treatment period. Supporting laboratory data including normal ranges and abnormal laboratory flags will be provided using by-patient listings. Separate listings will be produced for clinically significant laboratory abnormalities (ie, those that meet Grade 3 or 4 criteria according to CTCAE).

10 REFERENCE LIST

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11 APPENDICES

APPENDIX I. SCHEDULE OF EVENTS

Procedure	Screening (within 30 days prior to Day 1)[1]	Day 1 of Every 21-day *Induction* Cycle +/-4 days	Day 1 of Every 28-day *Maintenance* Cycle +/-4 days	Day 1 of Every 3 Cycles +/-4 days (or as clinically indicated)	End of Treatment visit (within 28 +/-7 days of last dose of study medication)
Informed Consent	X				
Registration	X				
Medical History	X				
Physical exam	X				X
Vital Signs	X	X	X		X
ECOG performance status	X	X	X		X
ECG				X	X
CBC (w/ platelets & differentials)[2]	X	X	X		X
Serum chemistry & electrolytes[3]	X	X	X		X
Hepatic function[4]	X	X	X		X
PSA	X	X	X		X
CT or MRI of pelvis/abdomen[5]	X			X[5]	
Bone scan[5]	X			X[5]	
Chest film or chest CT[5]	X			X[5]	
Docetaxel and carboplatin		X			
Rucaparib			X		
Adverse Events		X			X
Concomitant Medications	X				
Circulating tumor cells and cell free DNA collection		X	X	X	X
Collect archival tumor material	(Optional)				
Metastatic Biopsy	(Optional)				(Optional)

[1] Baseline evaluations will be done within 30 days prior to start of therapy. Except for laboratory tests, which should be completed within 14 days prior to registration. All screening should be complete prior to registration.

[2] For patients taking Coumadin, a baseline PT test will be done.

[3] Chemistry & electrolyte: albumin, BUN, calcium, CO2, chloride, creatinine, glucose, potassium, sodium, magnesium (during induction cycles or as clinically indicated), and phosphate (during induction cycles or as clinically indicated) .

[4] Hepatic function includes AST, ALT, alkaline phosphatase and total bilirubin.

[5]CT/MRI & Bone scan can be done up to 7 days before Day 1 of every 3rd cycle on Rucaparib

APPENDIX II. HOMOLOGOUS RECOMBINATION REPAIR GENES TO BE CONSIDERED FOR *SOMATIC/TUMOR* INACTIVATION

*ATM**
BARD1
*BRCA1**
*BRCA2**
BRIP1
CDK12
CHEK2
FANCA
NBN
PALB2
RAD51
RAD51B
RAD51C
RAD51D
RAD54L

*Eligibility based on germline-only mutation is limited to pathogenic and likely pathogenic mutations in *BRCA1, BRCA2 and ATM* per inclusion criteria 4.2. All other genes MUST demonstrate evidence of bi-allelic inactivation by UW-OncoPlex or Foundation One tumor or circulating tumor DNA testing, or evidence of mutational profile.

APPENDIX III. MODIFIED RECIST (V1.1) AND PCWG3 CRITERIA

The RECIST guidelines (Version 1.1) are described in Eisenhauer et al. 2009[42] and at http://www.eortc.be/Recist/Default.htm. and PCWG3 criteria as described by Scher, et al. 2016[22] A short summary is given below:

MEASURABLE DISEASE:

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

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

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

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

NON-MEASURABLE DISEASE:

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

Bone Lesions

For the purposes of this study, bone metastatic lesions should be recorded at baseline and followed during treatment using PCWG3 criteria. Bone lesions should not be recorded as target

or nontarget lesions according to RECIST 1.1 criteria.

Lesions with Prior Local Treatment
Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional are not measureable unless there has been demonstrated progression in the lesion.

Target Lesions
All measurable lesions up to a maximum of 5 lesions per organ (per PCWG3), representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Nontarget Lesions
RECIST Version 1.1 criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

EVALUATION OF TARGET LESIONS

Complete Response:
Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

Partial Response:
At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.

Stable Disease:
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Progressive Disease:
At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new extra-skeletal lesions is also considered progression. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

Appearance of 1 or more new extra-skeletal lesions and/or unequivocal progression of existing nontarget lesions. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

EVALUATION OF NON-TARGET LESIONS

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level.

Stable Disease/Incomplete Response:
Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.

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

Evaluation of Best Overall Response: Patients with Target (+/- NonTarget-) Disease			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Evaluation of Best Overall Response: Patients with NonTarget- Disease Only		
Nontarget Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic

deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

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

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

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started), including progression in bone per PCWG3 criteria.

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

PCWG3 CRITERIA FOR ASSESSMENT OF BONE DISEASE

PCWG3 criteria will be used to document evidence of disease progression in bone lesions as described by Scher, et al. 2016[2].

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

Criteria for progression in bone at study entry:

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

Documentation of baseline bone disease:

- Presence or absence of metastasis recorded first

- Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial

Following for bone progression during the study:

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

PCWG3 Criteria For Confirmation of Radiographic Progression in Bone by Investigator Assessment (to be used in conjunction with modified RECIST 1.1 criteria for visceral and nodal disease)

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

APPENDIX IV. CRITERIA FOR EVALUATION

Anti-Tumor Effects:

Median time to tumor progression by PCWG3 criteria. Radiographic progression free survival will be assessed as the time from day 1 of therapy until date of progression or death.

Percentage of patients achieving ≥50% reduction in PSA according to PCWG3 criteria.

Percentage of patients achieving ≥90% reduction in PSA according to PCWG3 criteria.

Percentage of patients achieving ≥30% reduction in measurable disease by RECIST 1.1

APPENDIX V. WHO/ECOG GRADING SCALE

ECOG Performance Status Scale

GRADE	SCALE
0	Fully active, able to carry out all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX VI. DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutch Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state, and federal guidelines.

APPENDIX VII. DEFINITIONS OF ADVERSE EVENTS

Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere. 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 CRF, not on the physical examination CRF, which is reserved for physical signs or findings).

Definition of a Serious Adverse Event

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

- Results in death. Any event resulting in death during the reporting period (from date of first dose of study drug through 28 days after last dose) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing that results in death must also be reported as an SAE.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity
- Results in a congenital anomaly or birth defect
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

Definition of an Adverse Event of Special Interest

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

Details on Clovis's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to Clovis expeditiously **within 24 hours** of knowledge of the event, during the study through 28 days after receiving the last dose of study treatment, and beyond the 28-day window period.

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
- 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 CTC Grade 5 (fatal outcome) indicated.

Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

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

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

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

Pregnancy or Drug Exposure during Pregnancy

Any pregnancy occurring in a partner of a study patient during study participation or within 6 months of last dosing must be reported to Clovis using the Pregnancy Report Form within the same timelines as an SAE.

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