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TITLE: A Phase Ib/II Study of Rucaparib (PARP inhibitor) combined with Nivolumab in Metastatic Castrate – Resistant Prostate Cancer and Advanced/Recurrent Endometrial Cancer.

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This is a multi-institutional study being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.

Protocol Version History:
Initial Version; 4/19/2018
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Amendment 2; 03/01/2019

SUMMARY

Study design:

This is a phase Ib/phase II, open label study of the immune checkpoint inhibitor nivolumab in combination with the PARP inhibitor rucaparib for patients with metastatic castration resistant prostate cancer (mCRPC) and metastatic/recurrent endometrial cancer.

To determine the feasibility of combination therapy with Rucaparib and Nivolumab, the first 4-12 patients, beginning with patients enrolled under Amendment 1, will be enrolled into the Phase Ib portion of this study. Patients who are non-evaluable for toxicity during this phase of the study will be replaced. These patients will undergo a pretreatment biopsy, then will begin combination therapy with Rucaparib and Nivolumab. Patients enrolled to the Phase Ib portion of the study will begin dosing of Rucaparib and Nivolumab on cycle 1 day 1. Rucaparib will be dosed 600 mg BID continuous daily dosing for a cycle length of 28 days. Nivolumab 480 mg will be administered intravenously on day 1. Subjects will then undergo a second biopsy at the end of the treatment cycle.

Dose-limiting toxicity (DLT) is defined as any grade 3 or 4 toxicity requiring interruption of rucaparib therapy for more than one week in the first 4 weeks of therapy. If two or fewer of the first 8 patients or 3 or fewer of the first twelve patients have dose-limiting toxicity, the combination will be deemed feasible. If the combination is deemed feasible, subsequent patients will be enrolled to the Phase II portion of the study.

Patients enrolled to the Phase II portion of the study will be randomized to either the single-agent rucaparib arm, the single-agent nivolumab arm, or the combination rucaparib and nivolumab arm. These patients will undergo a pre-treatment biopsy, then will begin study treatment. During the first cycle of treatment, patients randomized to single-agent rucaparib will be dosed 600 mg BID continuous daily dosing for a cycle length of 28 days. Patients randomized to single-agent nivolumab will be dosed at 480 mg on day 1 of a 28 day cycle. Patients randomized to the combination therapy arm will be dosed with rucaparib 600 mg BID daily and nivolumab 480 mg IV on day 1 of a 28 day cycle. At the end of this treatment cycle, subjects will undergo a second biopsy. For cycle 2 onwards, all subjects will be crossed over to receive the combination therapy of rucaparib plus nivolumab (unless they experience toxicity that makes this not feasible).

Primary objectives:

- Phase 1b: To determine feasibility of the combination of rucaparib and nivolumab in advanced endometrial and prostate cancer. Feasibility is defined as a dose-limiting toxicity (DLT) rate less than or equal to 25%. DLT is defined in Section 5.5.
- Phase II: To compare T cell inflammatory infiltrate within the tumor microenvironment after single agent rucaparib, single agent nivolumab, or the combination, by Nanostring RNA sequencing

Secondary objectives

- To estimate objective and biochemical (PSA, CA-125) response rates to rucaparib plus nivolumab.
- To estimate progression free survival of rucaparib plus nivolumab by radiographic and serologic (PSA, CA-125) criteria.
- To characterize baseline and changes in T cell inflammatory infiltrate within the tumor microenvironment after single agent rucaparib, single agent nivolumab, or the combination, by IHC.
- To correlate changes in T-cell inflammatory infiltrate with PTEN status.

Exploratory objectives:

- Assess DNA damage (p-gH2AX)/ HRD score in pre- and on-treatment tumor biopsy samples.
- Assess tumor infiltrating T-cell diversity. Using using flow cytometry
- Examine peripheral immune alterations, using flow cytometry

Key eligibility criteria:

- Patients must have histologically or cytologically confirmed endometrial cancer or mCRPC that is metastatic.
- They must have disease lesions amenable to safe biopsy and be willing to undergo two mandatory biopsies 4 weeks apart.
- ECOG performance status 0 or 1.
- Adequate organ function (liver, renal, hematologic).

Sample size

60 patients will be enrolled on the study, starting with patients enrolled under Amendment 1. In the Phase Ib portion of the study, the first 4-12 patients will be enrolled on the combination arm to ensure feasibility of the combination for 8 weeks. Patients who are non-evaluable for toxicity during this phase of the study will be replaced. If the combination is deemed feasible, then we will proceed to the Phase II portion of the study.

In the Phase II portion of the study, we will randomize 48-52 patients (depending on feasibility results) to either combination therapy, an initial 4 weeks single agent rucaparib followed by crossover to combination therapy, or an initial 4 weeks nivolumab followed by crossover to combination therapy, such that 20 patients will have been enrolled on each arm across the phase Ib and II study parts.

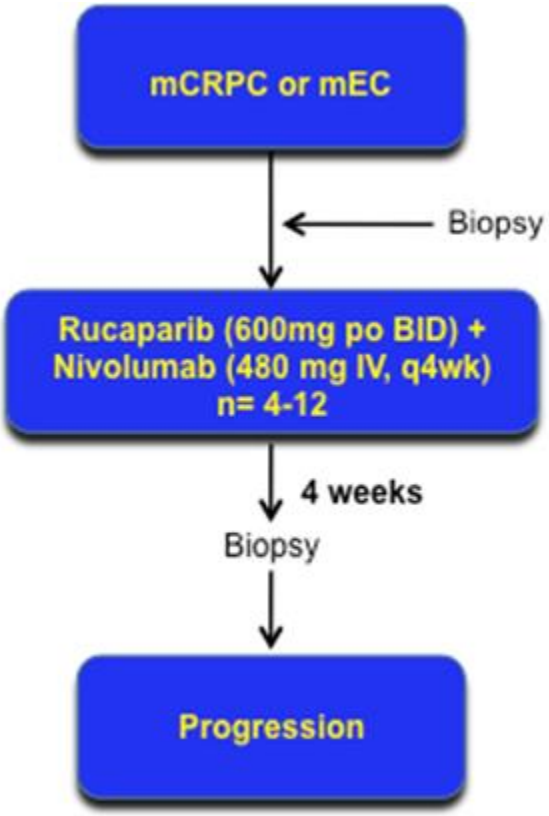
Therapies and route of administration: Nivolumab will be given at 480 mg IV q4 weeks and Rucaparib at 600 mg PO BID.

Key study procedures:

- Two mandatory tissue biopsies

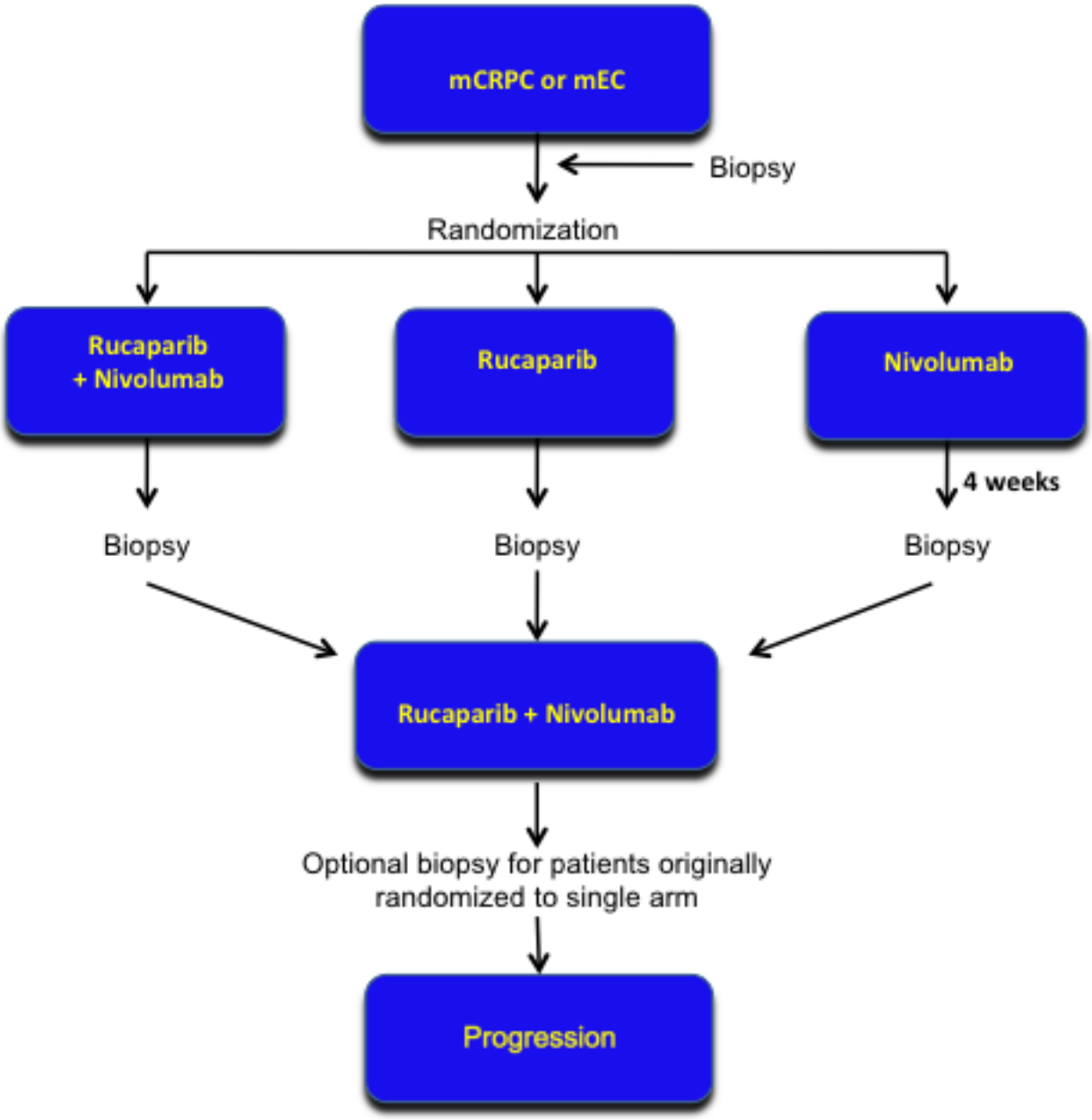
SCHEMA

Schema for Phase Ib feasibility lead-in (minimum n = 4, maximum n = 12 evaluable):



Schema for Phase II portion

Rucaparib (n = 20); Nivolumab (n = 20); Rucaparib + Nivolumab (n <=12)



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1. BACKGROUND

1.1 Metastatic Castration Resistant Prostate Cancer

Prostate cancer is the most common malignancy among men in the United States, and the second-most common cause of cancer-related mortality, with approximately 27,000 men dying of the disease each year [1]. Although most men are diagnosed with early stage, curable prostate cancer, prostate cancer (CaP) recurrence is seen in ~40% of patients over time [2]. The course of prostate cancer from diagnosis to death is often a series of clinical states progressing from localized disease to metastatic castration-resistant prostate cancer (mCRPC), a disease state characterized by resistance to standard androgen deprivation therapies that accounts for the majority of prostate cancer deaths.

Androgen deprivation therapy (ADT) remains the mainstay of initial treatment of metastatic disease, and 80-90% of patients with advanced disease will experience a response to ADT. Initial ADT results in a variable median progression-free survival of 12 to 33 months, at which time a castration-resistant phenotype commonly emerges. This accounts for the median overall survival of 60 months from the initiation of androgen deprivation[3].

The biology of metastatic prostate cancer and castration-resistance is complex. PTEN loss-of-function (PTEN LOF), found in up to 75% of mCRPC patients, contributes to tumor development, leads to poor clinical outcomes, and is associated with an immunosuppressive tumor microenvironment. Given the correlation between PTEN loss and a lack of responsiveness to immunotherapy in melanoma and leiomyosarcoma [4, 5], finding strategies to sensitize PTEN-deficient cancers to immunotherapy would have a significant impact on the therapeutic success for patients with lethal prostate cancer. In addition to its effects on the immune microenvironment, PTEN loss leads to genomic instability, causing these tumor cells to become reliant on DNA repair enzymes such as PARP. As such, PTEN-deficient tumors are potentially susceptible to PARP inhibition, which not only has direct anti-tumor activity, but could also induce DNA-damage associated increased tumor mutational burden and increased immunostimulatory activity. Preliminary data in the Patnaik laboratory has shown that rucaparib treatment can result in c-GAS/STING pathway induction in PTEN-proficient cell lines derived from the TRAMP and hi-myc models. In contrast, the corresponding isogenic cell lines generated with CRISPR/CAS9 mediated deletion of PTEN, are incapable of activating the pathway. Given the association between PTEN loss and immunosuppression, genomic instability and sensitivity to PARP inhibition, as well as the potentially immunostimulatory effects of PARPi, targeting PARP in combination with T cell checkpoint blockade therapy could represent a viable therapeutic approach to target PTEN-proficient cancers. In addition to PTEN potentially driving aggressive disease, its loss has also been implicated in resistance to androgen pathway inhibition[6].

1.2 Current Treatment Paradigms for Metastatic Castration-resistant Prostate Cancer

Over the last 10 years, multiple FDA-approved therapies have been shown to confer a modest survival benefit for patients with mCRPC, which include next generation hormonal therapies abiraterone acetate and enzalutamide, docetaxel and cabazitaxel chemotherapies, the vaccine-based immunotherapy sipuleucel-T, and the radionuclide Radium-223 dichloride [7-12]. Based

on their tolerability and proven efficacy in the pre-chemotherapy setting, abiraterone acetate and enzalutamide have become common first-line therapies for mCRPC; however, patients progress on these agents after a median duration of 16-18 months of treatment. Response rates to a second regimen of AR-directed therapy are low, therefore systemic chemotherapy is often considered as the next treatment option for patients who have progressed on AR-directed therapy. Docetaxel (75 mg/m2 every 3 weeks) plus prednisone demonstrated good activity (45% PSA response rate and 19.2 months overall survival [OS]) in chemotherapy-naïve CRPC patients who progressed on ADT. Radium Ra 223 dichloride received approval for treatment of bone-metastatic mCRPC based on modest efficacy with overall survival (OS) benefit (median of 14 versus 11.2 months for placebo)[13].

1.3 Immunotherapy in prostate cancer

There has been a resurgent interest in cancer immunotherapy, partly based on the profound and durable clinical responses following checkpoint blockade. However, there are still subsets of patients across all malignancies that fail to respond to these therapies. Despite the FDA approval of sipuleucel-T mCRPC, the majority of these patients do not exhibit clinically meaningful responses to immunotherapies. In a randomized 2:1, phase III, placebo-controlled trial of men with minimally symptomatic mCRPC, patients who received sipuleucel-T had a median OS of 25.8 months compared with 21.7 months in patients who received placebo[14].

Immune checkpoint blockade has shown limited success in mCRPC. For example, ipilimumab, a fully human monoclonal antibody that binds to the inhibitory cytotoxic T lymphocyte antigen 4 (CTLA-4), failed to show a benefit in overall survival compared with placebo in mCRPC patients [15]. Additionally, in a Phase I trial with nivolumab, none of the 17 patients with mCRPC experienced objective clinical responses[16]; thus, the clinical development of targeting PD-1/PDL-1 as a monotherapy was curtailed. There are several potential mechanisms to explain the lack of antitumor responses obtained with blockade of the PD-1/PD-L1 axis. These include a paucity of PD-L1 expression in the prostate tumor microenvironment[17], low mutational load, absence of MHC Class I expression and increased release of immunosuppressive cytokines resulting in increased infiltration of Treg and myeloid derived suppressor cell populations [18].

Therefore, there is a strong preclinical rationale for combining DNA-damaging agents, such as PARP inhibitors that can potentially increase mutational load and activate innate immune sensing pathways, with agents targeting PD-1/PD-L1 to successfully treat advanced prostate cancer.

1.4 PARP Inhibition in mCRPC

Deoxyribonucleic acid (DNA) is constantly damaged by both endogenous and exogenous (environmental) assaults. Normal cells repair single-strand breaks (SSBs) in DNA through a process known as base excision repair (BER) [19]. While there are several variations of BER, all pathways rely on the activity of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn repaired by homologous recombination (HR) DNA repair, a complex process involving multiple proteins, including those encoded by breast

cancer susceptibility gene 1 and 2 (BRCA1 and BRCA2), as well as RAD51, Fanconi anemia core complex, ataxia telangiectasia mutated serine/threonine kinase (ATM) and ataxia telangiectasia and RAD3-related (ATR) protein, among others [19].

Homologous recombination defects or PARP inhibition on their own can be overcome by a cell, but the combination is fatal, a concept termed "synthetic lethality", which forms the basis of the therapeutic approach of using PARP inhibition to kill cancer cells with a HR deficient background [19-21]. Recent efforts from the Stand Up to Cancer Dream Team East Coast demonstrated that somatic mutations in the HR genes ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51B, and RAD51C have been observed in approximately 20% of mCRPC patients [22]. Data from the recent phase II trial, TOPARP, investigating the poly (adenosine diphosphate (ADP)–ribose) polymerase (PARP) inhibitor olaparib in mCRPC, showed an 88% response rate in a heavily pre-treated mCRPC patient population with defects in DNA repair genes who received prior docetaxel (100%), abiraterone or enzalutamide (98%), and cabazitaxel (58%)[23]. Collectively, these data demonstrate that a substantial fraction of mCRPC patients with HRD will benefit from PARP inhibitor therapy [23]. Moreover, a recent study showed that approx. 12% of patients with metastatic prostate cancer have germline alterations in DNA mismatch repair genes[24]. While less common in prostate cancer, germline mutations in BRCA1 are also associated with more aggressive disease [25]. Prostate cancer patients with germline BRCA1/2 mutations have been demonstrated to be sensitive to PARPi in several studies.

1.5 Endometrial Cancer

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States with an expected 61,380 new cases and 10,920 deaths in 2017[26]. Approximately two thirds of women with endometrial cancer present with early-stage, uterus-confined disease which is typically treated surgically with or without radiotherapy with excellent outcomes. However, women with recurrent disease or metastatic disease are incurable with a five year survival rate of 17% and limited treatment options[27]. Endometrial cancers have been historically classified as either type I or type II cancers. Type I cancers comprise approximately 85% of endometrial cancers and are generally of low to intermediate-grade endometrioid histology. Type II cancers include non-endometrioid cases, most commonly of papillary serous or clear cell histology. The Cancer Genome Atlas (TCGA) project studied more than 500 newly diagnosed serous and endometrioid endometrial cancers, and categorized them into four molecular subgroups: Polymerase-E (POLE)-mutated, microsatellite unstable, copy number low, and copy number high. POLE mutated tumors have a good prognosis and rarely recur. The copy number high subgroup is characterized by p53 mutations and includes serous tumors and some of the grade 3 endometrioid tumors. Microsatellite unstable (MSI) and POLE-mutated tumors have a very high mutational burden and may be good candidates for immune checkpoint inhibitor therapy; pembrolizumab is now FDA approved for use in MSI tumors, including endometrial cancer, that have failed standard treatment options. PTEN mutations are very common in both the microsatellite unstable and the copy number low subgroups. [28].

1.6 Current Treatment of Metastatic Endometrial Cancer

Endometrial cancer, particularly type I lower grade endometrial cancer may be a hormonally sensitive disease. Responses up to 38% have been reported in studies of progestins for endometrial carcinoma. Responses are more likely among patients with grade 1 and 2 tumors with a prolonged time to recurrence. Type II cancers rarely respond to hormonal therapy, thus chemotherapy is usually the primary treatment for these patients [29]. First line treatment for metastatic or recurrent disease is the carboplatin/paclitaxel doublet. This produces response rates in the range of 40-50% and a median survival in the range of 15 months. Tumors resistant to carboplatin/paclitaxel have poor response rates to other agents, generally less than 10-15%. Antiangiogenic agents (including bevacizumab, sunitinib, and brivanib) have reported response rates in the 10-20% range, but no antiangiogenic agents or other newer targeted agents are approved for the treatment of endometrial cancer.

1.7 Immunotherapy in Endometrial Cancer

There are limited data on the use of immune checkpoint inhibitors in endometrial cancer. The endometrial cancer cohort of the KEYNOTE-28 pembrolizumab study selected patients for PD-L1 expression (but did not evaluate mutation burden or MSI status) and enrolled 24 heavily pretreated patients. The objective response rate was 13%, and all responses appeared durable, with patients remaining on treatment at the time of reporting[30]. As POLE mutation and MSI have been associated with a high number of tumor-infiltrating lymphocytes and a high neoantigen load[31], it has been hypothesized that these molecular subsets might respond well to immunotherapy. A trial selecting for MSI tumors independent of histology enrolled 9 endometrial cancer patients. Of 8 who appeared evaluable, all but one had disease shrinkage, and six had an objective response by RECIST including two complete responses. The responses appeared durable, and were continuing at the time of report[32]. Pembrolizumab is now FDA approved in MSI tumors, including endometrial cancer, that have failed standard treatment options.

1.8 PARP Inhibition in Endometrial Cancer

Loss of PTEN occurs in 30% to 60% of ECs, and in up to 80% of EC of endometrioid histology. Mutations of the PIK3CA gene are reported in 2% to 14% of type I and approximately 50% of type II endometrial cancers[33]. PTEN deficiency in endometrioid EC cells is associated with loss of HR DNA repair, which is hypothesized to sensitize them to PARP inhibitors. There is one case report of a patient with metastatic endometrial cancer with a significant response to olaparib on a phase I trial. Tumor biopsy confirmed no BRCA mutation but did show PTEN loss[34]. PTEN deficiency has been reported to predict for PARPi sensitivity in endometrial cancer cell lines [35] while other preclinical data suggest some endometrial cancers are sensitive to PARPi but this is unchanged by PTEN knockdown.

1.9 Rucaparib

There are a growing number of PARP inhibitors in clinical development, and demonstrated clinical activity as a single agent for treatment of ovarian, prostate, and breast cancer associated with a BRCA mutation (germline or somatic), as well as ovarian cancer patients without a BRCA mutation [36-45].

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

Rucaparib has been approved by the FDA for maintenance therapy in the treatment of platinum sensitive ovarian cancers, with a greater benefit seen in patients with a BRCA mutation. The therapeutic rationale for PARP inhibition with rucaparib in the presence of HRD is induction of synthetic lethality.

In clinical studies, the most common adverse reactions (Grades 1-4) in ≥20% of patients included anemia (34%), nausea (75%), fatigue (including asthenia) (68%), vomiting (43%), diarrhea (31%), dysgeusia (21%), dyspepsia (25%), headache (25%), decreased appetite (25%), nasopharyngitis/pharyngitis/URI (43%), cough (21%), arthralgia/musculoskeletal pain (32%), myalgia (25%), back pain (25%), dermatitis/rash (25%), and abdominal pain/discomfort (47%). Rucaparib is currently undergoing clinical development in several other cancers, including mCRPC.

The clinical data with PARP inhibitors provide a compelling evidence for use of rucaparib in the selected population of patients with mCRPC or endometrial cancer with predicted loss-of-function alterations in HR genes such as BRCA1/2 and ATM, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51B, RAD51D, and RAD51C. Its activity in a broader population within these diseases is unknown.

1.10 Nivolumab

PD-1 is a transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and APCs [46]. Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems [47-50]. PD-1/PD-L1 interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immunosurveillance and clearance [51]. Blockade of the PD-1 pathway has shown potent efficacy and byFDA approval in multiple cancers. Nivolumab has been studied in a variety of preclinical in vitro assays, and anti-tumor activity using a murine analog of nivolumab has been shown in a number of immunocompetent mouse cancer models.

Rationale for Flat Dose Regimens

Nivolumab is currently FDA approved in the treatment of a variety of malignancies including melanomas, non-small cell lung cancers, renal cell carcinoma, hodgkins lymphoma, colorectal, and liver malignancies. The standard dosing regimen is either 240mg every 2 weeks or 480mg every 4 weeks. A flat dose of nivolumab 480 mg Q4W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients.. Across the various tumor types, nivolumab has been shown to be safe

and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Hence, a flat dose of 480 mg nivolumab Q4W will be pursued in this study.

1.11 Rationale for combination of Rucaparib with Nivolumab

There has been a resurgent interest in cancer immunotherapy, partly based on the profound and durable clinical responses following checkpoint blockade. However, there are still subsets of patients across all malignancies that fail to respond to these therapies. Despite the FDA approval of sipuleucel-T in mCRPC, the majority of these patients do not exhibit clinically meaningful responses to immunotherapies[9] . One of the most common alterations in mCRPC patients and the single most common alteration in endometroid endometrial cancer is loss of PTEN function. PTEN deficiency is associated with an immunosuppressive tumor microenvironment [52-55]and a non-T cell inflamed phenotype, which predicts for a lack of response to immunotherapy[56]. Given the correlation between PTEN loss and a lack of responsiveness to immunotherapy, finding strategies to sensitize PTEN-deficient cancers to immunotherapy would have a significant impact on the therapeutic success of immune checkpoint inhibitors for patients with lethal prostate and endometrial cancers.

In addition to its suppressive effects on the immune microenvironment, PTEN loss leads to genomic instability, causing these tumor cells to become reliant on DNA repair enzymes such as PARP [57]. As such, PTEN-deficient tumors are particularly susceptible to PARP inhibition [35]. In addition to direct anti-tumor activity, PARP inhibition has been shown to have immunostimulatory activity via induction of senescence and other mechanisms [35, 54, 58]. Given the association between PTEN loss and immunosuppression, genomic instability and sensitivity to PARP inhibition, as well as the potentially immunostimulatory effects of PARPi, targeting PARP in combination with T cell checkpoint blockade therapy could represent a viable therapeutic approach to target PTEN-deficient cancers. Given the preponderance of PTEN deficiency in both mCRPC and advanced endometrioid EC, these diseases have been chosen for this initial feasibility study. The combination of PD-L1 and PARP inhibitors have been deemed feasible in multiple studies which reported most the common adverse effects as fatigue, anemia, hepatitis in less than 25% of patients[59-61].

This combination is thus being evaluated here as well as several additional phase 2 studies (See ClinicalTrials.gov). Under the initial version of the protocol, each of the first 4 patients enrolled experienced an anemia DLT. As a result, the protocol was extensively amended to exclude patients at high risk for anemia, and to redefine the DLT as a grade ≥3 toxicity only in the first 4 weeks of treatment, since that period is also critical for the laboratory based endpoints.

1.12 Correlative Studies Background

1.12.1 Assessing changes in a T-cell inflamed gene signature and immune infiltrates within the tumor microenvironment

In a number of malignancies, the prevalence of T cell infiltration into the tumor is associated with enhanced clinical outcomes and response to immunotherapy[62]. Research conducted by

our team at the University of Chicago found that tumors with a T cell-inflamed gene signature are associated with increased T-cell infiltration and as such respond better to immunotherapy[54, 63, 64]. Furthermore, an analysis of melanoma patients showed that loss of PTEN is associated with the lack of a T-cell inflamed gene signature[54]. In addition, biallelic loss of PTEN was recently identified as a resistance mechanism to PD-1 immunotherapy in a patient with uterine leiomyosarcoma, who had an exceptional response to this therapy[4].

In the context of primary prostate cancer, our preliminary research has shown that 90% of primary prostate cancers are T-cell non-inflamed "cold" tumors (Figure 1), and a preliminary analysis of metastatic prostate lesions have found a similar preponderance of T-cell non-inflamed tumors (Figure 1B). Furthermore, when these tumors were evaluated for PTEN status, it was found that loss of PTEN was associated with the lack of a T-cell inflamed gene signature (Figure 1C-D).

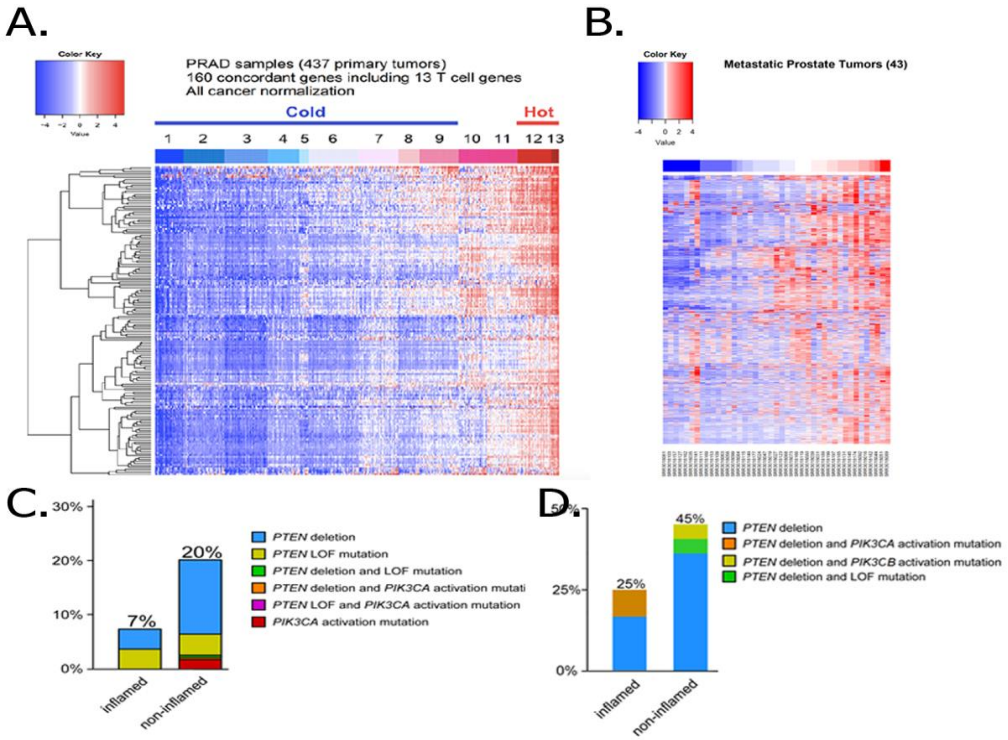

Figure 1. Prostate cancer patients have a range of T cell-inflamed or non-inflamed phenotypes. Preliminary analysis of RNAseq data of primary prostate cancer samples on the TCGA database (panel A) or metastatic prostate cancer samples from the Stand Up to Cancer Dream Team (panel B) identifies subsets of patients with high (red), medium, or low (blue) expression of the T cell-inflamed tumor microenvironment gene signature. These inflamed or non-inflamed tumors were then analyzed for the frequency of primary (panel C) or metastatic (panel D) tumors with alterations to the PTEN pathway (either PTEN loss or PI3K activation).

1.12.2 Measuring DNA damage responses in tumor cells

One of the central cell autonomous consequences of PTEN LOF is increased defects in homologous recombination of double-stranded DNA breaks[57], which causes PTEN-deficient cells to become increasingly reliant on the function of PARP. Thus, treatment with PARP inhibitors results in increases in unresolved DNA damage and ultimately cell death. As a result, one of the central means of monitoring the efficacy of PARP inhibitors is monitoring persistent

DNA damage using markers such as p-γH2AX. The H2A family member H2AX is a component of histones that is phosphorylated following DNA damage, and is an initiating step of recruiting the DNA repair complex, and as such serves as a biomarker for DNA damage[65]. In addition to evaluating these specific alterations following DNA damage, another means of monitoring defects in DNA repair following PARP inhibition is through calculating a homologous recombination deficiency score using commercially available tests such as the myScore HRD™ test from Myriad Genetics, which measures alterations to BRCA1/2 (two genes whose loss are commonly associated with DNA damage repair defects) as well as global alterations to loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST), to provide a comprehensive evaluation of features associated with increased DNA damage[66]. Given the underlying hypothesis that the central pharmacological readout of PARP inhibition is increased DNA damage, these biomarkers can be used to evaluate DNA damage in both tumor biopsies and circulating tumor cells, and have been incorporated into clinical trials evaluating these inhibitors in patients with advanced cancers[67-70].

1.12.3 Assessing T-cell diversity

While increased T cell infiltration has been shown to correlate with enhanced prognosis and improved responses to immunotherapy, utilizing next generation sequencing (NGS) to further characterize these responses has allowed for the advancement past enumeration and towards evaluating the nature of these T cell responses. This is accomplished through NGS of the complementarity determining regions (CDRs) of the T cell receptor variable beta (TCR Vβ) region, which allows for a quantitative evaluation of the diversity of the infiltrating T cell responses (i.e. the number of different antigens being recognized), with the rationale being that increased T cell diversity is a measure of 'antigen-spread', where infiltrating T cells recognize an increasing number of tumor-associated antigens and thus potentially have enhanced anti-tumor recognition. Given the underlying hypothesis that PARP inhibition alters the tumor microenvironment to promote a T-cell inflamed gene signature, and when combined with checkpoint blockade can increase T cell activation and proliferation, evaluating T cell diversity can provide a surrogate biomarker of enhanced T cell responsiveness not just in the periphery but within the tumor itself.

The evaluation of T cell diversity has been incorporated into a number of clinical trials, including several trials evaluating checkpoint blockade, which have shown that checkpoint blockade results in an increased T cell repertoire (as measured by increased TCR diversity), and that this increased diversity can correspond with enhanced clinical responses[71, 72]. Additionally, using this means of analysis to detect the expansion of particular clonotypes can provide information as to the evolving nature of the anti-tumor immune response, as an evaluation of ipilimumab-treated patients with either metastatic melanoma or prostate cancer showed that overall survival associated with the maintenance of high-frequency clones observed at baseline and not a global increase in T cell clonality[73]. T cell diversity both at the site of disease as well as in peripheral blood will be monitored to identify whether changes within the tumor microenvironment are also observed in the periphery.

2 OBJECTIVES

2.1 Primary Objectives

- Phase 1b: To determine feasibility of the combination of rucaparib and nivolumab in advanced endometrial and prostate cancer. Feasibility is defined as a dose-limiting toxicity (DLT) rate less than or equal to 25%. DLT is defined in Section 5.5.
- Phase II: To compare T cell inflammatory infiltrate within the tumor microenvironment after single agent rucaparib, single agent nivolumab, or the combination, by Nanostring RNA sequencing

2.2 Secondary Objectives

- To estimate objective and biochemical (PSA, CA-125) response rates to rucaparib plus nivolumab.
- To estimate progression free survival of rucaparib plus nivolumab by radiographic and serologic (PSA, CA-125) criteria.
- To characterize baseline and changes in T cell inflammatory infiltrate within the tumor microenvironment after single agent rucaparib, single agent nivolumab, or the combination, by IHC.
- To correlate changes in T-cell inflammatory infiltrate with PTEN status.

2.3 Exporatory Objectives

- Assess DNA damage (p-gH2AX)/ HRD score in pre- and on-treatment tumor biopsy samples.
- Assess tumor infiltrating T-cell diversity. Using flow cytometry
- Examine peripheral immune alterations.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients must have the ability to understand and the willingness to signed a written informed consent document.

3.1.2 Patients must have histologically or cytologically confirmed CRPC or endometrial cancer that is metastatic. Evidence of disease progression on a prior therapy is not required.

3.1.3 Patients must have at least one lesion that is amenable to biopsy and the treating physician must deem this safe.

3.1.4 Patient must be willing to undergo two mandatory research-only biopsies.

3.1.5 For prostate cancer patients: subjects must be surgically or medically castrated, with serum testosterone levels ≤ 50 ng/mL Patients being treated with GnRH agonists must have such therapy continued throughout the study.

3.1.6 *Prostate cancer patients:*

Patients should have received at least one AR-targeted therapy with abiraterone acetate or enzalutamide. Multiple lines of prior, therapy, except as noted in Section 3.2.4 and 3.2.5 below are permitted. A washout of two weeks from prior endocrine therapy (other than GnRH agonist); four weeks washout period from prior cytotoxic chemotherapy or other anticancer agents is required (prior to day 1 of study therapy); six weeks washout period to allow for anti-androgen withdrawal for patients managed with bicalutamide.

Endometrial cancer patients:

An unlimited number of prior hormonal and/or chemotherapy regimens are permitted. A washout of two weeks from prior endocrine therapy (other than GnRH agonist) and four weeks from prior cytotoxic chemotherapy or other anticancer agents is required (prior to day 1 of study therapy).

3.1.7 At least 5 days should have elapsed since any non-study related minor surgical procedure and at least 21 days since any major surgical procedure prior to the first dose of rucaparib and the first dose of nivolumab.

3.1.8 Must have an ability to swallow pills or capsules. Patients should have no current clinical evidence of bowel obstruction.

3.1.9 Age must be ≥ 18 years.

3.1.10 ECOG performance status must be ≤ 1

3.1.11 Patients must have normal hepatic, renal and marrow function as defined below:

- Hemoglobin ≥ 10 g/dL (without transfusion in the last 4 weeks)
- leukocytes ≥ 3,000/mcL
- absolute neutrophil count ≥ 1,500/mcL
- platelets ≥ 100,000/mcL
- total bilirubin within normal institutional limits
- ALT and AST ≤ 1.5 × institutional upper limit of normal
- creatinine ≤ 1.5 × institutional upper limit of normal

OR

- creatinine clearance ≥ 45 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.12 Patients must have a serum albumin > 2.5

3.1.13 Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of study drug. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first dose of study drug are strongly encouraged to receive palliative radiotherapy prior to enrollment.

3.1.14 Reproductive Status

Rucaparib caused post-implantation loss (100% early resorptions) at all doses administered in an embryo-fetal development study. Based on its mechanism of action, nivolumab can cause fetal harm when administered to a pregnant woman. Pregnant women are therefore not eligible for this study.

- Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test result less than 3 days prior to administration of the first dose of rucaparib.
- WOCBP must not be considering getting pregnant during the study.
- WOCBP and their male partners must agree to use a highly effective, reliable form of contraception described in section 3.3 during treatment; for 6 months following the last dose of rucaparib; and for at least 5 months following the last dose of nivolumab.
- Men who are sexually active with WOCBP must agree to use a highly effective, reliable form of contraception described in section 3.3 during treatment; 6 months following the last dose of rucaparib; and for a period of 7 months after the last dose of nivolumab .
- In addition to the above methods of contraception, use of a condom by male patients is recommended to prevent transfer of drug through semen.

3.2 Exclusion Criteria

3.2.1 Patients with active, known, or suspected autoimmune disease. Subjects with vitiligo, type I diabetes, mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, childhood asthma that is not currently active, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.2 Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration except for adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease.
Note: Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study drug is permitted.

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 Prior exposure to PD-1 or PD-L1 inhibitors, other immune checkpoint inhibitors (e.g. anti-LAG-3, and anti-CTLA-4 antibodies), or PARP inhibitors.

3.2.5 Prior exposure to Ra223 or other systemic radionuclides

3.2.6 Patients with a “currently active” second invasive malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and have been free of disease for ≥ 1 years.

3.2.7 Patients with known and untreated or progressing brain metastases are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

Patients whose brain metastases have been treated with surgery and/or radiotherapy and are without evidence of progression on scan for at least 4 weeks, and are off steroids or antiseizure medications, will be eligible .

3.2.8 Patients with symptomatic or impending spinal cord compression are not eligible unless appropriately treated.

3.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab or rucaparib.

3.2.10 Patients on parenteral nutrition are not eligible. Patients must not have a pre-existing duodenal stent or any gastrointestinal disorder or defect that would, in the opinion of the treating investigator, interfere with absorption of rucaparib.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, requirement for oxygen therapy, ongoing or active infection other than minor urinary tract infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12 Known history of chronic hepatitis B or C as evidenced by:

- Positive test for hepatitis B surface antigen
- Positive test for qualitative hepatitis C viral load (by polymerase chain reaction [PCR])

*Note: Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible.

3.2.13 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with rucaparib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.14 Prior organ allograft or allogeneic bone marrow transplantation.

3.2.15 Adverse effect of prior therapy not improved to CTCAE Grade 1 or below with the exception of alopecia. Ongoing Grade 2 non-hematologic toxicity (e.g. neuropathy) related to most recent treatment regimen may be permitted with prior advanced approval from the Lead Principal Investigator.

3.2.16 Initiated denosumab or bisphosphonate therapy or adjusted denosumab or bisphosphonate dose/regimen within 4 weeks prior to first dose of rucaparib. Patients on a stable denosumab or bisphosphonate regimen are eligible and may continue treatment.

3.2.17 Evidence or history of active or latent tuberculosis infection including PPD recently converted to positive.

3.2.18 Use of non-oncology vaccines containing live virus for prevention of infectious diseases within 12 weeks prior to study drug. The use of inactivated seasonal influenza vaccines, e.g., Fluzone®, will be permitted on study without restriction.

3.2.19 Endometrial cancer patients who may require pelvic radiation to address vaginal bleeding should have such treatment prior to enrolling on the study.

3.3 Patients or Partners of Patients of Reproductive Potential

As noted in the inclusion criteria, pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study.

A woman is considered to be of childbearing potential unless one of the following applies:

- She is considered to be permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
- She is postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.

WOCBP and their male partners must practice total abstinence or use a highly effective, reliable method of contraception (failure rate < 1% per year) during treatment; for 6 months following the last dose of rucaparib; and for at least 5 months following the last dose of nivolumab . Men who are sexually active with WOCBP must use a highly effective, reliable means of contraception during treatment; for 6 months following the last dose of rucaparib; and for a period of at least 7 months after the last dose of nivolumab.

The following are the only forms of contraception allowable for the study:

- Ongoing use of progesterone-only injectable or implantable contraceptives (e.g., 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.
- In addition to the above methods of contraception, use of a condom by male patients is recommended to prevent transfer of drug through semen.

Patients will be instructed to notify their treating investigator if pregnancy is discovered either during or within 6 months of completing treatment with rucaparib or within 5 months of completing nivolumab for WOCBP and within 7 months of completing nivolumab for partners of men taking nivolumab.

3.4 Inclusion of Minorities

Men and women of all races and ethnic groups are eligible for the trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-treatment evaluations. Patients must meet all of the eligibility requirements listed in Section 2. Eligible patients will be entered on study centrally by the University of Chicago study coordinators. All sites should call the study coordinator at (773) 834-1746 or PhaseIICRA@medicine.bsd.uchicago.edu to verify availability of a slot.

Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, patients should ideally have their biopsy within 7 days and begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive study biopsy or protocol therapy following registration, the patient's registration on the study will be canceled. The study coordinator/CRA should be notified of cancellations as soon as possible.

4.2 Registration Process

When a potential patient has been identified, notify the CRA via phone or email to ensure a reservation on the study ((773) 834-1746 or PhaseIICRA@medicine.bsd.uchicago.edu) a minimum of 48 hours prior to expected study biopsy start date:

- Provider of information
- Treating Physician
- Patient name and hospital ID number
- Patient's zip code of residence
- Date & copy of signed informed consent
- Race, gender, date of birth of patient
- Diagnosis and date of initial diagnosis
- Complete Phase II Consortium Affiliate Clinical Trial Patient Registration Form
- Source documentation for eligibility and pre-study procedures

The research nurse or data manager at the participating site will then call the study coordinator to confirm all selection criteria listed in Section 3.

To complete the registration process, the UCMC Coordinator will:

1.) Assign a patient study number
2.) Register the patient on the study
3.) Fax or e-mail the patient study number to the participating site
4.) Fax or e-mail, within 48 hours of completed registration, the assigned treatment dose (for phase I portion) or treatment arm (for phase II portion)
5.) Call the research nurse or data manager at the participating site and verbally confirm registration.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.

- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.
- The date the patient is randomized if randomization is involved or receives treatment for the first time will be considered the patient's "OnStudy Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the CRA on this date. Subjects that sign consent and do not go "OnStudy" will be recorded in the database with the date they signed consent and the reason for not going "OnStudy" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

4.3 Treatment Allocation and Randomization Processes

4.3.1 Treatment Allocation for Phase I-B portion

Under the initial version of the protocol, each of the first 4 patients enrolled experienced an anemia DLT. As a result, the protocol was extensively amended to exclude patients at high risk for anemia, and to redefine the DLT as a grade ≥3 toxicity requiring dose interruption for > 7 days only in the first 4 weeks of treatment, since that period is also critical for the laboratory based endpoints. See also 5.5

All patients on phase IB will initially receive combination therapy consisting of rucaparib (600mg PO BID) plus nivolumab (480mg, IV q4wk) for four weeks. A minimum of 4 and a maximum of 12 evaluable patients enrolled under Amendment 1 or later will be studied to determine feasibility of this combination (see stopping rules in study design-statistics in section 14.1). Patients who are non-evaluable for toxicity during this phase of the study will be replaced. In this cohort, following four weeks of combination treatment, patients will receive an on-treatment tumor biopsy. After biopsy, they will continue to receive both rucaparib and nivolumab until disease progression or unacceptable toxicity.

- Enrollment on the study will be held for 4 weeks after the first four, the first eight, and the first 12 evaluable subjects (if applicable) on the IB portion of the study while they are being assessed for toxicity, unless it is already clear that the dose level will be feasible (e.g. if three of the first four evaluable patients have completed 4 weeks therapy with no DLT, enrollment does not need to be held to allow the fourth pt to complete Assess DNA damage (p-gH2AX)/ HRD score in pre- and on-treatment tumor biopsy samples.
- Assess tumor infiltrating T-cell diversity. Using flow cytometry
- Examine peripheral immune alterations.

weeks, as it is clear that enrollment will continue regardless of whether this patient experiences DLT or not). If the combination arm is deemed feasible (as defined in section 13.1) then we will proceed to the Phase II portion of the study, in which subjects will be randomized to single-agent Rucaparib, single-agent Nivolumab, or combination therapy with Rucaparib and Nivolumab. If the combination is deemed infeasible the protocol may be amended to explore alternative dosing regimens.

4.3.2 Treatment Allocation for Phase II portion

If the combination therapy is deemed feasible, patients will be enrolled to Phase II. Patients will be randomized to combination therapy, rucaparib alone, or nivolumab alone. Twenty patients will be assigned to each of the single agent arms, and up to 16 patients will be randomized to the combination treatment arm, depending on the number of patients who completed at least 4 weeks of therapy with an attempted on therapy biopsy in the phase I-B portion and were considered evaluable. For example, if 8patients are entered into phase I-B, then 12will be randomized to combination therapy in phase II. II. Patients enrolled on the phase II portion of the study will receive a pre-treatment biopsy, followed by treatment with either rucaparib alone (600mg PO BID), nivolumab (480mg, IV q4wk) or both agents for four weeks. For these purposes, the first 4 patients enrolled under the initial version of the protocol, who all experienced a DLT, will not be considered evaluable.

Randomization will be performed by the University of Chicago study coordinator using the web-based randomization module in REDCap. The randomization sequence will be prepared by the study statistician using the method of permuted blocks once the Phase I-B portion of the study is completed. Participating sites will be notified by the coordinator within 48 hours of registered patient's open label, randomized treatment group assignment.

5. TREATMENT AND BIOPSY PLAN

5.1 Study Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dose modifications and discontinuations for Nivolumab and for Rucaparib are described in Section 8

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy, with the exception of the following:

- Prostate cancer patients who are chemically castrated would continue to receive an LHRH agonist or an LHRH antagonist.

- Medications for bone health (e.g. zoledronic acid or denosumab) should be continued if being taken prior to study entry..

Patients will complete and return study drug administration diaries, which are found in Appendix D. Patients will also return bottles of Rucaparib and any unused Rucaparib tablets so that the research nurse may review and assess patient compliance with drug dosing.

5.1.1 Phase I-B Portion

Patients enrolled to the Phase I-B portion of the study will begin with dosing of nivolumab and Rucaparib on cycle 1 day 1.

The first dose of Rucaparib 600 mg will be administered in clinic by the study nurse. Rucaparib will be dosed at 600 mg BID for a cycle length of 28 days. Nivolumab 480 mg will be

administered intravenously on day 1.

A mandatory research biopsy will be performed prior to start of study therapy, and at the completion of four weeks of combination therapy with Rucaparib and Nivolumab. The post-treatment biopsy will be performed between days 25 and 31.

Treatment will continue until disease progression or unacceptable toxicity.

5.1.2 Phase II Portion

If the combination treatment used in the Phase I-B portion has been deemed feasible, we will proceed with enrollment of subjects to the Phase II portion of the study.

As described above, n=20 patients will be randomized Rucaparib alone, n=20 to Nivolumab alone, and up to 12 patients to Rucaparib plus Nivolumab.. The maximum sample size for the entire trial will be N=60 patients, excluding the first 4 patients enrolled under the initial protocol version.

Patients in the Phase II portion of this study will be randomized for the first 4 week cycle either: single-agent Rucaparib; single-agent Nivolumab; or combination therapy with Rucaparib and Nivolumab.

A mandatory research biopsy will be performed prior to start of study therapy, and at the completion of four weeks of therapy. The post-treatment biopsy will be performed between days 25-31

After the completion of the first cycle of treatment, patients will receive combination therapy with Rucaparib and Nivolumab.

5.1.2.1 Single-agent Rucaparib Arm

Subjects randomized to this arm will begin single-agent Rucaparib 600 mg BID starting on cycle 1 day 1 and continuing through day 28 of the cycle. At the end of this cycle, a second mandatory biopsy will be performed.

Subjects will receive combination treatment with Rucaparib and Nivolumab starting on cycle 2 onwards. Patients will continue Rucaparib 600 mg BID. Nivolumab 480 mg IV will be dosed on day 1 of each cycle. Combination treatment will continue until disease progression or unacceptable toxicity.

5.1.2.2 Single-agent Nivolumab Arm

Subjects randomized to this arm will begin single-agent Nivolumab 480 mg IV starting on cycle 1 day 1. At the end of the 28-day cycle, a second mandatory biopsy will be performed.

Subjects will receive combination treatment with Rucaparib and Nivolumab starting on cycle 2

onwards. Subjects will continue Nivolumab 480 mg IV on day 1 each cycle. Subjects will start Rucaparib 600 mg BID starting on cycle 2 day 1 and continuing through day 28 of the cycle. Combination treatment will continue until disease progression or unacceptable toxicity.

5.1.2.3 Combination Rucaparib and Nivolumab Arm

Subjects randomized to this arm will receive combination treatment with Rucaparib and Nivolumab starting on cycle 1 day 1. Subjects will begin Nivolumab 480 mg IV on day 1 . Subjects will begin Rucaparib 600 mg BID starting on cycle 1 day 1 and continuing through day 28 of the cycle. At the end of this cycle, a second mandatory biopsy will be performed.

Subjects will continue receiving combination treatment from cycle 2 onwards until disease progression or unacceptable toxicity.

5.2 Nivolumab

5.2.1 Nivolumab Administration

Nivolumab will be administered at 480 mg flat dose on day 1of a 28-day cycle. Nivolumab may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons.

Nivolumab will be administered as a 30 minute IV infusion. There are no premedications recommended for Nivolumab treatment.

Sites should make every effort to target nivolumab infusion timing to be as close 30 minutes as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 40 minutes is permitted (i.e., infusion time of 20-70 minutes). The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion-related reactions are described in later sections.

5.2.2 Nivolumab Packaging, Labeling and Storage
Nivolumab will be provided as investigational supply by Bristol-Myers Squibb, Co.

PRODUCT INFORMATION TABLE: Please also see Nivolumab Investigator Brochure.

Table Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection	100 mg (10 mg/mL)	10 mL vial	Clear to opalescent colorless to pale yellow liquid. May contain particles.	2 to 8°C. Protect form light and freezing.

*Nivolumab may be labeled as BMS-936558-01 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions".

5.2.2 Management of Nivolumab-related Infusion Reactions

Since Nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported within 24 hours to BMS Global Safety at Worldwide.Safety@BMS.com and reported as an SAE if criteria are met. Refer to sections 9.6.3 and 9.7.4 for details. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated):

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours.)

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; monitor subject until resolution of symptoms. Bronchodilator or corticosteroid therapy may also be administered as appropriate. The infusion may be restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab, will be administered at that visit. The amount of study drug infused must be recorded on the case report form.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

Late-occurring symptoms: In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

For Grade 3 or Grade 4 symptoms: (Severe reaction; Grade 3: prolonged [e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]; Grade 4: life-threatening; pressor or ventilatory support indicated.)

Immediately discontinue study drug infusion. Begin an IV infusion of normal saline and treat the subject as follows: recommend bronchodilators; epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration; and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.3 Rucaparib

5.3.1 Description of Treatment(s) and Storage

This study will use the investigational drug rucaparib. Rucaparib camsylate (also known as CO-338; formerly known as PF-01367338-BW and AG-014447) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib 300 mg tablets for oral administration will be supplied by Clovis.

A brief description of the investigational product is provided below.

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

The physical appearances of the tablets are unique in order to ensure proper identification. The 200 mg tablets are blue, round (11 mm) tablets de-bossed with ‘C2’. The cosmetic blue film

coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, FD&C Blue #1 colorant, brilliant blue FCF aluminum lake, and FD&C blue indigo carmine aluminum lake. The 250 mg tablets are white, diamond shaped (15 mm x 11 mm) tablets de-bossed with 'C25'. The cosmetic white film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, and talc. The 300 mg tablets are yellow, oval tablets (16 mm x 8 mm) de-bossed with 'C3'. The cosmetic yellow film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, and irradiated yellow iron oxide.

5.3.2 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 between 15° and 30° C (59 and 86° F). Patients will be dispensed one or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28 days treatment per cycle, including a small overage.

Bottles containing rucaparib tablets will be labeled according to national regulations for investigational products.

5.3.3 Administration

All patients enrolled in this study will receive rucaparib at an initial dose of 600 mg BID. Patients may take rucaparib with or without food. Each dose should be taken with at least 8 oz (240 mL) of room temperature water. 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 (i.e., does not take it within 4 hours of the scheduled time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up. Dosing with rucaparib may be held or reduced as described in Section 9.2

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.

Patients will be provided a sufficient quantity of study drug for 28 days or until the next study drug dispensation visit (slight excess may be appropriate). Patients will also be provided with a patient diary to record daily doses. Patients will be instructed to bring their patient diary, their rucaparib tablets, and all containers (empty, partially used, and/or unopened) to the next scheduled visit for reconciliation by site personnel.

5.4 Research Biospy Plan

Two mandatory research biopsies will be collected during this study. The feasibility of performing research biopsies should be determined prior to study enrollment. One biopsy will be obtained within 7-21 days of being enrolled on study, but prior to the start of study treatment. A second biopsy will be obtained after a four-week (28 day) cycle of treatment. This biopsy will be

performed between days 25 and 31. and before starting any crossover therapy. It is required that patients have taken rucaparib for at least the 7 days leading up to the biopsy date. The biopsy date may be delayed to allow for this. Patients should have a complete blood count and coagulation studies performed and within normal limits prior to each biopsy

5.4.1 Rationale for Collection of Research Biospies

Pre-treatment biospies are collected in order to assess the microenvironment of the tumor prior to treatment.

On-treatment metastatic biopsies are collected between days 25-31 in order to assess changes in the T cell inflammatory infiltrate within the tumor microenvironment, as described in the primary objectives.

5.4.2 Handling of Biopsy Samples

Biopsies will be obtained under radiologic or other guidance, as appropriate, per institutional procedures. A minimum of 4 core biopsies are requested. However, less than the goal amount of tissue is acceptable, and should be based upon the clinical judgment of the clinician performing the procedure. One core will be collected into a PAXgene tube for RNA collection, and a second core placed in neutral buffered formalin and then embedded in FFPE (Formalin Fixed Paraffin Embedded) no more than 16 hours after exposure to neutral buffered formalin, and then placed in 18% EDTA for slow decalcification until core is pliable enough for cutting on microtome. A third core will be placed in EDTA followed by zinc-based fixative and also embedded in paraffin embedded block. A fourth core will be placed in a centrifuge tube for flow cytometry.

Biopsies will be performed at the University of Chicago and Northwestern University only, and a team from Dr. Patnaik lab will be present on the day of biopsies to collect and transport the specimens. The team should be notified at least 48 hours ahead of scheduled biopsy date.

The best ways to reach the laboratory members would be to contact:
Dr. Priyanka Duttagupta: Ph: 773-795-0995. Email: pgupta6@medicine.bsd.uchicago.edu
Dr. Raanan Alter: Ph: 847-707-2708. Email: Raanan.Alter@uchospitals.edu

5.5 Definition of Dose-Limiting Toxicity (Phase I-B portion)

There will be a 4 week DLT monitoring period (after combination treatment) during the phase IB portion of the study, in which patients will be assessed for toxicity weekly for the first two weeks, then every two weeks until the end of the 4 week monitoring period. Any grade 3 or 4 toxicity requiring interruption of rucaparib therapy for more than one week in the first 4 weeks, is considered a DLT.

Subjects who are taken off study treatment during the first 4 weeks of Phase IB due to reasons other than a DLT (and without experiencing DLT), will be replaced.

5.6 Determination of Feasibility of Combination Arm (Phase I-B portion)

Under the initial version of the protocol, each of the first 4 patients enrolled experienced an anemia DLT. As a result, the protocol was extensively amended to exclude patients at high risk for anemia, and to redefine the DLT as a grade ≥3 toxicity requiring dose interruption for > 7 days only in the first 4 weeks of treatment. These initial 4 patients will thus not be utilized to determine feasibility.

With Amendment 1, four patients will be enrolled to the Phase I-B portion. If a DLT is observed in 3 or more of these patients, the combination treatment will be declared infeasible and the trial will be terminated or amended. If no DLT is observed, an additional 4 patients will be enrolled, and if $\leq$ 2 of 8 patients have a DLT, the combination will be declared feasible and the trial will proceed to Phase II. If $\geq$ 4 of 8 patients have DLTs then the combination will be declared too toxic and the study terminated or amended. If exactly 3 of 8 patients have a DLT, then four more patients will be enrolled for a total of 12 patients. At this stage, if $\leq$ 3 of 12 have a DLT, the combination will be considered feasible and the study will proceed to phase II. Otherwise, if $\geq$ 4 of 12 have a DLT, the combination will be declared too toxic and the study will be stopped or amended.

5.7 General Concomitant Medications/Treatments and Supportive Care Guidelines

Because there is a potential for interaction of Nivolumab and rucaparib with other concomitantly administered drugs, including drugs metabolized through the cytochrome P450 system for rucaparib, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

5.7.1 Concomitant Medication

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 30 days after the last dose of study treatment. All concomitant medications, (e.g.: supportive care drugs for antiemetic management and prophylaxis and drugs used to treat adverse events or chronic diseases) and non-drug supportive interventions (e.g.: tranfusions should be recorded in the concomitant medications and treatments case report form (CRF).

Medications intended solely for supportive care (i.e., antiemetics, analgesics, and megestrol acetate for anorexia) are allowed.

5.7.1.1 Drug Interactions with Rucaparib

Based on in vitro CYP interaction studies, caution should be used for concomitant medications

with a narrow therapeutic window that are substrates of CYP2C19, CYP2C9, and/or CYP3A. Selection of an alternate concomitant medication is recommended. Caution should also be exercised for concomitant use of certain statin drugs (e.g. rosuvastatin and fluvastatin) due to potential increase in exposure from inhibition of BCRP and CYP2C9. An updated list of clinically relevant P450 drug interactions (e.g: Flockhart Table http://medicine.iupui.edu/clinpharm/ddis/main-table/) should be reviewed while screening patients for study.

Patients taking warfarin should have international normalized ration (INR) monitored regularly according to standard institutional practices

Because rucaparib is a moderate inhibitor of P-gp in vitro, caution should be exercised for patients receiving rucaparib and requiring concomitant medication with digoxin. Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice.

5.7.1.2 Concomitant Medications for Management of Castration-Related Symptoms

Treatment with androgens, estrogens, or progestins to control hot flashes is not allowed. However, selective serotonin re-uptake inhibitors (SSRIs) or gabapentin are permitted for the management of hot flashes.

5.7.1.3 Use of Steroids

Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes[74]. Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes [75]. Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of Immune-related Adverse Events (irAEs), steroids are permitted according to the modalities indicated in Management of irAEs in the Adverse Effect portion of this protocol (Section 8.2)

- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.

- Prophylactic use, e.g., for the prevention of acute infusion-related reactions: is prohibited. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

- For treatment of nivolumab associated immunotherapy toxicity (See Section 8.0)

5.7.2 Palliative Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician, but will be considered as evidence for disease progression.

5.7.3 Surgical Procedures

In case of major surgical procedure, treatment should be delayed. Re-initiation of study treatment should be discussed with the Lead PI.

5.7.4 Supportive Care Guidelines for Rucaparib and Nivolumab

Detailed criteria for determining relatedness of a toxicity to rucaparib and/or nivolumab and dose modifications is provided in Section 8.0. There will be no dose reductions for nivolumab.

Patients should use appropriate sun protection while taking rucaparinb due to increased susceptibility to sunburn.

Supportive care guidelines for immune-related adverse events should be managed according to Appendix 3 of the nivolumab investigator's brochure and ASCO Guidelines (see www.asco.org/supportive-care-guidelines OR PMID: 29442540).

5.8 Duration of Therapy

Therapy with Rucaparib or Nivolumab or Rucaparib/Nivolumab will continue until one of the following events occurs.

- Progression of disease according to Prostate Cancer Clinical Trials Working Group 3 criteria [76] or GCIG CA-125 criteria are met,
- Progression of disease according to RECIST 1.1 criteria,
- Unacceptable toxicity is encountered,
- Patient decides to withdraw from the study
- Patient is withdrawn from study at the discretion of the investigator,
- Intercurrent illness that prevents further administration of treatment,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
- Lost to follow-up/Non-compliance,
- Study termination

5.9 Duration of Follow Up

Patients will be followed for survival after discontinuation from active treatment until the end of study or until death, whichever occurs first, but no longer than 2 years after treatment discontinuation. Patients removed from study for unacceptable adverse event(s) will be followed

until resolution or stabilization of the adverse event. Subjects will be followed for AEs/SAEs for 100 days after their last dose of study drug(s).

5.10 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.8 apply. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. STUDY ASSESSMENTS

These assessments are summarized below and in the study calendar in Section 7.0.

6.1 Pre-treatment Screening Evaluation (Phase I-b and II)

Eligible patients who have signed informed consent and have had eligibility confirmed will be seen in the outpatient clinic within 28 days of starting the study. They will undergo a history and physical examination, and will have ECOG performance status, concomitant medications, and a baseline adverse event evaluation documented at this visit.

Patients will also have standard of care screening labs drawn as part of eligibility testing within 28 days of initiating therapy. These labs include: CBC (white blood cell count, hemoglobin, platelet count, white blood cell differential) and serum chemistries (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, alkaline phosphatase, and albumin). A serum cholesterol will also be obtained. Serum testosterone will be obtained from patients with mCRPC. PT, INR will be collected prior to each biopsy.

WOCBP must have a negative serum pregnancy test result less than 3 days prior to administration of the first dose of rucaparib.

Disease burden must be evaluated within 30 days prior to study entry. Disease evaluation may be performed with: a nuclear medicine bone scan or Fluoride PET; CT or MRI of the abdomen and pelvis; and CT chest (when clinically indicated).

A mandatory research biopsy will be collected after enrollment and prior to the first dose of study treatment.

Study entry date is defined as the day of the first pre-treatment biopsy.

6.2 On Study Visits

6.2.1 Phase I-B Portion

On study visits will be every 2 weeks, and after week 12, visits will be every 4 weeks. Patients

are seen frequently during the first portion of study therapy to ensure adequate patient safety while on study. On-study visits can occur +/- 3 days of the scheduled visit.

The following procedures and assessments will be completed on Day 1 of each cycle:

- Physical exam;
- Vital signs including Weight;
- Concomitant medications and procedures;
- ECOG performance status;
- CBC with differential;
- Serum chemistry
- Cholesterol monthly for the first three cycles and then as clinically indicated
- AE monitoring
- Thyroid function tests (Cycles, 1, 2, and 3, then as clinically indicated)
- PSA or CA125

For WOCBP, a serum pregnancy test must be performed < 3 days prior to Day 1 of every cycle from Cycle 2 and beyond.

The following procedures and assessments will be completed on Day 15 of each cycle when the patient is seen:

- Physical exam;
- Vital signs;
- Concomitant medications and procedures;
- ECOG performance status
- CBC with differential
- Serum chemistry
- AE monitoring

Refer to the Study Calendar for patients enrolled to Phase I-b for details.

The second mandatory research biopsy will be obtained at the completion of four weeks of study therapy.

Disease assessment with imaging will be repeated every 12 weeks while on study, starting at first day of concomitant daily study drug administration. The same method of assessment and the same technique that was used to assess disease at screening should be used.

6.2.2 Phase II Portion

On study visits will be every 2 weeks and . after week 12, visits will be every 4 weeks. Patients are seen frequently during the first portion of study therapy to ensure adequate patient safety while on study. On-study visits can occur +/- 3 days of the scheduled visit.

The following procedures and assessments will be completed on Day 1 of each cycle:

1. Physical exam;
2. Vital signs including Weight;
3. Concomitant medications and procedures;
4. ECOG performance status;
5. CBC with differential;
6. Serum chemistry;
7. Cholesterol for the first three cycles and then as clinically indicated;
8. AE monitoring;
9. Thyroid function tests (Cycles, 1, 2, and 3, then as clinically indicated);
10. PSA or CA125

For WOCBP, a serum pregnancy test must be performed < 3 days prior to Day 1 of every cycle from Cycle 2 and beyond.

The following procedures and assessments will be completed on Day 15 of each cycle when the patient is seen:

1. Physical exam;
2. Vital signs;
3. Concomitant medications and procedures;
4. ECOG performance status;
5. CBC with differential;
6. Serum chemistry;
7. AE monitoring

Refer to the Study Calendar for patients enrolled to Phase II for details.

The second mandatory research biopsy will be obtained as close as possible to the completion of four weeks of study therapy, and before starting a crossover therapy.

Disease assessment with imaging will be repeated every 12 weeks while on study, starting at first day of any study drug administration. The same method of assessment and the same technique that was used to assess disease at screening should be used.

6.3 Off Study Assessments

Patients will be followed with the assessments described in Sections 6.2.1 and 6.2.2 and the study calendars in Sections 7.1 and 7.2 until taken off study. Upon study discontinuation, subjects will undergo a complete evaluation with a history and physical examination, ECOG performance status, concomitant medications, and toxicity evaluation documented at this visit.

Standard laboratory studies, specifically, CBC with platelets, and serum chemistries will also be collected at this visit unless already collected within past 2 weeks. PSA and testosterone will be collected from mCRPC patients and CA-125 will be collected from endometrial cancer patients unless already collected in past 2 weeks.

A serum pregnancy test will also be performed at the End of Treatment Visit for WOCBP.

Radiologic tumor assessments will be performed, unless already performed within four weeks of being taken off study. Study participant refusal or inability to undergo these evaluations will be noted. This visit should be done on the day patients are taken off study medication but may be completed within 30 days of coming off treatment.

In addition, an optional tumor biopsy may be obtained at time of disease progression for those patients who are being removed from study treatment for progression, to elucidate resistance mechanisms to the combination therapy.

7. STUDY CALENDAR

7.1 Phase I-b portion

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. Laboratory evaluations, physical examination, and assessment of concomitant medications and adverse events may be performed +/- 3 days prior to the scheduled visit. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. A cycle of therapy in the Phase I-b portion of this study is defined as four weeks (28 days) of therapy.

	Pre-Study	C 1 day 1 (+/- 3 days)	C 1 day 8 (+/- 3 days)	C 1 day 15 (+/- 3 days)	C1 day 22 (+/- 3 days)	C 2 day 1 (+/- 3 days)	C2 day 8 (+/- 3 days)	C 2 day 15 (+/- 3 days)	C 2 day 22 (+/- 3 days)	Day 1 of subse-quent cycles (+/- 3 days)	Day 15 of subse-quent cycles	End of Tx [j]	28-day follow-up	Long Term Follow Up ([l, m])
Nivolumab		A				A				A				
Rucaparib		B	B	B	B	B	B	B	B	B	B			
Informed consent[a]	X													
Demographics	X													
Medical history	X													
Survival status														X
Concomitant med and procedure review	X	X----------X												
Physical exam	X	X		X		X		X		X	X	X	X	
Vital signs	X	X		X		X		X		X	X	X	X	
Height	X													
Weight	X	X		X		X		X		X	X	X	X	
Performance status	X	X		X		X		X		X	X	X	X	
CBC w/diff, plts	X	X	X	X		X		X		X	X	X	X	
Serum chemistry[b]	X	X	X	X		X		X		X	X	X	X	
Thyroid Function	X	X				X				X[d]		X	X	

Panel[c]														
Cholesterol[n]	X					X				X				
Testosterone[e]	X											X	X	
PSA or CA125		X				X				X		X	X	
Hep B Virus Testing (HBs-Ag; HBs-AB, HBV-DNA)	X													
Hep C Virus Testing (HCVAb, HCV RNA)	X													
PT, INR	X				X							X[k]		
Adverse event evaluation		X----------X										X		X[k,m]
Tumor measurements [f]	X	Tumor measurements are repeated every 12 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.										X		
Radiologic evaluation [f]	X	Radiologic measurements should be performed every 12 weeks.										X		
Bone Scan[g]	X	Radiologic measurements should be performed every 12 weeks.										X		
B-HCG[h]	X	X				X				X		X		
Mandatory Correlative Studies: 1 Red top 10 mL (serum/plasma)[i]		X				X				X[d]		X		
Mandatory Correlative Studies: 2 10 mL purple top (whole blood)[i]		X				X				X[d]		X		
Tumor Biopsy	X				X[o]							X[k]		

A: *Nivolumab*: Starting dose: 480 mg IV every four weeks
B: *Rucaparib*: Starting dose: 600 mg PO BID.
a: Written informed consent must be obtained before any study-specific screening assessments are performed.
b: Serum chemistry includes: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, cholesterol.
c: Thyroid Function Panel includes: TSH, reflexive free T4, and free T3.
d: Cycle 3 day 1, Cycle 4 day 1, then corresponding to all imaging assessment time points.
e: Prostate cancer patients only.
f: Assessment of effect by Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1.
g: For patients with bone metastases.
h: Serum pregnancy test for women of childbearing potential. Must be performed <3 days prior to day 1 of every cycle.
i: See sections 11.1 and 11.2 for details regarding required samples.
j: Off-study evaluation.
k: Tumor biopsy optional only at off-study evaluation.
l: Follow patients till the end of study or until death, whichever comes first.
m: All SAEs and AEs must be collected from during the treatment period and for a minimum of 100 days of the last dose of nivolumab.
n: For patients getting rucaparib alone or rucparib/nivolumab combination therapy
o: Tumor biopsies are to be at or before C1D28

7.2 Phase II portion

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Scans and x-rays must be done ≤ 4 weeks prior to the start of therapy. Laboratory evaluations, physical examination, and assessment of concomitant medications and adverse events may be performed +/- 3 days prior to the scheduled visit. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. A cycle of therapy in the phase II portion of this study is defined as four weeks of therapy.

	Pre-Study	C1 day 1 (+/- 3 days)	C1 day 8 (+/- 3 days)	C1 day 15 (+/- 3 days)	C1 day 22 (+/- 3 days)	C2 day 1 (+/- 3 days)	C2 day 8 (+/- 3 days)	C2 day 15 (+/- 3 days)	C2 day 22 (+/- 3 days)	Day 1 of subse-quent cycles (+/- 3 days)	Day 15 of subse-quent cycles	Off Study [k]	28-day follow-up visit	Long Term Follow Up [m, n]
Randomization		X[a]												
Randomized study treatment		A	A	A	A									
Combination treatment						B	B	B	B	B	B			
Informed consent [b]	X													
Demographics	X													
Medical history	X													
Survival status														X
Concomitant med review	X	X----------									X			
Physical exam	X	X		X		X		X		X	X	X	X	
Vital signs	X	X		X		X		X		X	X	X		
Height	X												X	
Weight	X	X		X		X		X		X	X	X	X	
Performance status	X	X		X		X		X		X	X	X	X	
CBC w/diff, plts	X	X	X	X		X		X		X	X	X	X	
Serum chemistry [c]	X	X	X	X		X		X		X	X	X	X	
Thyroid Function Panel[d]	X	X				X				X[e]		X		
Cholesterol[o]	X					X				X			X	
Testosterone[f]	X					X				X		X		
PSA or CA125	X					X				X		X		
Hep B Virus Testing	X													

	Pre-Study	C1 day 1 (+/- 3 days)	C1 day 8 (+/- 3 days)	C1 day 15 (+/- 3 days)	C1 day 22 (+/- 3 days)	C2 day 1 (+/- 3 days)	C2 day 8 (+/- 3 days)	C2 day 15 (+/- 3 days)	C2 day 22 (+/- 3 days)	Day 1 of subse-quent cycles (+/- 3 days)	Day 15 of subse-quent cycles	Off Study [k]	28-day follow-up visit	Long Term Follow Up [m, n]
(HBs-Ag; HBs-Ab, HBV-DNA)														
Hep C Virus Testing (HCV Ab, HCV RNA)	X													
PT, INR	X				X							X[l]		
Adverse event evaluation		X----------										X		X[m]
Tumor measurements[g]	X	Tumor measurements are repeated every 12 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.										X		
Radiologic evaluation[g]	X	Radiologic measurements should be performed every 12 weeks.										X		
Bone Scan [h]	X	Radiologic measurements should be performed every 12 weeks.												
B-HCG[i]	X	X				X				X		X		
Mandatory Correlative Studies: 1 10 mL red top (serum/plasma)[j]		X				X				X[e]		X		
Mandatory Correlative Studies: 2 10 mL purple tops (whole blood)[j]		X				X				X[e]		X		
Tumor Biopsy	X				X							X[l]		

A: Subjects shall be randomized to either: Rucaparib 600 mg PO BID daily for 4 weeks, starting on cycle 1 day 1; or Nivolumab 480 mg IV every four weeks for 4 weeks, starting on cycle 1 day 1; or the combination treatment arm (Rucaparib 600 mg PO BID daily and Nivolumab 480 mg IV every four weeks for 4 weeks.)

B: All subjects shall receive combination treatment with Rucaparib 600 mg PO BID daily and Nivolumab 480 mg IV every 4 weeks starting at cycle 2

a: Randomization will occur after eligibility has been confirmed, but before a pre-treatment biopsy is obtained.

b: Written informed consent must be obtained before any study-specific screening assessments are performed.

c: Serum chemistry includes: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], and sodium.

d: Thyroid Function Panel includes: TSH, reflexive free T4, and free T3.

e: Cycle 3 day 1, Cycle 4 day 1, then corresponding to all imaging assessment time points.

f. Prostate cancer patients only

g: Assessment of effect by both the Response Evaluation Criteria in Solid Tumors (RECIST1.1)

h: For patients with bone metastases

i: Serum pregnancy test for women of childbearing potential. Must be performed <3 days prior to day 1 of every cycle.

j: See sections 11.1 and 11.2 for details regarding required samples.

k: Off-study evaluation.

l: Tumor biopsy optional only at off-study evaluation

m: Follow patients till the end of study or until death, whichever comes first.

n: All SAEs and AEs must be collected from during the treatment period and for a minimum of 100 days of the last dose of nivolumab.

o: For patients getting rucaparib alone or rucparib/nivolumab combination therapy

8. DOSING DELAYS/DOSE MODIFICATIONS

8.1 General Guidelines

Every effort should be made to administer study treatment on the planned dose and schedule. If a toxicity is seen, the treating physician should ascertain and document relatedness to either or both of the study drugs.
Note that a rise in creatinine or a transaminitis within the first 4 weeks or myelosuppression during combination therapy are most likely related to rucaparib rather than nivolumab. In general, these toxicities should be managed as per rucaparib dose modification guidelines in Section 8.3 below. For creatinine elevations or transaminitis noted after 4 weeks, or for myelosuppression that does not resolve in a timely manner, an immune related AE should be considered and treated accordingly. In unclear cases, biopsy or other work up for an immune related AE or a myelodysplastic syndrome may be necessary.

The maximum time rucaparib may be held due to toxicity is 28 days and the maxium time nivolumab may be held due to toxicity is 84 days. If drug holds exceed this time frame, the patient must be discontinued from study participation. Exception: subjects completing a steroid taper for nivolumab toxicity or for whom nivolumab is permanently discontinued, may resume rucaparib after a longer interval if clinically appropriate.

8.2 Nivolumab-related Toxicity

When encountering nivolumab related toxicities, please reference Appendix 3 of the nivolumab investigator's brochure and the published ASCO guidelines for immunotherapy toxicity management (www.asco.org/supportive-care-guidelines0. In general:

- For all grade 3-4 toxicities, steroid therapy should be initiated and therapy should be discontinued.
- For grade 1 or 2 toxities, treatment may resume when toxicity resolves to baseline.

No dose modifications are permitted for nivolumab in this study. Doses may be omitted based on persistent toxicity as per above general guidelines.

8.3 Rucaparib Dose Modifications

The most common effects of rucaparib treatment include: gastrointestinal disorders (nausea, vomiting, diarrhea, and constipation); asthenia/fatigue; elevations in clinical chemistries (ALT/AST, creatinine, and cholesterol); myelosuppression (decreased hemoglobin, lymphocytes, platelets, and neutrophils); dysgeusia; and decreased appetite.

Modification of rucaparib doses may be a necessary component of AE management. Dose interruptions, with or without subsequent dose reductions, may help to ameliorate AEs attributed to rucaparib therapy. Additional guidance for management of ALT/AST, cholesterol elevations, and myelosuppression ifor subjects taking rucaparib is provided below

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

- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines)
- 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.

If not otherwise specified below, 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 dose reduction to dose level -3, or if dosing with rucaparib is interrupted for > 28 consecutive days due to toxicity, rucaparib treatment should be discontinued.. For patients on combination therapy, nivolumab may be continued at the investigator's discretion.

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

Dose reduction steps are presented below:

Rucaparib Dose Reduction Steps

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

8.4 Management of Anemia including Evaluation for MDS/AML and Follow-up of Patients who Discontinue Treatment with Ongoing Anemia

- If the patient develops anemia CTCAE Grade ≥ 3, , rucaparib treatment should be held and dose reduced. If rucaparib is held due to anemia, once itimproves to CTCAE Grade ≤ 2, daily dosing should then be resumed at either the same dose or a lower dose, per treating investigator discretion.
- If the duration of dosing is interrupted for > 28 consecutive days due to anemia CTCAE Grade ≥ 3, treatment should be permanently discontinued,.

- In addition, if a patient develops anemia CTCAE Grade ≥ 3, thenthen weekly complete blood counts should be performed until resolution of the event. In addition, serum folate levels should be checked.
- If, after 42 days of interruption of rucaparib, the anemia has not improved to CTCAE Grade ≤ 1 then the patient should be considered for analysis of the bone marrow with cytogenetic studies according to standard hematologic practice.
- The bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

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

8.5 Management of Rucaparib Treatment-Emergent ALT/AST Elevations

- Grade 4 ALT/AST elevations:
  a. hold rucaparib until values have returned to Grade 2 or better, then resume rucaparib with a dose reduction.
  b. Monitor liver function tests weekly for 3 weeks after rucaparib has been restarted.
- Grade 3 ALT/AST elevations:
  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.
  c. If patient is trying to cross over to combination therapy, dose reduction of rucaparib may also be employed in an attempt to reduce transaminitis to grade 1 or less.

Subjects with grade 2 or higher transaminitis on single agent rucaparib may continue on rucaparib and or dose reduce per package insert guidelines. However nivolumab may not be started unless transaminitis is grade 1 or lower. Subjects with persistent transaminitis on single agent rucaparib at 12 weeks or later (such that addition of nivolumab is not feasible) may elect to discontinue rucaparib and start single agent nivolumab when transaminitis resolves.

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.

8.7 Treatment of Overdose

There is no specific treatment in the event of rucaparib overdose, and symptoms of overdose are not established. In the event of suspected overdose, physicians should follow general supportive measures and should treat symptomatically.

9. ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms, and review of the patient's own record of adverse events.

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs for 100 days after their last dose of study drug(s).

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. Assessment of toxicities and adverse events will be graded according to CTCAE version 4.03. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

9.2 Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) are defined as serious or non-serious AEs of scientific and medical concern specific to 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 such as regulatory agencies might also be warranted.

9.2.1 Myelodysplastic Syndrome and Acute Myeloid Leukemia

As of June 27, 2016 there have been 3 events of myleodyplastic syndrome (MDS) and 3 events or Acute Myeloid leukemia (AML) reported in patients participating in Clovis-sponsored clinical studies. The 3 events of MDS were reported in open-label clinical studies. More than 1,000 patients have received oral rucaparib and these events have been observed in <0.6% of all patients on these studies. Events of MDS and AML have also been reported with another PARP

inhibitor [77].

9.2.2 Reporting of AESIs to Clovis

Details on Clovis's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. As of protocol writing they include the below, however updates may occur.

- MyelodysplasticSyndrome and Acute Myeloid Leukemia

These AESIs are to be reported to Clovis expeditiously **within 24 hours** of investigator knowledge of the event, according to the procedures below.

9.3 Serious Adverse Events

9.3.1 Definition of Serious Adverse Event

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- Death
- Is immediately life-threatening (e.g. places subject at immediate risk of death, this does not include events that might have caused death if they occurred a greater severity)
- Results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of IMEs include: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

Additional study-specific events to be reported as SAEs are described below in Section 9.6.2 and 9.7 .

9.3.2 Events or Outcomes Not Qualifying as Serious Adverse Event
The following are not considered SAEs and therefore do not need to be reported as such:

1. Pre-planned or elective hospitalization including social and/ or convenience situations (e.g., respite care)

2. Hospital visits of less than 24 hours duration (e.g., patient presents to the emergency

room, but is not admitted to a ward)

3. Overdose of either Clovis study drug, nivolumab, or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as a nonserious AE.

4. 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.

9.4 Suspected Adverse Reactions

An adverse event (AE) is considered to be a suspected adverse reaction if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater frequency than expected from historical controls.

9.5 Unexpected Events

Unexpected events are those not listed at the observed specificity or severity in the protocol, investigator brochure, and/or FDA-approved package. This includes adverse events listed in the protocol or consent as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which have not been previously observed with the investigational agent(s).

9.6 Adverse Event Reporting Requirements

9.6.1 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported using the Serious Event Reporting Form and/or MedWatch Form discussed below must <u>also</u> be reported in routine study data submissions.**

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. The Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and their causal relationship.

9.6.2 Serious Adverse Event Reporting **<u>to</u>** the Coordinating Center

Use the UCCCC protocol number and the protocol-specific patient ID assigned during trial

registration on all reports.

All serious adverse events (as defined in sections 9.3, 9.4, and 9.5) require expedited reporting to the University of Chicago Comprehensive Cancer Center (UCCCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Investigator, the University of Chicago CRA and the CCTO within 24 hours of discovery. Reports should be made using the 'Serious Event Report' Form. Please scan and send via email (preferred) or fax to the following:

University of Chicago Phase II CRA General:
PhaseIICRA@medicine.bsd.uchicago.edu
Phone: 773-834-1746
Fax: 773-702-4889

UCCCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu and to the Phase II CRA at PhaseIICRA@medicine.bsd.uchicago.edu within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA, Clovis or BMS. The U of C CCTO will report all events to the FDA as per the current FDA guidelines. The U of C study coordinator will also report to Clovis and BMS.

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

9.6.3 Serious and Unexpected Adverse Event reporting **by** the Coordinating Center

The designated UCCCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB). When reported to the FDA, a copy of the completed Form 3500A (MedWatch) will be provided to the responsible Regulatory Manager by the CCTO IND Coordinator for distribution to all participating sites.

Reporting to Clovis:

In addition to the FDA, a copy of the completed MedWatch Form 3500A will be submitted to Clovis Oncology, which is providing rucaparib for this study. All SAEs and AESIs, regardless of

relationship to study drug, must be reported to the Clovis Oncology **within 24 hours** of Lead Investigator knowledge of the event, during the study through 30 days after receiving the last dose of study treatment, according to the procedures below. After the 30-day specified window, only SAEs considered to be treatment-related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report.

The MedWatch Form 3500A must be used for reporting SAEs and AESIs. This may be sent to: (Drugsafety@clovisoncology.com or fax: +1.303.261.8319).

Preganacies occurring in a trial subject or female partner should be reported within 48 hours of Lead Investigator knowledge of the event.

Reporting To Bristol-Myers Squibb (BMS):

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety (worldwide.safety@bms.com).
- Medwatch should be used to report SAEs. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
    - Other important findings which may be reported as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
    - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor-investigator will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
    - In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within **within 24 hours** of knowledge of the event. SAEs and pregnancies must be recorded on a MedWatch Form.
SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

All SAEs should be followed to resolution or stabilization.

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

<u>Potential Drug Induced Liver Injury (DILI)</u>
Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Pregnancy
If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including five months after the last dose of nivolumab and 6 months after the last dose of rucaparib, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

The sponosor-investigator must immediately notify Worldwide Safety @BMS.com of this event via the MedWatch Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS].

Any pregnancy that occurs in a female partner of a male study participant up to 7 months after last dose of nivolumab should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Overdose
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE to BMS.

9.7 Other Safety Considerations

9.7.1 Laboratory Data

All laboratory data obtained during the course of the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose reduction or delay, requirement for additional medication or monitoring) or is considered to be of clinical significance by the investigator should be reported as an adverse event or serious adverse event as appropriate, unless this value is consistent with the patient's present disease state or is consistent with values obtained prior to entry into the study.

9.7.2 Procedure in Case of Pregnancy or Drug Exposure during Pregnancy

The effect of rucaparib and nivolumab in pregnant and lactating women is not known, and the exposure of a fetus or nursing infant is considered a potential risk. Both drugs can cause fetal harm when administered to a pregnant woman based on its mechanism of action.

- Female patients of reproductive potential and their male partners must practice total abstinence or use a highly effective method of contraception as dexcribed in section 2.3 during treatment and for 6 months following the last dose of rucaparib and for at least 5 months following the last dose of nivolumab..

- Men who are sexually active with WOCBP must agree to use a reliable form of contraception described in section 2.3 during treatment, and for 7 months after the last dose of nivolumab and 6 months following the last dose of rucaparib.

If a patient becomes pregnant during the study the investigator is to stop dosing with study drugs immediately.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a study patient or partner of a study patient during study participation or within 6 months of last dosing of rucaparib 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.

AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/AESI processes using the appropriate AE or SAE/AESI forms.

9.7.3 Medication Errors

Any medication error that results in an adverse event, even if it does not meet the definition of serious, requires reporting to the UCCCC CCTO as above.

9.7.4 Infusion Reactions

As noted in section 5.2.2, all grade 3 or 4 infusion reactions should be reported within 24 hours to BMS Global Safety at Worldwide.Safety@BMS.com and reported as an SAE if criteria are met. Refer to section 9.6.3 for details.

9.8 Follow-Up of Adverse Events

Any SAE or AE assessed as possibly related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 100 days after last dose of nivolumab must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to possibly-related serious adverse events that occur greater than 30 days after last dose of study treatment. The status of all other continuing adverse events will be documented as of 100 days after last dose of nivolumab.

10. PHARMACEUTICAL INFORMATION

The study drugs will be requested by the Principal Investigator (or their authorized designees) at

the University of Chicago. Other sites that require study agent will submit a completed Clinical Drug Request Forms to the University of Chicago Investigational Drug Service by fax (773) 834-7461. Orders received on Fridays will not be shipped until the following business day.

For questions about drug orders, transfers, returns, or accountability call (773) 834-7466 Monday through Friday between 8:00 am and 4:30 pm (CST) or email IDS.PHARMACY@uchospitals.edu.

The investigator is responsible for maintaining accurate records of the delivery of study drugs, drug inventories, use by each enrolled subjects, and disposition of study drugs. This responsibility may be delegated to an appropriate pharmacist or another appropriate individual under the supervision of the investigative site.

10.1 Rucaparib

Rucaparib will be provided by Clovis and shipped to the University of Chicago for use on site and distribution to participating institutions upon patient registration and treatment allocation.

10.1.1 Description of the Dosage Form

Refer to section 5.3.2 for a description of the containers in which all tablets are provided, a brief description of the investigational product, and storage conditions. Each bottle provided to the subjects will be labeled with the protocol number, dosing and storage instructions, and expiration date. Bottles of drug will be labeled and dispensed as described in section 5.3.2.

10.1.2 Destruction of Study Drug Provided by Clovis

Sites are required to submit a Study Drug Destruction Authorization Form to Clovis Supply Chain (Rucasupply@clovisoncology.com) for **ALL** undispensed study drug that they would like to destroy, regardless of whether the drug will be destroyed locally or returned to a local depot for destruction.

It is expected that returned, unused, damaged, expired or otherwise out of specification study drug will be destroyed by the site where possible, using internal site procedures for the safe disposal of cytotoxic materials for chemotherapy comparators and internal site procedures for the safe disposal of non-cytotoxic materials for rucaparib. For all sites able to destroy materials please submit local SOPs/processes to your MSA.

If a site has damaged/out of temperature specification, soon to expire/expired, or is requesting final drug destruction authorization at site close out, please notify your MSA. The MSAs must complete and submit a **Study Drug Destruction Authorization Form** to Clovis Supply Chain (Rucasupply@ClovisOncology.com) for review and approval. Only after the request is approved by Clovis Supply Chain can unused study drug be destroyed. The quantity of bottles of study drug shipped, destroyed and returned must be reconciled. Destruction of study drug should be

clearly documented in the site's pharmacy records.

In all cases, after the study drug has been destroyed, a confirmation of study drug destruction must be provided for documentation purposes and recorded in the site's Drug Inventory Log.

For sites that do not allow on-site destruction, please contact your MSA for further instructions. Refer to **Study Drug Return Form** for study drug return guidelines to depot.

10.2 Nivolumab

Nivolumab will be provided by Bristol-Myers Squibb and shipped to the University of Chicago for use on site and distribution to participating institutions upon patient registration and treatment allocation. The nivolumab will be provided as a 100 mg/10 mL solution in a single-dose vial. A flat dose of 480 mg will be given to each patient, therefore five 100 mg/10 ml solution will be given per treatment, and the remaining 20 mg will be discarded upon administration. Each infusion provided to the subjects will be labeled with the protocol number, dosing and storage instructions, and expiration date. The contents of the label will be in accordance with applicable regulatory requirements.

10.2.1 Description of the Dosage Form

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

10.2.2 Drug Product Preparation

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection will be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab for injection will be provided in the clinical protocol, pharmacy binder, pharmacy manual, investigators brochure or pharmacy reference sheet. Care will be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

10.2.3 Recommended Storage and Use Conditions

Vials of nivolumab injection must be stored at 2° C to 8° C (36° F to 46° F) and protected from light and freezing.

10.2.4 Undiluted Nivolumab Injection and Diluted Nivolumab injection in the IV Container

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

10.2.5 Nivolumab Preparation and Dispensing

See the Dosage and Administration Instruction (DAI) for instructions on how to prepare the investigational product for administration.

Nivolumab will be administered at the investigational sites. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g. physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic and investigational agents.

The contents of the nivolumab vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

For administration in this trial, nivolumab must be diluted with 0.9% sodium chloride (normal saline solution). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the DAI. Must use tubing with in-line, low protein binding 0.2 micron filter made of polyether sulfone (PES) during administration.

Nivolumab must not be used for any purpose other than the trial. The administration of trial drug to patients who have not been enrolled into the trial is prohibited.

Vials are single-use. Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

10.2.6 Destruction of Study Drug Provided by BMS

For this study, study drugs supplied by BMS, such as partially used study drug containers, vials and syringes, will be destroyed on site.

On-site destruction is allowed provided the following minimal standards are met:

1. On-site disposal practices must not expose humans to risks from the drug.
2. On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
3. Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
4. Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
5. Accountability and disposal records are complete, up-to-date, and available for the monitor to review throughout the clinical trial period.
6. A copy of the drug destruction certificate must be maintained for provision to BMS at the end of the study.

Conditions for destruction will be handled as per institutional policy. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

11.1 Biomarker Studies

11.1.1 Sample Collection

Upon entry into the study, each subject will be assigned a unique identification number. All materials collected from that subject will be labeled with that number only, for reasons of confidentiality, and specimens may be listed with unique codes for individual subjects and obtained at the different time points. Blood will be stored in liquid nitrogen, and sera and bone marrow aspirates will be aliquoted and stored at –80°C in the research laboratory of the co-PI PI (Dr. Patnaik) for immune analyses.

Blood sample collection will occur at the time points listed in the table below:

Time Point	Collection Tube	Tube Volume	Number of Tubes
Cycle 1 Day 1	Purple top EDTA	10 mL	2
	Red top with clot activator	10 mL	1
Cycle 2 day 1	Purple top EDTA	10 mL	2
	Red top with clot activator	10 mL	1
Cycle 3 day 1	Purple top EDTA	10 mL	2
	Red top with clot activator	10 mL	1
Cycle 4 day 1	Purple top EDTA	10 mL	2
	Red top with clot activator	10 mL	1
Every 12 weeks thereafter	Purple top EDTA	10 mL	2
	Red top with clot activator	10 mL	1
End of Treatment	Purple top EDTA	10 mL	2
	Red top with clot activator	10 mL	1

There is an option for further collection while on study protocol.

11.1.2 Sample Processing

Spin down red top tube for serum at 2600 x g for 10 minutes. Aliquot supernatant into 4 cryovials containing 1 mL each.

Spin down purple top EDTA tubes at 2600 x g for 10 minutes. Aliquot supernatant into 8 cryovials containing 1 mL each.

Add PBS to purple top tubes and gently resuspend blood.

Pour suspension over Ficoll and spin down to separate PBMCs. Wash with ACK as needed to remove remaining RBCs. Once pellet is white in color, count cells, resuspend in freezing media and aliquot PBMCs into 4 cryovials containing 1mL each.

All samples will be labeled with the patient ID number, time point (e.g.: cycle/day), and date of draw.

11.1.3 Sample Storage and Shipment

All tubes will be stored in cryovials in -80°C freezers and batched shipped on dry ice to:

Attention: Dr. Priyanka Duttagupta (in Dr. Patnaik's laboratory)
Knapp Center for Biomedical Discovery
900 E. 57th St.
Room 7220 (Bench LB-38)
Chicago, IL 60637
Ph : 1-773-795-0995

Blood will then be stored in the laboratory of Dr. Patnaik in liquid nitrogen and used for immune analyses.

11.2 Special Studies

11.2.1 Immunological Monitoring

We will evaluate changes in T-cell inflamed gene signature and STING pathway activation by RNA-seq, immune infiltration by IHC and flow cytometry obtained from tumor biopsies, and T-cell diversity/ctDNA analysis with peripheral blood collection. To collect samples for evaluation of peripheral immune responses, blood will be collected by a peripheral blood draw (up to 30-40 mL) pre-treatment, following the four week lead in period, and at time of progression. Heparinized whole blood will be interrogated for immune alterations as defined in the assays below. Remaining heparinized blood samples will be cryopreserved in liquid nitrogen using 90% fetal calf serum and 10% DMSO. Sera will be prepared from non-heparinized blood samples and stored in aliquots at -80^{o}C.

For collection of immune cells from bone biopsies, 10mL bone marrow aspirates will be collected using a 20mL syringe (containing 1mL sodium heparin, 1000 USP units/mL). 4mL of aspirate will be placed into four PAXgene Bone Marrow RNA tube, immediately inverted 5 times, and kept at room temperature for 2 hours before transfer to -20^{o}C freezer (and transferred to a -80^{o}C freezer the following day). Remaining 6mL of bone marrow aspirate will be transferred to a 15mL centrifuge tube, and centrifuged at 1200xg for 20min at 4^{o}C. Following centrifugation, supernatant (equivalent to sera) collected and aliquoted to cryovials for cryopreservation at -80^{o}C (being careful not to remove cloudy layer, which contains PBMC). Resuspend pellet in monolayer (approximately 1.5mL), and aliquot 400µl to immune analysis (described below). Aliquot remaining 1mL into two cryovials, and freeze in Mr. Frosty containers at -80^{o}C.

11.2.2 Assess changes in T-cell inflamed gene signature, STING pathway activation and macrophage subsets by Nanostring

RNA samples isolated from tumor biopsy samples will be used to isolate RNA for sequence analysis by Nanostring, as we have previously published[5]. The purpose of these studies is to determine whether PTEN-deficient patients lack a T-cell inflamed gene signature prior to treatment, and whether treatment with rucaparib, nivolumab, or both results in a T cell-inflamed gene signature and STING pathway activation within the tumor immune microenvironment. A cryopreserved PAXgene RNA tube will be used to isolate RNA using an RNeasy kit (QIAGEN, Venlo, Netherlands) according to the manufacturer's protocol. The expression profile of 770 genes included in the PanCancer Immune Profiling Panel (Nanostring Technologies) and 30 candidate genes potentially associated with immune resistance described in our previous study, will be determined for each sample using the Nanosting nCounter analysis system. Normalization of the raw Nanostring data will be conducted using the expression of 40 reference genes by nSolver Analysis Software v1.1 (Nanostring Technologies). We will utilize the quantification methods as previously published to calculate a Tumor Inflammation Signature (TIS) score and adopt their threshold in the definition of inflamed versus non-inflamed tumor [78, 79].

11.2.3 Assess changes in T cell and myeloid immune infiltrates within the tumor microenvironment by IHC

Tissue biopsies will be obtained from metastatic lesions (the same lesion per patient) prior to treatment and following four week lead-in period. The purpose of these studies is to determine the impact of tumor PTEN and HRD status on the immune profile at baseline, and how treatment with rucaparib, nivolumab, affects infiltration of T cells (or other immune populations) into the tumor microenvironment, and whether treatment alters the expression of activation or regulatory ligands on various immune populations (such as activation marker 4-1BB or regulatory molecules such as PD-1 on T cells) or tumor cells (e.g. MHC class I or PD-L1). Biopsy samples obtained pre-treatment and after the four week lead-in period will be stained with antibodies specific for CD3, CD4, CD8, FoxP3, 4-1BB, PD-1, HLA-A2, and potentially other markers. Staining and quantification will be reviewed by a pathologist blinded to the treatment groups to determine CD8+ T cells per field, CD4+FoxP3+ (Treg):CD8+ T cell ratio, PD-L1 expression, and whether these or the expression of CD8+ T cells expressing one regulatory receptors (or tumor cells expressing one or more regulatory ligands) change following the four week lead in treatment period.

11.2.4 Assess changes in immune populations within the tumor microenvironment and in peripheral blood by flow cytometry

The frequency of immune populations within the tumor microenvironment and in the peripheral blood will be assessed by flow cytometry. The purpose of these studies will be to conduct an unbiased evaluation of immune populations that are altered within the tumor microenvironment and the periphery, to determine whether treatment with rucaparib, nivolumab, or both agents combined result in an increase infiltration of inflammatory immune cells into the tumor (and whether this alterations in the tumor microenvironment are also detected in circulation). Specifically, bone marrow aspirates and peripheral whole blood will be stained in replicates in 96-well round bottom microtiter plates (Corning, Cambridge, MA). Cells will then be stained with cell surface markers to characterize the various immune populations (including, but not limited to, CD3, CD4, CD8, CD11b, CD11c, CD14, CD16, CD19, CD33, CD45, CD56, CD66b, CD209), various markers of immune activation or inhibition (such as 4-1BB, PD-1, or PD-L1), and intracellular markers such as Foxp3 to identify regulatory T cells. Samples prior to treatment and following the four-week lead in period will be analyzed to determine alterations in immune populations following treatments.

11.2.5 DNA damage (p-γH2AX) / HRD score

The prevalence of DNA damage in biopsy samples pre-treatment and following the four-week lead in period will be quantitated by p-γH2AX staining and HRD score (Myriad Genetics) in order to determine if rucaparib, nivolumab, or both in combination result in increased DNA damage. To calculate the HRD score, we will utilize the clinically validated myChoice® HRD test from Myriad Genetics, as has been reported[80]. For these studies, paraffin-embedded tumor slides will be provided to Myriad Genetics, which will extract DNA from these slides for next-generation sequencing and genomic analyis. Using this data, algorithms will be used to assess genomic instability using loss of heterozygosity, telomeric abnormalities, and large-scale state transitions.

Using the sum of these measurements, tumor biopsy samples will be classified as HRD-positive or HRD negative (and will further be characterized for loss of BRCA1/2, as well as PTEN status). Using the results from these assays, HRD positivity will be defined as any tumor biopsy that scores greater than 42 or has a deleterious mutation to BRCA1/2, and HRD negativity will be determined by any test that scores less than 42 and does not have BRCA1/2 deleterious mutations. Since HRD scores are a dynamic variable a range of cutoffs may be evaluated based on emerging data.

For evaluation of p-γH2AX expression on tumor biopsies, paraffin-embedded tumor tissue will be stained immunohistochemically for p-γH2AX as has been published[81]. Paraffin-embeded tissue will be stained for Ser139-phosphorylated γ-H2AX, and developed using DAB with a hematoxylin counterstain. Stained sections will be quantified by a blinded pathologist counting the number of p-γH2AX positive tumor cells.

Additional methods for assessing HRD scores and/or DNA damage will be considered.

11.2.6 Tumor-infiltrating T-cell diversity

Clonality of tumor-infiltrating T cells will be evaluating using TCF β-chain sequencing, as our collaborators have published[82]. The purpose of these studies will be to determine whether rucaparib, nivolumab, or both agents in combination result in an increase in the diversity of T cell clones infiltrating the tumor immune microenvironment. For these studies, a cryopreserved PAXgene RNA tube will be used to isolate total RNA using RNeasy mini kits (Qiagen). To convert to cDNA, samplmes will be amplified using 5' rapid amplification of cDNA end (RACE) method using Switching Mechanism at 5' end of RNA Transcript (SMART) kits (Clonentech, Mountain View, CA). The TCRα and TCRβ chains will be amplified separately using reverse primers specific to the constant region of each chain and forward primers for the SMART adapter. Amplicon size and quality will be assessed by the TapeStation system (Agilent Technologies, Santa Clara, CA). PCR products in the 300-950 bp range were selected using the Pippin Prep system (Sage Science, Beverly, MA). Samples will be barcoded using the Nextera XT Index PCR kit (Illumina, San Diego, CA) and pooled in groups of eight α and eight β per sequencing run. Sequencing was performed on the Illumina MiSeq platform, using 600v3 reagents (Illumina) using 300-bp paired-end reads. To identify V, (D), J and C segments in individual sequencing reads, each of the sequence reads in FASTQ files were mapped to the reference sequences provided by IMGT/GENE-DB using Bowtie2 aligner (Version 2.1.0). Raw FASTQ files were analyzed using Tcrip software.

11.3.7 PTEN Immunohistochemistry

Tumor biopsy sections prior to treatment will be evaluated for PTEN status [83] with immunohistochemistry using a CLIA/CAP-accredited assay. We will evaluate the impact of PTEN status on immune contexture within the tumor microenvironment. Slides will be microwaved for antigen retrieval in citrate buffer, and developed using diaminobezandine (DAB) with a hematoxylin counterstain. Slides will be interpreted by a blinded pathologist, who will also identify/characterize tumor tissue histology. This pathologist will manually circle tumor and exclude normal tissue, and sections will be analyzed for the frequency of positive cells per field.

12. MEASUREMENT OF EFFECT

Measurement of effect will be assessed by both the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

For prostate cancer patients, the Prostate Cancer Working Group criteria (PCWG3) will also be used to assess response.

12.1 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

12.1.1 Categorizing Lesions at Baseline

Measurable disease include the following:

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10mm or greater when assessed by CT or MRI (slice thickness 5-8mm).
- Superficial lesions with longest diameter 10mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15mm or greater when assessed by CT.

The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease includes the following:

- Lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9mm)
- Pleural or pericardial effusions
- Ascites
- Inflammatory breast disease,
- Leptomeningeal disease
- Lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers
- Abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques
- Bone disease (with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.)
- A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

<u>Normal sites</u>

Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above.If non-cystic lesions are also present, these are preferred as target lesions.

Normal nodes: Nodes with short axis <10mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

12.1.2 Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5mm should be recorded.

NOTE: When nodal lesions decrease to <10mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

12.1.3 Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent

objective statuses are indeterminate.

Target disease

- **Complete Response (CR):** Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10mm). All target lesions must be assessed.
- **Partial Response (PR):** Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- **Stable:** Does not qualify for CR, PR or Progression. All target lesions must be assessed.

Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- **Objective Progression (PD):** 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5mm.
- **Indeterminate:** Progression has not been documented, and:
- One or more target measurable lesions have not been assessed; or
- Assessment methods used were inconsistent with those used at baseline; or
- One or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure); or
- One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- **CR:** Disappearance of all non-target lesions and normalization of tumor marker levels.
  All lymph nodes must be 'normal' in size (<10mm short axis).
- **Non-CR/Non-PD:** Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- **PD:** Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- **Indeterminate**: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion. Supplemental Investigations If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be
investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Objective/Subjective

Progression Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status.
Every effort should be made to document objective progression even after discontinuation of treatment.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

□ See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Only for non-randomized trials with response as primary endpoint. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

If the protocol allows enrollment of patients with only non-target disease, the following table should be used:

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
□ 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

12.2 Outcome Measures for Prostate cancer patients based on PSA Decline

The following parameters will be recorded after the initial 12 weeks of therapy and at 12-week intervals thereafter.

- PSA decline and response will be measured according to PSAWG-2 (2008) criteria.
- PSA changes from baseline will be calculated for all patients and reported as a waterfall plot.
- Time to progression (TTP) based on revised PSA Working Group-2 criteria (2008 version).

- PSA progression free survival: PSA measurements will be taken at screening (baseline) and subsequently at time points as indicated in the schedule of visits. Any unscheduled PSA measurement will be utilized in the periodic assessment of PSA progression.
- The maximal decline in PSA for each patient will be recorded for each patient.
- The date of the maximal PSA decline (nadir date) will be recorded for each patient, as will the duration from the start of therapy to the nadir PSA.

12.2.1 Prostate-Specific Antigen Working Group Criteria [84]

***Progressive Disease after Androgen Deprivation Eligibility Criteria*:**
PSA evidence for progressive prostate cancer consists of a PSA level of at least 5 ng/ml which has risen on at least 2 successive occasions, at least 2 weeks apart. If the confirmatory PSA (#3 below) value is less (i.e., #3b) than the screening PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression.

Procedures for Assessing PSA Progression Post Study Treatment:
PSA measurements will be taken on a monthly basis. PSA increases and decreases will be tracked in order to assess disease response.
PSA partial response is defined by at least a 50% decline from screening (baseline) PSA value. The declined must be confirmed by a second PSA value obtained 4 or more weeks later.
PSA progressive disease may be defined in both patients who have not shown a decrease in their PSA and those who have. For patients who have not shown a decrease, progressive disease is defined as an increase of 25% over the screening (baseline) PSA value and an increase in the absolute-value PSA level by at least 5ng/mL. This increase should be confirmed by a second value.
For those patients whose PSA have decreased but has not reached response criteria, progressive disease is defined as 25% increase over the nadir PSA value provided that the increase is at least 5ng/mL and is confirmed.

Duration of PSA Response:
Duration of PSA Response is measured from the time when the PSA value first declines by at least 50% of the screening (baseline) and that was eventually confirmed by a second value. It is calculated until the time at which there is an increase of 50% of PSA nadir, provided the absolute increase is at least 5 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 50% above the nadir.
If the PSA never shows a 50% increase over the nadir value, then the patient will be censored at the last PSA measurement.

Time to Disease Progression:
For patients who have achieved a $\geq$ 50% decrease from the screening (baseline) PSA, assessment of time to disease progression is when the PSA has increased 50% above the nadir and at a minimum of 5ng/mL. For patients without a PSA decrease of this magnitude or without a decrease, the time for progression is calculated at the time a 25%

increase from screening (baseline) PSA has been achieved.

12.3 Duration of Response

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

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

12.4 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression (by either PSA or RECIST) or death, whichever occurs first.

13. DATA REPORTING

The University of Chicago Comprehensive Cancer Center maintains a secure, password protected, and regularly backed up commercial clinical trials database called eVelos. Data reporting will be performed utilizing the eVelos electronic data capture system. The University of Chicago study coordinator will provide study staff at participating sites with the applicable user registration information (e.g.: login credentials). All data for this trial will be stored in eVelos.

Patients on the trial will be registered into the Velos database centrally at the University of Chicago by the study coordinator. Data will be entered by the site Data Manager and stored within the database using the patient-study number as well as a unique identifier generated by study coordinator.

Data entry guidelines will be sent to all participating sites for reference when completing data entry. All required data must be recorded in the eVelos database at the completion of each cycle. AEs are to be entered in real time.

SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) or fax to the University of Chicago (PhaseIICRA@medicine.bsd.uchicago.edu or qaccto@bsd.uchicago.edu; Fax: 773-702-4889).

All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into eVelos within 48 hours of patient registration. In addition to direct data entry, site staff may be required to provide supporting source documentation.

Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments,

laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

Under the initial version of the protocol, each of the first 4 patients enrolled experienced an anemia DLT. As a result, the protocol was extensively amended to exclude patients at high risk for anemia, and to redefine the DLT as a grade ≥3 toxicity only in the first 4 weeks of treatment, since that period is also critical for the laboratory based endpoints. Data from these patients will be reported, but they will not be utilized to assess feasibility, and data from biopsies obtained, because of variability in drug exposure, will be utilized for descriptive purposes, but not for assessment of the primary phase II endpoint.

A total of 60 patients with prostate or endometrial cancer will be enrolled into the trial (20 per treatment arm) starting with enrollment under Amendment 1. To assess the primary phase 1b endpoint, i.e., feasibility (acceptable safety profile) of the combination therapy, the first 4-12 patients will be accrued to the Rucaparib+Nivolumab arm. Based on historical data, we assume a dose-limiting toxicity (DLT) rate for single-agent nivolumab of 15%, and a DLT rate for single-agent Rucaparib of 10%. We expect non-overlapping toxicity for the combination and therefore set the maximum tolerable toxicity rate for Rucaparib+Nivolumab at 25%. Thus, if there is early evidence that the true toxicity rate exceeds 25%, we will consider termination of the trial or a dose modification. Four patients will be enrolled and if DLT is observed in 3 or more patients the combination treatment will be declared infeasible and the trial will be terminated. Otherwise an additional 4 patients will be studied and if $\leq$2 of 8 have DLT the combination will be declared feasible and the trial will proceed to Phase II. If $\geq$ 4 of 8 have DLTs then the combination will be declared too toxic and the study terminated. If exactly 3 of 8 have DLT, then four more patients will be entered for a total of 12. At this stage if $\leq$3 of 12 have DLT the combination will be considered feasible and the study will proceed to phase II; otherwise if $\geq$ 4 of 12 have DLT, the combination will be declared too toxic and the study will be stopped or modified. Patients who are non-evaluable for toxicity will be replaced.

If the combination treatment in the Phase I-B portion has been deemed feasible, we will proceed with enrollment of subjects to the Phase II portion of the study. In this phase, n=20 patients will be randomized to Rucaparib alone, n=20 to Nivolumab alone, and up to 12 patients to Rucaparib plus Nivolumab, depending on the number of toxicities observed and the number of replacements required in phase I-B, as described in Section 3.3.2. The randomization sequence for phase II will be generated by the study statistician only after phase I-B has been completed using the method of permuted blocks, in order to accommodate the imbalance in the numbers to be assigned to the three treatment arms. No patients will be replaced in phase II, so that the maximum sample size for the entire trial will be N=60 patients, starting with enrollment under Amendment 1.

For the phase II primary objective, assuming Rucaparib+Nivolumab is determined to be feasible, we will assess changes in T cell immune infiltrates within the tumor microenvironment by nanostring. Additional secondary objectives include determination of response rates and progression free survival to combination therapy, assessment of changes in T cell immune infiltrates by IHC and correlation of T-cell infiltrate changes with tumor PTEN status. Details regarding the analysis of these endpoints are provided in section 14.4 below. Analysis of response rates and progression-free survival is described in section 14.5.

14.2 Sample Size/Accrual Rate

A total of 64 patients on the whole study, 20 patients on each arm as discussed above plus the initial 4 patients accrued prior to Amendment 1. We plan to accrue approximately four patients monthly.

14.3 Stratification Factors

None.

14.4 Phase II Primary Endpoint: Assess changes in T-cell inflamed gene signature by Nanostring.

The frequencies of patients for each study arm (and all arms combined) with T cell inflamed versus patients without a T cell inflamed gene signature, as defined in Section 11.2.2, will be summarized in tabular format. Comparisons between the treatment arms will be performed using a chisquare test. The sample size of n=20 per group will provide 80% power to detect true differences in the percentage of patients with an inflamed signature of between 33% and 43%, depending on the underlying proportion.

14.5 Phase II Secondary Endpoint: Response rate and time to disease progression for prostate cancer and endometrial cancer patients

Time to disease progression (obtained via imaging and PSA/CA-125 levels), as well as progression-free survival, will be estimated by the Kaplan-Meier method, controlled for by disease site. Response rates will also be summarized by disease site, along with 90% confidence intervals. It is recognized that the limited sample size for this phase Ib/II study will not provide sufficient power to detect statistically significant improvements in response and progression-free survival rates from historically reported rates.

As criteria for what would be considered encouraging results, if the observed response rate was >30% and/or the observed progression-free survival rate at 12 months was > 50%, we believe this would indicate a sufficient level of activity to warrant further study for prostate cancer patients (based on approximate single agent response rates of 10% and 20% to nivolumab and rucaparib, respectively. Additionally, if the observed response rate was >20% and/or the observed progression-free survival rate at 6 months was > 40%, we believe this would indicate a sufficient level of activity to warrant further study for endometrial cancer patients (assuming that the

majority of patients would have microsatellite stable (MSS) disease. The activity of rucaparib is unknown and activity of checkpoint inhibitors in small studies for non-microsatellite-instable (MSI) non- POLE- mutated endometrial cancer is generally < 10%)

14.6 Phase II Secondary Endpoints: Assess changes in immune populations in the tumor microenvironment by IHC.

Changes in T cell and myeloid immune infiltrates based on IHC (number of cells/high powered field) from baseline to four weeks post treatment within each study arm will be evaluated using nonparametric, Wilcxon signed-rank tests. We will then compare T cell immune infiltrates at four weeks based on IHC between the combination and single-agent treatment arms using nonparametric, Wilcoxon rank-sum tests. Assuming a standard deviation of 0.75 (range/4), and a 30% biopsy sample loss rate, n=20 subjects (14 with paired biopsies available) per group (pooled over the two disease sites and across the two phases of the trial) will provide 80% power to detect a true difference in means of 0.82 (two-sided α=0.05). The associations between PTEN, HRD status and T-cell IHC will be analyzed by Wilcoxon rank-sum test.

14.7 Phase II Exploratory Endpoints:

Assess changes in immune populations in peripheral blood by flow cytometry.
The frequency of circulating immune cells in the periphery pre-treatment and following the four week lead in period will be summarized in terms of means, standard deviations, and ranges for each study arm (and for all arms combined), as will the frequency of different checkpoint biomarkers. . Paired t-tests will be used to compare the frequency of peripheral immune cells pre-treatment compared to four weeks post treatment Associations between PTEN, HRD status and changes in immune populations will be analyzed by Wilcoxon rank-sum tests.

PTEN and HRD status
The impact of PTEN and HRD status on T cell inflamed gene signature and STING pathway activation will also be analyzed by chisquare tests. A Cox proportional hazards regression model will be used to examine the association between the generation of a T cell-inflamed gene signature and the time to progression.

DNA damage (p-γH2AX) / HRD score
The frequency of p-γH2AX positive tumor cells, as well as the frequency of patients with a positive HRD score, as defined in Section 11.2.5, pre-treatment and after the four week treatment period will be summarized in tabular format for each treatment arm. Paired t-tests will be used to determine patients who have a significant increase in p-γH2AX or HRD positivity following the four week treatment period, and Fisher's exact test will be used to compare the degree of target inhibition between arms.

Tumor-infiltrating T-cell diversity
Sequencing results to the human TCR loci will be analyzed as our collaborators have published[85]. Briefly, human TCR loci will be mapped using the Bowtie2 aligned and the V-(D)-J regions of CDR3s will be decomposed. Simpson's DI will be used to quanify TCRα/β

clonality.

15. STUDY MANAGEMENT AND REGULATORY AFFAIRS

15.1 Multicenter Guidelines

The specific responsibilities of the Principal Investigator and the Coordinating Center are presented in Appendix B. Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements

The Study Lead PI/Coordinating Center is responsible for distributing all official protocols, amendments, and IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

15.2 Institutional Review Board (IRB) Approval and Consent

Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

15.3 Food and Drug Administration (FDA) Approval

This study will be conducted under an investigator-held IND at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

15.4 Required Documentation

Prior to the selection of a study site that is not a full member of the Personalized Cancer Care Consortium, the audit and trial oversight processes for the site must be reviewed and approved by the UC CCC Clinical Research Advisory Committee (CRAC).

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer. Documents should be sent by email to: PCCC_Regulatory@bsd.uchicago.edu.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial disclosure form(s) for the principal investigator and any sub-investigators who will be involved in the study
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

15.5 Data and Safety Monitoring

This study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported within 7 days. Please contact the University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) regarding questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures.

15.6 Auditing

In addition to the clinical monitoring procedures, the University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and Safety Monitoring plan. For institutions who are formal members of the Personalized Cancer Care Consortium (PCCC), the UC CCC will conduct on site quality assurance audits on average every two years during the enrollment and treatment phase of the study.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

15.7 Amendments to the Protocol

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the

University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.

- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.

- **The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.

- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

15.8 Annual IRB Renewals, Continuing Review and Final Reports

The University of Chicago IRB and the participating institutions' IRBs will complete a continuing review of the protocol at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

15.9 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at

least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

15.10 Obligations of Study Site Investigators

The Study Site Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B MULTICENTER GUIDELINES

Responsibility of the Study Lead PI

- The Study Lead PI will be the single liaison with regulatory and data management staff, outside sponsor/s, FDA, and funding agencies The Study Lead PI is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Study Lead PI. There will be only one version of the protocol, and each participating institution will use that document. The Study Lead PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Study Lead PI is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Study Lead PI.
- The Study Lead PI is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Study Lead PI will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

1. The Coordinating Center is responsible for maintaining copies of IRB approvals from each participating site.
2. The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
3. The Coordinating Center is responsible for the preparation of all submitted data for review by the Study Lead PI.
4. The Coordinating Center will maintain documentation of AE reports. The Coordinating Center will submit AE reports to the Study Lead PI for timely review.

APPENDIX C: PATIENT MEDICATION DIARY

Patient Name/ Initials_____ Study ID#: _____
Cycle Number:_____ Date of Clinic Visit :_____

Instructions for the Patient: You will take Rucaparib twice a day. You will take ____ pills in the morning, and you will take _____ pills in the evening. You will take Rucaparib every day for the next 28 days. Every time you take a dose of Rucaparib, write down the date, the time, and the number of pills of Rucaparib you took. If you have any comments or any side effects, write them down in the Comments section. Keep your Rucaparib pills in the bottle that they came in. Please bring this diary and your bottle of Rucaparib with you when you come back to see your study doctor. Even if the bottle is empty, please bring it back with you.

		Morning Dose		Evening Dose		Comments
Day	Date	Time	Number of Pills	Time	Number of Pills	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Patient Signature and Date:_____

Research staff only: Date tablets returned:_____ Number of tablets returned:_____
Signature of Research Staff and Date: _____