

CLINICAL STUDY PROTOCOL

Study Title: A Phase II trial of bevacizumab and rucaparib in recurrent carcinoma of the cervix or endometrium

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1 INTRODUCTION AND RATIONALE

1.1 Study Hypothesis

Deficiency in DNA repair process and sustained angiogenesis are critical for tumorigenesis and cancer progression [1]. Both poly (ADP-ribose) polymerase (PARP) inhibitors (sensing DNA damage) and vascular endothelial growth factor (VEGF) inhibitors (anti-angiogenesis) are currently under clinical evaluation in cancer treatment. Rucaparib, a PARP inhibitor, has been shown significant anti-cancer activity in BRCA mutant patients and BRCA wild-type patients with other defects in the homologous recombination repair pathway [2, 3]. The adverse events have been easily managed. Means to improve this clinical benefit for cancer patients are worthy of pursuit. Studies in pre-clinical setting suggested a potential synergistic effect of PARP inhibitors when combined with angiogenesis inhibitors [4-6]. We hypothesize that combination of rucaparib and bevacizumab will produce synergistic anti-cancer effect in patients with the carcinoma of the cervix or endometrium.

1.2 Rationale for Recurrent Cervical Cancer

Treatment options for women with recurrent cervical cancer remain limited, and cisplatin chemotherapy remains the backbone in nearly all treatment regimens offered to women with recurrent disease. A phase 3 randomized trial by the Gynecologic Oncology Group (GOG) evaluating cisplatin with paclitaxel demonstrated some improvement in the risk for progression (32% reduction, $p=0.003$), but only modest non-statistically significant improvement in survival (GOG 169) [7]. In another attempt to improve upon single agent cisplatin's therapeutic efficacy, cisplatin was combined with topotecan (GOG179). That resulted in a statistically significant 37% reduction in the risk of progression, and a significant 29% reduction in the risk of death.

Despite these statistically significant improvements, the median survival for the cisplatin/topotecan combination was only 9.4 months (vs. 6.5 months for cisplatin/paclitaxel) [8]. With the advent of anti-VEGF therapy and with bevacizumab (Bev) showing efficacy as a single agent in recurrent cervical cancer, bevacizumab was tested in combination with the cisplatin/paclitaxel (CP) doublet and the topotecan/paclitaxel (TP) doublet in GOG240 [9]. Results for this prospective, randomized, phase 3 study demonstrated a statistically significant survival benefit in the cisplatin/paclitaxel/bevacizumab treated women. Patients receiving CP/Bev showed a median survival of 17 months, which was significantly better than the 13.3 months for women receiving CP alone. This significant benefit was also seen in PFS. The CP and TP treatment regimens were compared to each other and TP was determined to not be superior to CP. Toxicity associated with the addition of Bev to the chemotherapy doublet regimens was in-line with, and not higher than, previously published gastrointestinal toxicities. In light of these findings, CP-Bev appears to be the favored treatment for advanced and/or recurrent cervical cancer and received FDA approval for such in 2014. However, with an OS of only 17 months and with the median age of affected women in their 40s, much room remains to improve survival rates for women with recurrent cervical cancer.

Although not a BRCA mutation mediated tumor, there is rationale for use of a PARP inhibitor in

cervical cancer. Expression of PARP has been demonstrated to be higher in cancer cells as compared to normal cells, and an overexpression of PARP correlates with drug resistance to chemotherapy [10]. Cervix cancer cells have shown two-fold elevated levels of PARP-1 expression as compared to normal cells. Preclinical work in cervical cancer using the PARP inhibitor veliparib plus topotecan has demonstrated enhanced cancer cell death after exposure to the combination that was attributed to collapsed topotecan poisoned replication forks, formation of topotecan related single strand DNA nicks, and conversion of these nicks into double strand breaks [11]. This data was taken into a Phase I/II trial of topotecan + veliparib in women with recurrent adenocarcinoma or squamous cell carcinoma of the cervix [12]. Among 27 patients enrolled, two patients achieved partial responses (7.4%, 90% confidence interval 1–22%) after veliparib/topotecan treatment. One patient with squamous cell cancer had a partial response after four treatment cycles and then received three more cycles of therapy prior to disease progression and disease-attributed death. This patient had a response duration of four months. Another patient with adenosquamous cell cancer had 11 cycles of veliparib/topotecan therapy with a censored tumor response duration of 6.7 months. In addition, ten (37%) patients had stable disease. Three of these patients had a duration of stable disease of more than six months. Twelve (44%) patients had a best response of progression of disease. Two patients had an indeterminate response status. The median PFS was two months (90% confidence interval: 1–3 months), and median OS was eight months (90% confidence interval: 6–10 months) [12].

The topotecan + veliparib study had a correlative science component that evaluated primary tumors (pre-treatment archival) for PARP-1 nuclear staining intensity. Among 16 archived untreated primary cervical cancer samples, 12 (75%) had high (2–3+) PARP-1 nuclear staining intensity. By primary cervical cancer histology, four (67%) of six adenocarcinomas, one (50%) of two adenosquamous cancers, and seven (88%) of eight squamous cell cancers had high (2–3+) PARP-1 nuclear staining intensity. Of the nine persistent/recurrent ($n = 5$) or metastatic ($n = 4$) cervical cancers representing disease treated by protocol veliparib/topotecan therapy, eight (89%) had high (2–3+) PARP-1 nuclear staining intensity. The median PARP-1 histological score (i.e., product of staining intensity and percent positive cells) was 168 (range: 0–299) in the 16 primary cervical cancers. Among those 16 primary cervical cancers, a low PARP-1 histological score correlated with a likelihood of veliparib/topotecan treatment response (Spearman correlation coefficient: -0.63 , $P = 0.011$). A patient with a low PARP-1 histological score dichotomized by its median was more likely to have longer PFS (HR: 0.25, $P = 0.023$) and OS after protocol veliparib/topotecan therapy (HR: 0.12, $P = 0.005$) compared to a patient with a higher histological score. Too few persistent/recurrent or metastatic samples were obtained for PARP-1 correlative analyses [12].

In a second study, Thaker et al. added veliparib to cisplatin and paclitaxel for treatment of chemotherapy naïve patients with advanced or recurrent cervix cancer [13]. In this phase I study, the objective response rate among 29 patients with measurable disease was an encouraging 34%, with an additional 41% with stable disease. Median progression free survival was 6.2 months (95% CI, 2.9-10.1), and overall survival was 14.5 months (95% CI, 8.2-19.4). The results were more

striking by the fact that patients had to have a history of chemo-radiation for their primary disease and then to have progressed (i.e., not primary Stage IVB disease). While the Kunos study was not as encouraging, there is a strong possibility this was due to sub-therapeutic doses of veliparib as compared to the Thaker study [13].

These two papers suggest a role for PARP inhibition in cervical cancer even though baseline homologous recombination deficiency is not as common as compared to ovarian cancer. Data would suggest that induction of hypoxia caused by radiation or therapeutic agents (such as bevacizumab) may impact DNA repair by various mechanisms that may be therapeutically exploited. These mechanisms include exploiting the “chronic” hypoxia induced by bevacizumab, which leads to translational downregulation of DNA repair and may lead to susceptibility in these hypoxic cells to DNA damaging agents or synthetically lethal agents such as a PARP inhibitor like rucaparib [14].

This current study aims to test the hypothesis of whether cervix cancer treated with the combination of bevacizumab and rucaparib demonstrates inhibition of DNA repair via pre- and post-treatment biopsies.

1.3 Rationale for Endometrial Cancer

Endometrial cancer is the 4th most common cancer in women, affecting 60,050 women in the United States in 2016 and resulting in 10,470 deaths [15]. Although the vast majority of patients will have early stage disease, treatment options for advanced or recurrent endometrial cancer are limited. Numerous cytotoxic agents have been evaluated, but only a few drugs have been identified to have definitive cytotoxic activity: doxorubicin, cisplatin/or carboplatin and paclitaxel, which have been recommended for first line chemotherapy [16-19].

A recently published phase III trial evaluating ixabepilone as the experimental treatment arm versus standard therapy with adriamycin or every three weeks’ treatment with paclitaxel in recurrent or advanced (with one prior regimen) endometrial cancer demonstrated only 15% complete or partial response in the control arm. Median progression free survival (PFS) was 3.4 vs 4 months ($p=0.80$), and median overall survival (OS) was superior in the control arm (11 vs 12 months [$p=0.0397$]), calling for discontinuation of the study due to futility [20]. Clearly, better treatments are needed. The grim outcomes with cytotoxic therapies have prompted the Gynecologic Oncology Group (GOG) to evaluate biologic agents, including anti-angiogenic agents like bevacizumab [21, 22]. Single agent bevacizumab, a monoclonal antibody directed against VEGF-1, has been studied by the GOG in study 229E, which revealed a response rate (RR) of 13.5%, and 6-month progression-free rate of 40%. The overall median PFS was 4.2 months, and the median OS was 10.5 months [21].

Bevacizumab remains one of the most promising agents for endometrial cancer in the recurrent setting. The aforementioned data led to two studies that incorporated bevacizumab into primary treatment of endometrial cancer. GOG protocol 86P randomized chemotherapy naïve women with advanced or recurrent disease and no curative options in a 1:1:1 fashion to TC + bevacizumab x 6 and bevacizumab maintenance until progression, TC + temsirolimus x 6 and temsirolimus

maintenance until progression or ixabepilone/carboplatin + bevacizumab and bevacizumab maintenance until progression. PFS was the endpoint for this trial. As compared to the historical control of TC, none of the arms had improved PFS, but the TC + bevacizumab arm did have a significantly improved OS, which warrants further exploration [23]. Similarly, the MITO-END-2 trial randomized patients to either TC or TC + bevacizumab x 6-8 cycles and bevacizumab maintenance until progression. Here, the addition of bevacizumab significantly improved the PFS over TC alone (HR 0.57 (0.34, 0.96; p=0.036) [24]. This study further confirmed the activity of bevacizumab in endometrial cancer and justifies exploration of best practices for when to use bevacizumab and with which other agents to combine it.

Although not a traditionally *BRCA* mutation-mediated tumor, there is rationale for use of a PARP inhibitor in endometrial cancer. Expression of PARP has been demonstrated to be higher in cancer cells as compared to normal cells, and overexpression of PARP correlates with drug resistance to chemotherapy [10]. Although the role of phosphatase and tensin homologue (*PTEN*) gene in controlling the signaling pathway of phosphoinositide 3 kinase (*PI3K*) is well established, a new functional role of *PTEN* in maintaining genomic stability has been elucidated [25]. It was observed that embryonic mouse cells who are deficient in *PTEN* exhibit genomic instability from defects in RAD51-mediated DNA double stranded break repair (DSBR) or defects in cell cycle checkpoints [26, 27]. Given that the exquisite sensitivity of *BRCA* mutated cells to PARP inhibitors is likely due to defects in RAD51-mediated DSBR by homologous recombination [28, 29], it is plausible that *PTEN* deficiency may also lead to HR defects and thus sensitivity to PARP inhibition. Mendes-Pereira et al demonstrated *in vitro* and *in vivo* (mice modeling) that *PTEN* induced HR deficiency can be exploited with use of olaparib.[30]. Therein, the authors first confirmed that *PTEN* mutant human cells had lower levels of RAD51 (as previously shown in mice), then translated that this deficient expression indeed significantly impaired DSBR by homologous recombination. *PTEN* deficient cells were 20-fold more sensitive to PARP inhibitor exposure (olaparib) than their wild type counterparts; they were also more sensitive to cisplatin (but only 5-fold), but no difference was seen with paclitaxel, which does not target HR deficiency, thereby serving as a negative control. Similar results have been reported by other authors studying patients with endometrioid adenocarcinoma of the endometrium [31, 32].

Given that up to 80% of endometrioid endometrial cancers lack *PTEN* expression, there is good rationale for evaluation of targeted therapies. Previously, *PTEN* mutations have been exploited with use of mammalian target of rapamycin (mTOR) inhibitors or *PI3K* inhibitors. However, *PTEN* now seems to be an attractive target for PARP inhibitors. The aforementioned data demonstrates the utility of PARP inhibitors in non-*BRCA* mediated HR deficiency. Additionally, inhibition of angiogenesis is a promising avenue of targeted therapy in endometrial cancer. For advanced or recurrent endometrial cancer patients, for whom there are few, if any effective therapies beyond first line chemotherapy, the combination of bevacizumab and rucaparib represents an exciting opportunity to explore a novel approach with sound rationale.

1.4 Summary of Investigational Product

Rucaparib is a small molecule inhibitor of PARP-1, PARP-2, and PARP-3 that has demonstrated

clinical activity in a number of tumor types, especially those associated with a deleterious mutation in *BRCA1/2* or other *HRR* gene, and/or high level of genomic loss of heterozygosity (LOH). Rucaparib is approved in the United States (US) for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer who have been treated with two or more prior chemotherapies, and for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy [33-35].

Prior Experience with Rucaparib

An overview of data from nonclinical and clinical studies of rucaparib are provided below and described in detail in the rucaparib Investigator's Brochure (IB). A summary of the benefit-to-risk ratio is also provided in the rucaparib IB.

1.4.1 Non-clinical Experience with Rucaparib

1.4.1.1 Pharmacology of Rucaparib

The results from nonclinical studies are consistent with the anticipated mechanism of action and pharmacological effects of PARP inhibition. Pharmacological assessment demonstrated that rucaparib is a potent and selective inhibitor of PARP-1, PARP-2, and PARP-3 and has robust and durable *in vitro* and *in vivo* activity in multiple cell lines and patient-derived xenograft models with mutations in BRCA1, BRCA2, PALB2, RAD51C, and RAD51D. Rucaparib was also active in a BRCA wild-type model, consistent with *in vitro* data suggesting that rucaparib is active in cells with other defects in HRR through synthetic lethality. *In vitro* screens suggested that rucaparib has a limited potential for off-target effects. Safety pharmacology studies suggest that when given orally, rucaparib poses a low risk for causing neurobehavioral and cardiac effects in patients.

1.4.1.2 Pharmacokinetics, Metabolism, and Drug-Drug Interaction Potential of Rucaparib

In pharmacokinetic (PK) studies, rucaparib demonstrated species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. *In vitro* data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and dogs after oral dosing.

In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1) and may inhibit P-gp and BCRP in the gut.

1.4.1.3 Animal Toxicology of Rucaparib

Oral dosing of rucaparib in single- and repeat-dose toxicity studies in rats and dogs resulted in

toxicity to the hematopoietic, lymphopoietic, and gastrointestinal systems. These toxicities were generally both reversible upon recovery and predictive of toxicities observed in patients. Rucaparib was shown to be clastogenic in an *in vitro* chromosomal aberration assay suggesting potential genotoxicity in humans.

Reproductive and development toxicity studies in rat showed that rucaparib caused maternal toxicity and was embryotoxic. Although no rucaparib related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility [36-39].

Complete information on the pre-clinical studies can be found in the Rucaparib Investigator's Brochure (IB).

1.4.2 Clinical Experience with Rucaparib

Rucaparib, both as monotherapy and in combination with nivolumab, is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer with and without evidence of HRD. Rucaparib clinical studies have evaluated/are evaluating patients with relapsed, high-grade ovarian cancer (OC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) in both the treatment and maintenance settings.

Rucaparib is also being evaluated as treatment for patients with metastatic castration-resistant prostate cancer (mCRPC), both as monotherapy and in combination with nivolumab.

Clinical pharmacology studies are ongoing in patients with advanced solid tumors to more fully characterize rucaparib drug-drug interactions (DDI), mass balance and drug metabolism, as well as PK and safety in patients with moderate hepatic impairment.

Additional studies of rucaparib as monotherapy and in combination with other anticancer therapies are planned in ovarian and prostate cancer, as well as other tumor types.

The rucaparib clinical studies and results are described in more detail in the rucaparib IB.

1.4.2.1 Clinical Pharmacology, Pharmacokinetics, and Metabolism of Rucaparib

Assessment of rucaparib PK in cancer patients showed an approximate dose-proportional exposure after once daily (QD) or BID dosing, rapid absorption with maximum plasma concentration (C_{max}) achieved within 1.5 to 6 hours, and distribution into tissue. The oral bioavailability was 36% and terminal half-life ($T_{1/2}$) ranged from 11 to 29.8 hours.

Rucaparib was moderately bound to human plasma proteins *in vitro* 97(70%). The steady-state was achieved following one week of dosing with rucaparib BID, with approximately 4-fold accumulation. A high-fat meal increased the C_{max} and area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24h}) of rucaparib by 20% and 38%, respectively, as compared with these parameters under fasted conditions. The effect of food on rucaparib PK is not considered to be clinically significant, thus rucaparib can be taken with or without food.

Drug interactions with rucaparib as a substrate were assessed in a population PK analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultra-rapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyperinducers) did not

significantly impact the steady-state exposure of rucaparib at 600 mg BID. Current smokers had overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play a limited role in rucaparib metabolism, and no rucaparib dose adjustment is needed when concomitantly administered with CYP inhibitors.

Concomitant treatment with proton pump inhibitors (PPIs) showed no clinically significant effect on rucaparib PK. No dose modification of rucaparib is required for patients who are receiving concomitant treatment with a PPI. Results from Study CO-338-044 evaluating potential drug-drug interactions (DDI) with rucaparib, indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on Pgp. Caution should be exercised in the concomitant use of drugs that are substrates of the above CYP enzymes.

1.4.2.2 Overview of Efficacy

Rucaparib has demonstrated clinical benefit in the treatment and maintenance settings in ovarian cancer patients [34, 35]. Based on these results, rucaparib was approved in the US for the treatment of patients with a deleterious BRCA mutation (germline and/or somatic) associated epithelial ovarian cancer (EOC), FTC, or PPC who have been treated with two or more chemotherapies, and for the maintenance treatment of adult patients with EOC, FTC or PPC (regardless of BRCA status) who are in a complete or partial response to platinum-based chemotherapy [33].

In addition to BRCA1 and BRCA2, ovarian cancer patients with a deleterious RAD51C or RAD51D mutation also derived clinical benefit from rucaparib in the treatment (Study CO-338-017; ARIEL2) and maintenance (Study CO-338-014; ARIEL3) settings [3, 40].

While rucaparib has demonstrated significant clinical benefit in ovarian cancer in the treatment and maintenance settings, rucaparib clinical activity is not limited to ovarian cancer. Rucaparib recently received a Food and Drug Administration (FDA) Breakthrough Therapy Designation (BTD) based on preliminary clinical activity in 25 patients with mCRPC harboring a deleterious BRCA mutation and measurable disease at baseline enrolled in Study CO-338-052 (TRITON2) [41]. Clinical benefit from rucaparib treatment has also been observed in mCRPC patients with a deleterious PALB2 mutation [41].

Rucaparib clinical data further supports the hypothesis that patients with BRCA-mutated solid tumors from indications beyond ovarian and prostate cancers may likely benefit from rucaparib treatment. In a Phase 1 dose-escalation study (CO-338-010) of rucaparib in patients with an advanced solid tumor, four breast cancer patients and one pancreatic cancer patient, all harboring a deleterious BRCA mutation, achieved a Response Evaluation Criteria in Solid Tumors (RECIST)-confirmed partial response (PR) [42]. In RUCAPANC (CO-338-023), a Phase 2 study assessing the efficacy of rucaparib in BRCA-mutated pancreatic cancer, clinical benefit was observed (objective response rate [ORR] of 33.3% and disease control rate [DCR] of 44.4%) in the subgroup of patients who had received only one prior chemotherapy regimen for locally advanced/metastatic disease [43]. Similarly, clinical benefit (ORR of 36.8% and median progression-free survival [PFS] of 9.1 months) was also observed with maintenance treatment of

rucaparib in patients with platinum-sensitive BRCA mutated pancreatic cancer [44].

1.4.2.3 Overview of Safety

Results of a recent integrated safety analysis in over 1,000 patients with ovarian or prostate cancer who received 600 mg BID rucaparib in the treatment or maintenance setting showed that the most common treatment-emergent adverse events (TEAEs) reported were primarily mild to moderate (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1-2) in severity and included gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, anemia/decreased hemoglobin, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased, decreased appetite, and dysgeusia. The most common TEAE \geq Grade 3 include anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue. Section 6.6 of the rucaparib Investigator's Brochure (IB) serves as guidance to the investigator on adverse drug reactions (ADRs) for rucaparib, based on incidence of TEAEs by all CTCAE grades and by CTCAE \geq Grade 3.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin (and associated increase in mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]), increased ALT, increased AST, and increased serum creatinine, most commonly occurring. Decreased platelets, neutrophils, leukocytes, lymphocytes and increased cholesterol were observed to a lesser extent. The transient elevations in ALT/AST with rucaparib treatment were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity and generally resolved over time. Furthermore, no cases met Hy's law criteria for drug-induced liver injury (DILI) [45, 46], and few patients discontinued rucaparib due to ALT/AST elevations [34, 35]. Similarly, elevations in creatinine were self-limiting and generally stabilized over time. The majority of creatinine elevations were Grade 1 or Grade 2. Elevated serum creatinine levels resolved upon interruption or discontinuation of rucaparib were not accompanied by changes in blood urea nitrogen (BUN) and did not lead to discontinuation of rucaparib treatment. Increased creatinine with rucaparib treatment is likely due to the potent inhibition by rucaparib of MATE1 and MATE2-K renal transporters.

An updated analysis of safety presented in the United States (US) prescribing information (USPI) [33] and the EU Summary of Product Characteristics (SmPC) [47] demonstrate that safety results in ovarian cancer patients treated with rucaparib have remained consistent with those previously reported, and that the safety profile across both the treatment and maintenance indications is consistent.

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

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESIs), as these events have been observed in patients exposed to cytotoxic chemotherapy (e.g., platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies

diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation [48, 49]. Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib. Clovis has added these potential risks to all Informed Consent Forms (ICFs) / Patient Information Sheets (PISs). AESI's (both serious and non-serious) will be reported to Clovis within 24 hours of awareness and will continue to be reported to Clovis under SAE reporting requirements.

More information on AESIs for rucaparib is provided in the rucaparib IB.

1.4.2.4 Completed Studies

A4991002 was a Phase 1 open-label, dose-escalation study of IV rucaparib in combination with temozolimide (TMZ) in 32 patients with advanced solid tumors or malignant melanoma. A4991005 was a Phase 2, open-label study of IV rucaparib in combination with TMZ in 46 patients with metastatic melanoma. The results from these studies are available in manuscript form [50, 51]. Clinical data indicate that rucaparib exposures were similar between extensive metabolizers and poor metabolizers of CYP2D6.

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

In addition, a phase II study ([NCT00664781](#)) was carried out in patients with advanced breast and/or ovarian cancer with proven BRCA-1/2 mutation [2]. The investigators reported that Rucaparib was well tolerated in patients up to doses of 480 mg per day; because dose levels at 480 mg twice a day or 600 mg twice a day resulted in DLTs (CTCAE grade 3 fatigue) and drug discontinuation because of persistent fatigue in two patients. The treatment with intermittent dosing of intravenous rucaparib resulted in an objective response rate (ORR) of only 2% but with 41% (18 out of 44) patients achieved stable disease for ≥ 12 weeks and 3 patients maintaining disease stabilization for > 52 weeks. The ORR for oral rucaparib (across all six dose levels) was 15%. In the oral cohorts, 81% (22 out of 27) of the patients had ovarian cancer and 12 out of 13, who were dosed continuously, achieved RECIST complete response/partial response (CR/PR) or stable disease (SD) ≥ 12 weeks, with a median duration of response of 179 days (range 84-567 days) [2].

1.4.2.5 Preliminary Data from On-going Clinical Studies

Study CO-338-010 ([NCT01482715](#))

Study CO-338-010 is a 3-part, open-label, Phase 1/2 study of oral rucaparib monotherapy administered daily in continuous 21-day cycles. Part 1 (Phase 1) evaluated PK and safety of escalating doses of rucaparib in patients with solid tumors dose (N = 56; enrollment complete) and identified 600 mg BID as the recommended starting for Phase 2 based on safety, PK, and the clinical activity profile [42]. Part 2 (Phase 2) is evaluating the efficacy and safety of rucaparib in

patients with relapsed, high-grade ovarian cancer associated with a *BRCA* mutation. Part 2A enrolled platinum-sensitive patients (i.e., disease progression occurred at least 6 months after last dose of platinum was administered) with a *gBRCA1/2* mutation who had received two to four prior treatment regimens (N = 42, enrollment complete). Part 2B is enrolling patients with a *gBRCA1/2* or *sBRCA1/2* mutation who received at least three prior chemotherapy regimens (N = 40 planned). Part 3 enrolled patients with relapsed solid tumor and a *BRCA* mutation to characterize the PK, food-effect, and safety of a higher dose strength tablet (enrollment completed).

Dose levels of 40 to 500 mg QD and 240 to 840 mg BID rucaparib were evaluated in the 56 patients enrolled in Part 1. A dose-limiting toxicity (DLT) of National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0 (v4.03) [52] Grade 3 nausea was observed in 1 of the 6 patients at 360 mg BID rucaparib in Cycle 1. No DLTs were observed at any other dose level in Cycle 1. However, similar to other PARP inhibitors, non-DLT myelosuppression was observed beyond Cycle 1.

Dose proportional PK were observed up to 600 mg BID. The mean T_{max} and mean $T_{1/2}$ were approximately four hours and 17 hours, respectively. Oral administration of 600 mg rucaparib with a high-fat meal resulted in a moderate increase of C_{max} and AUC of rucaparib compared with that under fasted conditions. The increases in rucaparib exposures were not considered clinically significant, thus rucaparib can be taken with or without food. In pooled plasma samples from three patients who received 600 mg rucaparib BID, rucaparib, an oxidation and deamination product (M324), and a subsequent N-methylated metabolite (M338) were tentatively identified as major circulating moieties. M324 was a major metabolite in rats and dogs, but M338 was not observed in animals. This is to be further evaluated in a [^{14}C] rucaparib study in patients.

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

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

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

period of continuous dosing. All treatment-related AEs were successfully managed with concomitant medication and treatment interruption and/or dose reduction, or supportive care (in the case of myelosuppression AEs).

Extensive centrally reviewed electrocardiogram (ECG) monitoring was conducted in the Phase 1 portion of Study CO-338-010 and results are available for 55 of 56 treated patients. No patient had a QTcF measurement ≥ 500 msec and only one patient had a QTcF measurement ≥ 480 msec. This measurement occurred in a patient receiving 480 mg BID rucaparib and concomitant administration of citalopram, a medication with known potential to cause QT prolongation. This patient continued to receive rucaparib monotherapy at a dose of 480 mg BID with no further QTcF measurement ≥ 480 msec. Only one patient had a QTc increase from baseline > 60 msec. This patient had a history of QT prolongation prior to study entry and received one dose of rucaparib before discontinuing from the study due to eligibility violation. Overall, rucaparib in doses up to 840 mg BID exhibited a mean change of QTcF from baseline of 11.3 msec at the maximum concentration (5565 ng/mL) observed in the study. At a dose of 600 mg BID, the mean values for change of QTcF in Cycle 1 ranged from 5.0 to 14.0 msec. Overall, the alteration of the mechanism of repolarization was minimal. There were no AEs suggestive of cardiac arrhythmia (e.g., presyncope, syncope, sudden death) in any patient.

Study CO-338-017 (ARIEL2) ([NCT01891344](#))

ARIEL2 is a 2-part, single-arm, open-label Phase 2 study in patients with relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer. The primary purpose of this study is to define a tumor-based molecular signature of HRD in ovarian cancer that correlates with response to rucaparib and enables selection of appropriate ovarian cancer patients for treatment with rucaparib [3]. Tumor HRD status is assessed using next generation sequencing, with an algorithm for HRD status based on the presence of a *BRCA1/2* mutation (germline or somatic) and/or degree of tumor genome-wide loss of heterozygosity (genomic LOH), a phenotypic consequence of HRD. Patients are prospectively classified into one of three subgroups: tumor BRCA mutant (tBRCA^{mut}), tumor BRCA wild-type with high genomic LOH (*BRCA*^{wt}/LOH^{high}; also referred to as BRCA-like), and tumor BRCA^{wt} with low genomic LOH (*BRCA*^{wt}/LOH^{low}; also referred to as biomarker negative). Part 1 enrolled ovarian cancer patients with relapsed, platinum-sensitive disease who had received ≥ 1 prior platinum-based regimen (N = 204; enrollment complete). Enrollment of patients known to harbor a *gBRCA1/2* mutation was capped in order to maximize the ability to assess rucaparib activity in the *BRCA*^{wt} patient population. A total of 17 patients known to harbor a germline *BRCA1/2* mutation were enrolled. Another 23 patients were identified as having a *BRCA1/2* mutation (three germline, 20 somatic) based on analysis of their tumor.

Efficacy data indicate a RECIST ORR in *BRCA1/2*^{mut} tumor-evaluable patients of 80.0% (32/40 patients), median DOR of 11.2 months (95% CI: 7.4, 13.7), and median PFS of 12.8 months (95% CI: 9.0, 14.7). The objective response rate was similar in patients with a germline (85.0%; 17/20) or somatic *BRCA1/2* mutations (75.0%; 14/19). Clinical activity was also observed in patients with a BRCA-like molecular signature as assessed by genome-wide loss of heterozygosity (genomic

LOH). A RECIST ORR of 29.0% (24/82 patients), median DOR of 11.0 months (95% CI: 7.6, 20.6), and median PFS of 5.7 months (95% CI: 5.3, 7.6) was observed in patients with a BRCA-like tumor (*BRCA*^{wt} with high genomic LOH) versus a RECIST ORR of 10.0% (7/70 patients), median DOR of 5.8 months (95% CI: 4.6, 8.5), and median PFS of 5.2 months (95% CI: 3.6, 5.5) in patients with a *BRCA*^{wt}/low genomic LOH tumor [3].

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

An exploratory objective in ARIEL2 was to assess rucaparib efficacy in tumors with an alteration in a HR gene other than *BRCA1/2*. The overall frequency of non-*BRCA1/2* HR gene mutations was low (11%, 22/204 tumor samples) and the presence of a mutation did not always correlate with LOH, with the exception of tumors with a *RAD51C* or *RAD51D* mutation, which consistently exhibited high genomic LOH. RECIST and/or cancer antigen-125 (CA-125) responses were observed in patients with a *RAD51C* (75%, 3/4), *ATM* (50%, 1/2), *ATR* (100%, 1/1), *BRIP1* (50%, 1/2), *NBN* (100%, 2/2), and *RAD51D* (50%, 1/2) mutation. (Clovis, data on file) ARIEL2 Part 2 is currently enrolling advanced ovarian cancer patients (N=300 planned) who have received at least three prior chemotherapy regimens (N = 300 planned) in order to refine the BRCA-like molecular signature (i.e., genomic LOH) and assess its predictive utility in a more heavily pre-treated patient population.

Similar to the safety profile in Study CO-338-010 Part 2A, the most frequent (reported in ≥ 15% of patients) treatment-related AEs (all grades) included gastrointestinal-related toxicities (nausea, constipation, vomiting, and diarrhea), asthenia/fatigue, elevations in ALT/AST, anemia/decreased hemoglobin, dysgeusia, and decreased appetite. The most common grade 3 or worse treatment-emergent adverse events were anaemia or decreased haemoglobin (22%), and elevations in ALT or AST (12%) [3].

Study CO-338-014 (ARIEL3) ([NCT01968213](#))

ARIEL3 is a double-blind, placebo-controlled, Phase 3 study of rucaparib as switch maintenance treatment in patients with relapsed, platinum-sensitive, high-grade ovarian, fallopian tube or primary peritoneal cancer who achieve a response to platinum-based chemotherapy (N = 540 planned; enrollment completed). The primary endpoint is PFS in HRD within subgroups as determined by next generation sequencing analysis of archival tumor tissue using an optimized algorithm from Study CO-338-017 (ARIEL2).

Study CO-338-023 (RUCAPANC) ([NCT02042378](#))

Study CO-338-023 (RUCAPANC) is a single-arm, open-label Phase 2 study of rucaparib treatment in patients with previously treated locally advanced or metastatic pancreatic ductal

adenocarcinoma and a known deleterious *BRCA* mutation. The primary endpoint is efficacy as measured by objective response rate (ORR). Of the 19 patients evaluable for response, two achieved a confirmed PR and one achieved a confirmed CR. These patients all received only one prior line of therapy. The overall safety profile was similar to that observed in ovarian cancer patients.

1.5 Summary of Bevacizumab Clinical Experience

1.5.1 Bevacizumab for Cancer Treatment

Bevacizumab is a monoclonal antibody that exerts anti-cancer effects by inhibiting VEGF and slowing the growth of new blood vessels. Bevacizumab has been studied in Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In a large phase III study (NCT00109070), the efficacy and safety of bevacizumab added to the standard first-line chemotherapy were evaluated in patients with metastatic colorectal cancer. The addition of bevacizumab to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival and progression-free survival [53].

Bevacizumab was then approved by the FDA on 26 February 2004 for first-line treatment in combination with IV 5-FU-based chemotherapy for subjects with metastatic colorectal cancer. Based on anti-cancer advantage demonstrated in many clinical studies, the FDA has approved bevacizumab in combination with chemotherapy for various types of metastatic or advanced cancer, including colorectal cancer, lung cancer, breast cancer, brain cancer, kidney cancer, cervical cancer, and recently, ovarian cancer.

Pharmacokinetic data with 5 mg/kg every two weeks shows comparability with 7.5 mg every three weeks and 10 mg/kg every 2 weeks is comparable to 15 mg/kg every three weeks.

1.5.2 Safety Profile for Bevacizumab

Bevacizumab-associated adverse events identified in clinical trials include hypertension, wound healing complications and increased risk of bleeding [54, 55]. Gastrointestinal perforation and thromboembolic events have been reported although the incidence is rare [56, 57]. These and other safety signals are described in further detail as follows. Additional information is provided in the bevacizumab Investigator's Brochure.

Hypertension: Hypertension is one of the most frequently described adverse effects of bevacizumab based therapy and oral medications have been used to manage the hypertension when indicated. The frequency of all grades of hypertension associated with bevacizumab is 20–30%. Hypertension is often asymptomatic. However, patients can develop seizures and impaired vision. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) [54]. The management should include control of hypertension, management of specific symptoms, and discontinuation of bevacizumab.

Wound healing complications: Wound healing complications have been reported in patients receiving bevacizumab. However in an analysis of pooled data from two trials in metastatic colorectal cancer, with cancer surgery 28-60 days before study treatment, wound healing

complications occurred in 3/230 (1.3%) bevacizumab-treated patients and 1/194 (0.5%) control patients [58]. Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half-life of bevacizumab is 20 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

Hemorrhage: Overall, grade 3–4 bleeding events with bevacizumab occur at a rate of 1.2%– 4.6% in a pooled database from six clinical trials in multiple tumor types [54]. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage. The tumor-associated hemorrhage tends to occur in patients with lung and GI cancers; but may also occur in patients with central nervous system metastases. Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20-40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than five minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Thromboembolic Events: Bevacizumab is a VEGF inhibitor and can increase the risk for both venous and arterial thromboembolic events (VTE or ATE). A meta-analysis of 1,745 patients with various tumor types demonstrated a two-fold higher ATE incidence in patients receiving bevacizumab and chemotherapy than in those receiving chemotherapy alone (3.8% versus 1.7%; $p=0.031$) [54]. In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of VTE that was not statistically significant in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). Furthermore, subjects with certain baseline characteristics (age ≥ 65 years and/or a history of a prior arterial TE event) may be at higher risk of experiencing such an event. See the bevacizumab Investigator Brochure for additional information on risk factors. Aspirin may be used as a prophylaxis of ATE in patients at high risk of such events; and the use of aspirin ≤ 325 mg daily was allowed in the several randomized studies.

Gastrointestinal perforation Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab and chemotherapy [56]. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab.

1.6 Study Rationale

Both rucaparib and bevacizumab have shown anti-cancer effects for patients with advanced or metastatic cancer [2, 3, 9, 21]. Both drugs have been approved by the FDA for treatment of patients with ovarian cancer. A phase II trial has demonstrated that treatment with bevacizumab as a single agent at 15 mg/kg intravenously every 21 days was well tolerated and active in patients with recurrent cervical cancer; approximately 24% patients survived progression free for at least six

months, and 11% of patients had a partial response [59]. Another phase II trial of bevacizumab as single agent treatment in recurrent or persistent endometrial cancer revealed a response rate (RR) of 13.5%, and 40% progression-free at six months [21]. Further, clinical studies have demonstrated that the use of bevacizumab in combination with other chemotherapies is safe and effective with a significant improvement in overall survival of patients with advanced cervical cancer or endometrial cancer [21, 60]. As discussed in sections 1.2 and 1.3, although not a traditionally BRCA mutation-mediated tumor, there is rationale for use of a PARP inhibitor in cervical cancer and endometrial cancer. More important, studies in a pre-clinical setting suggested a potential synergistic effect of PARP inhibitors when combined with angiogenesis inhibitors [4-6]. To better define the potential benefit of adding bevacizumab to rucaparib in patients with recurrent cervical or endometrial cancer, we plan to perform a prospective phase II trial. We anticipate that combination of rucaparib and bevacizumab will produce a synergistic anti-cancer effect in patients with the carcinoma of the cervix or endometrium who have progressed disease after the first line chemotherapy.

1.6.1 Rationale for Multi-center Study

In order to have a faster enrollment and data readout, up to four study sites are planned to participate in this study.

1.7 Rationale for Correlative Studies

We will assess microsatellite instability in the biopsies of patients with recurrent endometrial cancer. Additionally, biopsies will be assessed for DNA damage via a proprietary assay (PADDA) as well as RAD51C assay [61]. Furthermore, we will assess circulating tumor DNA and other biomarkers in blood samples.

DNA damage is constantly generated in living cells. Additional insults to the DNA result from exposure to genotoxic substances. DNA damage is the main initiator of cancer and plays a key role in the pathogenesis of aging and neurodegenerative diseases [62-64]. Available data indicate that variations in DNA damage and DNA repair capacity influence patients' risk to develop cancer and patient's response to chemo- and radio-therapy [65]. However, no predictive markers of cancer risk or response to treatment have yet been established.

There are no assays with sufficient sensitivity to quantify or map endogenous DNA damage. Currently, the most reliable strategies to detect induced DNA damage are PCR-based assays [66-69]. However, existing assays have two major limitations: they require high doses of damaging agent to generate detectable levels of lesions [70], and they are not practically feasible for population screening. Therefore, due to technical limitations, the precise levels of DNA damage, and how those levels impact cell fate and human health, are largely unknown.

Recently, we developed a novel and highly sensitive primer-anchored DNA damage detection assay (PADDA). In contrast with available assays, PADDA is able to map and quantify endogenous and induced DNA damage [71, 72]. PADDA reliably discriminates *in vivo* levels of persistent endogenous DNA damage in yeast and mice [71, 72] and demonstrated a strong correlation between persistent nucleotide damage and the later establishment of mutations

precisely in those nucleotides [71]. PADDA does not require hazardous reagents, sophisticated equipment or specialized skills [72] and can be used on a real-time PCR system to ease population screenings. Additionally, we validated PADDA for the study of human samples, established a tissue bank of head and neck squamous cell carcinoma patients and teamed with physicians to move this novel assay to clinical application.

Furthermore, RAD51 plays an important role in DNA double-strand break repair. Cytoplasmic expression (RAD51C(+)) was associated with poor prognosis and aggressive behavior in various cancer [73, 74]. RAD51 foci has been shown to predict tumor response to cancer therapy in diverse contexts [75, 76]. The higher expression of RAD51 gene could mediate cancer stem cells resistance to PARP inhibitors in both BRCA1-mutant and BRCA1-wild-type Triple-Negative breast cancer [75]. In this study, we plan to study RAD51 nuclear foci by immunostaining as described in a published paper [75].

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To estimate the proportion of patients with persistent or recurrent cervical or endometrial cancer, who survive progression-free for at least six months, treated with combination bevacizumab and rucaparib.

2.2 Secondary Objectives

- To estimate the proportion of patients with persistent or recurrent cervical or endometrial cancer, who have objective tumor response (complete or partial), treated with combination bevacizumab and rucaparib.
- To determine the nature and degree of toxicity of combination rucaparib and bevacizumab in this cohort of patients.
- To estimate the progression-free survival (PFS) of patients with persistent or recurrent cervical or endometrial cancer treated with combination rucaparib and bevacizumab
- To estimate the overall survival (OS) of patients with persistent or recurrent cervical or endometrial cancer treated with combination rucaparib and bevacizumab

2.3 Translational Objectives

- To obtain the fresh tumor biopsies after consent and prior to study treatment in eligible patients to determine MSI, HRD status, and degree of DNA damage via a novel DNA damage assay (PADDA) as well as RAD51C assay
- To determine whether these marker expression levels alone or in combination are associated with response, PFS, and/or overall survival.

3 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Inclusion Criteria

1. Patients with histologically-documented carcinoma of the cervix or endometrium;

2. Patients with measurable and/or evaluable lesions as defined by RECIST 1.1
3. Women at least 18 years of age
4. Patient with persistent or recurrent squamous cell or adenocarcinoma of the cervix, or any carcinoma or carcinosarcoma of the endometrium who has undergone at least one prior line of systemic therapy. Prior bevacizumab is allowed. (**Note:** previous cisplatin during radiation therapy should NOT count as a prior line of systemic therapy)
5. ECOG performance status of 0, 1, or 2;
6. Patient should agree to have tumor biopsy and baseline blood draw for correlative studies. If unable to be safely biopsied and patient desires enrollment, may be enrolled per principal investigator discretion.
7. Adequate organ function should be confirmed by the following laboratory values obtained ≤ 14 days prior to first dose of rucaparib. Suggested criteria for adequate organ function include:
 - a. Bone Marrow Function
 - i. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - ii. Platelets $> 100 \times 10^9/L$
 - iii. Hemoglobin ≥ 9 g/dL independent of transfusion ≤ 14 days prior to screening hemoglobin assessment
 - b. Hepatic Function
 - i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ upper limit of normal (ULN); if liver metastases, then $\leq 5 \times$ ULN
 - ii. Bilirubin $\leq 1.5 \times$ ULN; $< 2 \times$ ULN if hyperbilirubinemia is due to Gilbert's syndrome; and
 - iii. Serum albumin ≥ 30 g/L (3.0 g/dL)
 - c. Renal Function
 - i. Serum creatinine $\leq 1.5 \times$ ULN; or
 - ii. Measured or calculated creatinine clearance (CrCL) ≥ 30 ml/min. For calculated CrCL, the Cockcroft Gault formula or institutional standard formula can be used.
8. Patients must have a life expectancy of at least three months (to be able to complete one cycle of study treatment)
9. Patients should have no major existing co-morbidities or medical conditions that will preclude therapy in the view of the principal investigator
10. Prior bevacizumab is allowed if off drug ≥ 28 days prior to study enrollment
11. Ability to understand and the willingness to sign a written informed consent document.
12. Women of childbearing potential must not be considering getting pregnant and must avoid pregnancy during the study and for at least six months after the last dose of rucaparib or longer if requested by local authorities. See Section 3.3 for more information.

3.2 Exclusion Criteria

1. Have active second malignancy, i.e., patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment; However patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed >6 months prior and/or bone marrow transplant (BMT) >2 years prior to first dose of rucaparib;
2. Prior treatment with any PARP inhibitor.
3. Untreated or symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
4. Received treatment with chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C); or radiation, biologic/targeted agents, experimental drugs within 3 weeks prior to first dose of rucaparib; and/or ongoing adverse effects from such treatment > NCI CTCAE V4.0 Grade 1 (Grade 2 non-hematologic toxicity to most recent treatment may be permitted with prior advanced approval from Sponsor).
5. Hospitalization for bowel obstruction within 3 months prior to enrollment.
6. Patients must have no history of gross hemoptysis (defined as bright red blood of a ½ teaspoon or more) or coagulopathy. Patients with history of major tumor-related bleeding that is not controlled despite locoregional treatment or at high risk of recurrent tumor-related bleeding will be excluded.
7. Patients with history of hypertension must be well-controlled ($\leq 150/100$) on a stable regimen of anti-hypertensive therapy.
8. Patients with tumors that invaded major vessels (e.g. the carotid) as shown unequivocally by imaging studies will be excluded due to the possibility of increased risk for tumor bleeding with bevacizumab therapy.
9. Patients should not have a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study enrollment, or anticipation of need for major surgical procedure during the course of the study. No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to registration. No serious non-healing wound, ulcer, or bone fracture.
10. Patients should not have unstable angina or myocardial infarction within the previous 6 months; no uncontrolled hypertension; no symptomatic congestive heart failure; no serious cardiac arrhythmia requiring medication; no clinically significant peripheral vascular disease; no history of any CNS cerebrovascular ischemia or stroke within the last 6 months; no active serious infection.
11. Patients should not have other coexisting medical condition that would preclude full compliance with the study.

12. Patients may not be receiving any other investigational agents.
13. Patients should not have a history of prior severe infusion reaction to a monoclonal antibody. Patients with known hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies.
14. Pregnant women are excluded from this study because rucaparib and bevacizumab have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with rucaparib and bevacizumab, breastfeeding should be discontinued if the mother is treated with rucaparib and bevacizumab. Should a woman become pregnant or suspect she is pregnant while in this study, she should inform her treating physician immediately. See 3.3 for more information.
15. HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible drug interactions with rucaparib and bevacizumab.

3.3 Patients with Reproductive Potential

Pregnancy is an exclusion criterion. Women of childbearing potential must not be considering getting pregnant and must avoid pregnancy during the study and for at least 6 months after the last dose of rucaparib or longer if requested by local authorities.

Female patients of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to administration of the first dose of rucaparib. In addition, a serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Treatment Phase and at the time of treatment discontinuation. Treatment should be discontinued immediately in any woman found to have a positive pregnancy test while taking rucaparib.

Female patients are considered to be of childbearing potential unless 1 of the following applies:

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

Female patients of reproductive potential must practice highly effective methods (failure rate $< 1\%$ per year) of contraception with their partners, if of reproductive potential, during treatment and for 6 months following the last dose of rucaparib or longer if requested by local authorities.

Highly effective contraception includes:

- Ongoing use of progesterone only injectable or implantable contraceptives;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Bilateral tubal occlusion;

- Sexual abstinence as defined as complete or true abstinence, acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable; or
- Male sterilization, with appropriate post-vasectomy documentation of absence of sperm in ejaculate.

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

4 SUBJECT REGISTRATION AND ENROLLMENT

4.1 Required Protocol Specific Regulatory Documents

This protocol, the Informed Consent document, any information to be given to the patient, and relevant supporting information must be submitted to the IRB by the Principal Investigator and reviewed and approved by the IRB before the study is initiated.

The Sponsor must pre-approve the informed consent document prior to submission to the IRB. All regulatory documents must be available to the Sponsor prior to site activation. Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office (CTO) at SCC-IIT-Office@ouhsc.edu:

- A copy of the IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator
- Form FDA 1572 appropriately completed and signed with appropriate documentation.
- CAP and CLIA Laboratory certification and institution lab normal values
- Delegation of Authority Log
- Executed clinical trial agreement (e.g., contract)

4.2 Patients Registration and Enrollment

Patients must have signed and dated all applicable consents and authorization forms to be registered in Velos eResearch database system, which is sponsored by The University of Oklahoma Stephenson Cancer Center (OU-SCC).

First, the study site should send the required documentation to SCC-IIT-Office@ouhsc.edu to begin the registration process. A Screening identification (Screening ID) number will be provided by OU-SCC research staff. After all screening procedures and assessments have been completed and eligibility has been established, the subject Study ID number will be generated by OU-SCC. Once the patient has been provided a Study ID number, only the Study ID number should be used. Both patient ID numbers should be documented in Velos.

Patients must not start protocol treatment prior to registration. Patients will start protocol treatment only after pre-treatment evaluation is complete and eligibility criteria have been met.

NOTE: Per the Institutional Review Board (IRB) reporting, a patient is considered accrued once he or she signs a consent form for the study. A patient is considered enrolled once the patient begins treatment. Evaluable patients are defined in protocol Section 8.3.

5 STUDY MODALITIES

5.1 Bevacizumab

Bevacizumab is currently commercially available for cancer therapy, including treatment for cervix cancer. Please refer to the package insert for bevacizumab, see https://www.gene.com/download/pdf/avastin_prescribing.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf for the most complete and current information on the following:

5.1.1 Formulation

Bevacizumab (brand name: Avastin) is a recombinant humanized anti-VEGF monoclonal antibody composed of human IgG1 framework regions and antigen-binding complementarity-determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1).

Generic Name	Bevacizumab
Code Number	rhuMAb VEGF, RO4876646
Trade Name	Avastin®
Chemical Structure	human IgG1 framework regions and antigen-binding complementarity-determining regions from a murine monoclonal antibody
Molecular Weight	~149 000 daltons
Description	Clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion

Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and excipient/ chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is > 95%.

Bevacizumab may be supplied in 6-cc (100-mg) and 20-cc (400-mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI). Vials contain no preservative and are suitable for single use only.

5.1.2 Storage

Bevacizumab vials should be stored in a refrigerator at 2°C-8°C. Keep vial in the outer carton due to light sensitivity. DO NOT FREEZE. DO NOT SHAKE.

5.1.3 Preparation

Bevacizumab does not contain any antimicrobial preservative; therefore, care must be taken to

ensure the sterility of the prepared solution. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Bevacizumab should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/ml. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

5.1.4 Adverse Effects

Consult the package insert for the most current and complete information.

5.1.5 Suppliers

Commercially available from: Genentech, Inc. South San Francisco, CA 94080-4990, USA. Consult the prescription information and/or package insert for additional information.

5.2 Rucaparib

5.2.1 Formulation and Supplier

Rucaparib camsylate (also known as CO-338; formerly known as PF-01367338-BW and AG-014447) is an oral formulation. Rucaparib tablets for oral administration will be supplied to the study sites by Clovis. A brief description of the investigational product is provided below.

Drug Name:	Rucaparib
INN:	Rucaparib
Formulation (strengths expressed as free base):	Tablet; film coated; 200 mg (blue, round, debossed with C2), 250 mg (white, rounded diamond shape, debossed with C25), 300 mg (yellow, oval, debossed with C3)
How Supplied:	200, 250, and 300 mg (as free base) strength tablets in HDPE equivalent with child-resistant caps. Patients may receive one or more strengths.
Storage Conditions:	15 to 30°C (59-86°F)

5.2.2 Rucaparib Ordering, Dispensing, Stability and Destruction

Order instructions: The institutional pharmacy is responsible for managing the inventory of rucaparib. Sites will be required to register users in WebEZ system to place orders for study provided rucaparib.

Dispensing: All tablets are provided in high-density polyethylene (HDPE) bottles (or equivalent)

with child-resistant caps and should be stored in the provided containers between 15° to 30° C (59° to 86° F). Patients may 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 of treatment, including a small overage until the next rucaparib dispensation visit. Bottles containing rucaparib tablets will be labeled according to national regulations for investigational products.

Sites are to dispense enough rucaparib to patients to last until their next scheduled visit.

Stability: Unopened bottles of rucaparib tablets are stable to the date indicated on the package and can be stored at room temperature with no special storage requirements.

Destruction: prior to dispensing the next bottles of study medications, old study supplied medications are to be collected and logged on to the Drug Accountability Record. It is expected that returned, unused by assigned patient, damaged, expired or otherwise out of specification study drug will be destroyed by the site, using internal site procedures for the safe disposal of cytotoxic materials.

5.2.3 Adverse Effects:

Safety information from completed studies assessing oral rucaparib is summarized in rucaparib Investigator's Brochure and detailed safety data are included in the clinical study reports. Based on rucaparib's mechanism of action and data from completed studies, the following rucaparib associated toxicities could be expected:

- Nausea
- Asthenia / Fatigue
- Anemia / decreased hemoglobin
- ALT/AST elevations
- Vomiting
- Decreased appetite
- Constipation
- Dysgeusia
- Thrombocytopenia
- Diarrhea
- Blood creatinine increased
- Abdominal pain
- Dyspnea
- neutropenia/decreased ANC
- Increased cholesterol
- Decreased lymphocytes
- Photosensitivity has been observed in patients treated with rucaparib. Patients should avoid spending time in direct sunlight because they burn more easily during treatments with rucaparib. When outdoors, patients should use typical precautions such as applying

sunscreen (sun protection factor 50 or greater) and/or covering exposed skin with clothing and wearing a hat and sunglasses.

6 TREATMENT PLAN

An original, informed consent form, indicating prior approval by the institution's Human Rights or Clinical Trials Committee for participation in this study, must be forwarded to the SCC CTO Office.

6.1 Treatment Schedule for Bevacizumab plus Rucaparib

- Rucaparib 600mg, PO, BID on days 1 to 21. Cycle = 21 days
- Bevacizumab 15mg/kg, IV, on day 1 of every 21-day cycle. The total dose must be calculated using the most recent subject actual weight (obtained within 3 days of the dosing visit, and prior to the infusion). The dose will not be recalculated unless the patient has $\pm 10\%$ weight change.

Patients will receive bevacizumab and rucaparib until unacceptable toxicity or tumor progression.

6.2 Method of Bevacizumab and Rucaparib Administration

6.2.1 Rucaparib Administration

Each patient will receive oral rucaparib daily at 600 mg BID with 8 oz (240 mL) of room temperature water, taken on an empty stomach or with food. Tablets should be swallowed whole, without crushing or chewing. Patients should take rucaparib doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (i.e., does not take it within 4 hours of the scheduled time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up. Patients will be instructed to record daily doses taken or not taken in a patient diary. Treatment with rucaparib is continuous and each cycle will comprise 21 days.

6.2.2 Bevacizumab Administration

Each patient will receive bevacizumab 15 mg/kg IV per institutional standard.

Bevacizumab infusions should not be given bolus or IV push. Pre-medications may be given prior to bevacizumab according to institutional standards.

6.3 Dose Modifications

Toxicity and grades will be classified using the NCI Common Terminology Criteria for Adverse Events (CTCAE V4.0). A copy of the CTCAE V4.0 can be downloaded from the CTEP website (<http://ctep.cancer.gov>).

6.3.1 Rucaparib Dose Modification and Toxicity Management

Patients may develop study drug-related toxicities that may require dose reduction, dose delay, skipping doses or dose discontinuation. Treatment modifications will be made based on specified safety criteria. The following criteria will be used to determine dosing delay, restarting doses, dose reduction or discontinuing rucaparib.

If rucaparib is held, bevacizumab should also be held to maintain concurrent administration.

6.3.1.1 Criteria for Rucaparib Dose Modification

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. Anemia should be managed as described below.
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines).
- Grade 3 or 4 ALT/AST elevations should be managed as described below.
- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.
- For patients who meet treatment interruption guidelines above, treatment with rucaparib should be held until the toxicity improves to \leq CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, treatment should be interrupted, then resumed at a reduced dose following resolution of the event to \leq CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted; however, the investigator should consult with the sponsor's medical monitor before reducing to 300 mg BID. If a patient continues to experience toxicity despite dose reduction steps to 300 mg BID, or if dosing with rucaparib is interrupted for > 21 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed and documented between the investigator and the sponsor.

Dose reduction steps are presented in Table 1.

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

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

cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

Management of Rucaparib Treatment-Emergent ALT/AST Elevations:

- Grade 4 ALT/AST elevations
 - Hold rucaparib until values have returned to Grade 2 or better, then resume rucaparib with a dose reduction.
 - Monitor liver function tests weekly for 3 weeks after rucaparib has been restarted
- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:
 - Monitor liver function tests weekly until resolution to \leq Grade 2.
 - Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is $<$ ULN, alkaline phosphatase is $<$ 3 x ULN, and there are no other signs of liver dysfunction.
 - If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to \leq Grade 2 will be required before rucaparib can be resumed, either at the current dose or at a reduced dose.

Drug-induced liver injury (DILI) is described in the US FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation [45] and should be referenced when managing treatment-emergent ALT/AST elevations.

Rucaparib treatment must be interrupted if biochemical criteria for suspected DILI are met, according to presence of the following laboratory abnormalities:

ALT or AST $>$ 3 x ULN

and

Bilirubin $>$ 2 x ULN

While treatment is interrupted, the patient should be evaluated for the presence of confounding factors including malignant disease in the liver, co-administration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, rucaparib must be permanently discontinued.

All cases of possible DILI should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin.

Table 1 Rucaparib Dose Reduction Steps

Starting Dose	600 mg BID
Dose Level -1	500 mg BID

Dose Level -2	400 mg BID
Dose Level -3*	300 mg BID
*Consult with the sponsor before reducing to Dose Level – 3. Further dose reduction may be possible but requires consultation with the sponsor’s medical monitor.	

6.3.1.2 Criteria for Rucaparib Re-treatment

Treatment may resume if:

- ANC $\geq 1.0 \times 10^9/L$
- Platelet count $\geq 100 \times 10^9/L$
- Non-hematologic toxicities have returned to baseline or \leq CTCAE V4.0 Grade 1 severity (or, at the investigator’s discretion, \leq CTCAE V4.0 Grade 2 severity if not considered a safety risk for the patient). Grade 3 or Grade 4 ALT/AST elevations should be managed as described above.

6.3.2 *Bevacizumab Dose Modification and Toxicity Management*

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

If bevacizumab is to be discontinued due to adverse effects determined related to bevacizumab, rucaparib may be continued if at the discretion of the treating physician, it can be safely done so knowing the possible side effect profile of rucaparib. This may be done if the side effects of bevacizumab have resolved to \leq grade 1 and all other treatment parameters have been met. Once bevacizumab is held, it cannot start until the next cycle of rucaparib starts.

If bevacizumab is interrupted for ANY reasons for >4 weeks (unless otherwise specified), the patient should discontinue bevacizumab therapy on protocol.

Based on the safety profile of bevacizumab, the management for potential toxicity is summarized as below.

Infusion Reaction:

Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE V4.0 Grade 3 or 4 allergic

reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Thromboembolic Event:

- Arterial thromboembolic event \geq Grade 2: Bevacizumab should be discontinued
- Venous thromboembolic event \geq grade 4: Bevacizumab should be discontinued
- Venous thromboembolic event \leq grade 3:
 1. Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is $<$ 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over.
 2. If the planned duration of full-dose anticoagulation is $>$ 2 weeks, bevacizumab may be resumed during full-dose anticoagulation if all of the criteria below are met:
 - The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions)
 - The subject must not have had hemorrhagic events while on study
 - The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab.
 3. If thromboembolism worsen/recur upon resumption of study therapy, discontinue bevacizumab

Hypertension:

Subjects with baseline hypertension should be treated with anti-hypertensive medication as needed. The goal of blood pressure (BP) control should be consistent with general medical practice.

- Grade 3 (SBP \geq 160 mmHg or DBP \geq 100 mmHg):
 - Start or adjust anti-hypertensive medication
 - Hold bevacizumab until BP $<$ 160/90mmHg
 - For hypertension that is refractory requiring delay of bevacizumab for $>$ 4 weeks, discontinue bevacizumab
- Grade 4 (Hypertensive crisis or malignant hypertension): Discontinue bevacizumab

Hemorrhage:

- Grade 2-4 intracranial or pulmonary bleeding: Discontinue bevacizumab
- Grade 3 other hemorrhage not from CNS or pulmonary:
 - Patients receiving full-dose anticoagulation should discontinue bevacizumab.
 - For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:
 - the bleeding has resolved and hemoglobin is stable

- there is no bleeding diathesis that would increase the risk of therapy
- there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.
- Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
- Grade 4 other hemorrhage not from CNS or pulmonary: Discontinue bevacizumab

Wound healing complications:

- Grade 2: Hold bevacizumab until healing
- Grade 3-4: Discontinue bevacizumab

Proteinuria

- Grade 1 (urine dipstick 1+ or urine collection 0.15 to 1.0 g/24 hr): No bevacizumab modifications
- Grade 2 (urine dipstick 2+ to 3+ or urine collection > 1.0 to 3.5 g/24 hr):
 - For 2+ dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose.
 - For 3+ dipstick, obtain 24-hour urine prior to administration of bevacizumab.
 - Withhold bevacizumab for proteinuria >2 g/24 hr and resume when proteinuria is
 - ≤ 2 g/24 hr.
- Grade 3 (urine dipstick 4 + or urine collection > 3.5 g/24 hr): Withhold bevacizumab.
- Resume when proteinuria is ≤ 2 g/24 hr.
- Grade 4 (nephrotic syndrome): Discontinue bevacizumab.

Perforation of GI or any other organ:

- Any grade: Discontinue bevacizumab

Other Unspecified AEs related to bevacizumab:

- Grade 3: Hold bevacizumab until symptoms resolve to <Grade 1
- Grade 4 : Discontinue bevacizumab; However upon consultation with the study chair, resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the Grade 4 toxicity is transient, has recovered to \leq Grade 1 and unlikely to recur with retreatment.

6.4 Precaution for Concomitant Medication during the Study

6.4.1 Non-study Anti-cancer Agent

Patients may not use any non-study anti-cancer agent (investigational or non- investigational) during the study.

6.4.2 Hematopoietic Growth Factors and Blood Products

Hematopoietic Growth Factors and Blood Products will be allowed as concomitant therapy. Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Transfusion thresholds for

blood product support will be in accordance with institutional guidelines.

6.4.3 Pre-caution for CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the *in vivo* CYP interaction study (CO-338-044), rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used in patients on rucaparib taking concomitant medicines that are substrates of CYP1A2, CYP2C9, and/or CYP3A. (see IB, Appendix B). Although *in vitro* rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 *in vivo* cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers.

Table 2 Examples of CYP Substrates with Narrow Therapeutic Range

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

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

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

6.4.4 Precaution for Anticoagulants

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

6.4.5 Other Concomitant Medications

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

Rucaparib marginally increased digoxin area under the plasma concentration-time curve (AUC) by 20%. Caution should be exercised for patients receiving rucaparib and requiring concomitant medication with digoxin. Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice. *In vitro*, rucaparib is a potent

inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of the BCRP with 50% inhibitory concentration (IC₅₀) value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (e.g., rosuvastatin).

6.5 Supportive Care

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

6.6 Duration of Therapy

Patients will be treated until disease progression or toxicity unless patient withdraws consent. If the patient is showing clinical benefit with disease progression, the patient may continue treatment after consulting with the Principal Investigator and Medical Monitor.

6.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, and for survival for up to 2 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

7 STUDY PARAMETERS

7.1 Therapeutic Parameters

1. Pre-study scans should be performed within 4 weeks prior to registration.
2. All patients must have a pre-dosing weight taken at every visit, as appropriate.
3. All required pretreatment laboratory studies should be done as outlined in the study calendars in Sections 7.2.
4. Initial H&P and laboratory tests can be used for C1D1 if done within 72 hours

7.2 Study Calendar¹

Parameter	Prior to Study within 28 days of enrollment	Prior to Study within 14 days of enrollment	Day 1 or Prior to each cycle (+/- 3 days)	Day 15 of Cycle 1	Every 2 cycles (+/- 7 days)	End of treatment (within 30 days post last dose)	Every 3 months for 2 years ^e
Informed consent	X						
Inclusion /exclusion	X		X				
Demographics	X						

Parameter	Prior to Study within 28 days of enrollment	Prior to Study within 14 days of enrollment	Day 1 or Prior to each cycle (+/- 3 days)	Day 15 of Cycle 1	Every 2 cycles (+/- 7 days)	End of treatment (within 30 days post last dose)	Every 3 months for 2 years ^e
History & Physical ^f	X		X			X	
ECOG PS ^k	X		X			X	
Vital signs/weight ⁱ	X		X			X	
CT CAP or MRI	X				X	X	
Hematology ^g		X	X	X		X	
Serum Chemistries ^a		X	X	X		X	
PT/PTT/INR		X	If clinically indicated				
Urinalysis ^h		X	X			X	
Toxicity assessment ^c			X			X	
Serum Pregnancy Test ^d	X		X			X	
ECG ^j	X					X	
Concomitant Medications	X		X			X	
Blood sample for correlative study		X					

Parameter	Prior to Study within 28 days of enrollment	Prior to Study within 14 days of enrollment	Day 1 or Prior to each cycle (+/- 3 days)	Day 15 of Cycle 1	Every 2 cycles (+/- 7 days)	End of treatment (within 30 days post last dose)	Every 3 months for 2 years^e
Tumor tissue	X ^b						
Rucaparib dispensed/collected			X			X	
Bevacizumab infusion			X				
Survival						X	X

- a. Total protein, albumin, creatinine or estimated glomerular filtration rate (GFR) using the Cockcroft-Gault formula or institutional standard formula, blood urea nitrogen (BUN) or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase (LDH), glucose, sodium, potassium, magnesium, chloride, CO₂, calcium, phosphorus, at screening, during treatment at each study visit and at the End of Treatment Visit for all patients. Fasting is not required before blood sampling. Serum chemistry results must be reviewed by the investigator before the start of treatment with rucaparib and ongoing at times testing occurs. Additional and more frequent tests may be performed at the investigator's discretion.
- b. Patients must agree for pre-treatment biopsy. If fresh pre-treatment biopsy cannot be safely obtained, archival tumor tissue is acceptable.
- c. Any SAEs, AESIs, and treatment related Grade 3/4 AEs must be followed until resolution or stabilization, or until lost to follow-up.
- d. For women of childbearing potential only. A serum pregnancy test must be performed ≤ 3 days prior to first dose of rucaparib (a negative result is required before dosing can begin) and at the End of Treatment Visit. A serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Treatment Phase. A positive serum pregnancy test during study participation must be reported to the sponsor.
- e. Long-term follow up started 3 months post EOT with a window of +/- 2 weeks.
- f. Focused physical exam, including a pelvic exam. Physical examinations will also include an assessment of all the major body systems. Complete physical examination, along with body weight, will be performed during screening, at study visits during the Treatment Phase and at treatment discontinuation.

- g. Red blood cell (RBC) count and parameters (hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)) and reticulocyte count, white blood cell (WBC) count and differential (with ANC), and platelet count will be assessed at screening, during treatment at each study visit and at the End of Treatment Visit for all patients. Hematology results must be reviewed by the investigator before the start of treatment with rucaparib and ongoing at times testing occurs. Additional and more frequent tests may be performed at the investigator's discretion.
- h. Performed locally on a freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on the investigator's judgment, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at screening, during treatment at each study visit and at the End of Treatment Visit for all patients, but may be conducted at other times as clinically indicated.
- i. Vital signs will include blood pressure, pulse, and body temperature and will be taken after the patient has been resting for at least 5 minutes during screening, at study visits during the Treatment Phase and at the End of Treatment Visit. Height will be measured during the screening visit only. Weight will be measured per institutional guidelines during screening, during treatment at each study visit and at the End of Treatment Visit.
- j. For all patients, 12-lead ECGs will be performed at screening (within 28 days prior to enrollment) and at the End of Treatment Visit. The following will be measured or calculated: heart rate, PR, QRS, QT, and rhythm. The investigator or qualified designee will review the ECGs locally and assess the results as normal or abnormal (clinically significant or not clinically significant). If it is clinically indicated, ECGs can be performed at other times during the study.
- k. ECOG performance status will be assessed during screening, at study visits during the Treatment Phase and at the End of Treatment Visit. The ECOG performance status should be assessed by the same study personnel at each visit, if possible. For eligibility purposes, patients with borderline ECOG performance status should be considered carefully to avoid enrolling patients who may have significant impairment.
- l. During the COVID-19 crisis, protocol mandated visits may be performed via telemedicine or visits may be combined in order to prevent imminent safety risks to patients. All such changes to the visit schedule must be clearly documented in the subject's chart. Changes in study visit schedules or missed visits must be explained in the final clinical study report.

7.3 Biological Sample Collection for Correlative Studies

We will assess microsatellite instability in the biopsies of patients with recurrent endometrial cancer. Additionally, response rates will be correlated with Foundation Medicine somatic testing (obtained as part of standard of care). Fresh biopsies will be assessed for DNA damage via a proprietary assay (PADDA) as well as RAD51C foci assay [61, 75]. Additional correlative studies such as HRD may be performed if sufficient tissue is available.

- Patients must agree to have a fresh tumor biopsy, after a written consent and prior to study

treatment. Archival tumor tissue is only acceptable for pre-treatment sample if the fresh tumor biopsy cannot be safely obtained. However, if fresh frozen samples cannot be collected, PADDa assay will not be performed.

- Peripheral Blood should be collected prior to treatment.

Please see lab manual for more detailed information of sample collection and shipping.

7.4 Follow up Parameter

Follow-up is required as outlined in Sections 6.7 and 7.2. In brief, patients will be seen every 21 days (prior to each cycle of therapy) while receiving study treatment. CT scans to assess response will be performed prior to every odd cycle. Patients will also be seen 30 days after last study medication is issued as the end of treatment (EOT) visit for safety and efficacy assessment, with a window of +/- 7 days. For EOT visit, CT scan should be repeated if the previous CT scan done over 4 weeks. Required study procedures are based on the presence or absence of bevacizumab or rucaparib related cardiovascular or other toxicities. At the EOT, information collected for subsequent treatments and AESI will require appropriate documentation (i.e., laboratory and/or pathology reports) and should be reported. Additionally, birth control must continue for 6 months after discontinuation of rucaparib.

A patient is considered off study therapy when the patient has progressed or died prior to completion of study therapy, a non-protocol drug or therapy (directed at the disease) is initiated or all study therapy is totally discontinued. Survival and progression data will continue to be collected for up to 2 years.

8 EVALUATION CRITERIA

8.1 Parameters of Outcome –RECIST 1.1 Criteria

8.1.1 Definition of Measurable Lesions

Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.

8.1.2 Baseline Documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the progression of the measurable dimension of the disease. Tumor within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and each of these lesions should be followed as stable (the persistence of a non-target lesion), complete response (the disappearance of a non-target lesion) or progressive disease (the unequivocal progression of a non-target lesion).

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

Measurement of the longest dimension of each target lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline.

8.1.3 Definition of Disease Progression

Progression for patients with measurable disease at baseline is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)

Progression for patients with non-measurable disease at baseline is defined as increasing clinical, radiological, or histological evidence of disease since study entry.

8.1.4 Survival

Survival is the observed length of life from the date of study entry to death or the date of last contact.

8.1.5 Progression-Free Survival

Progression free survival is defined as the period from the date of study entry until disease progression or death (whichever occurs first). Cases who have not had an event will be censored at the date of last disease assessment documenting the patient was free of progression. Progression will be evaluated by RECIST v1.1.

8.2 Subjective Parameters

The performance status, specific symptoms, and side effects are graded according to the CTCAE V4.0.

8.3 Definition of Evaluable Patients

Evaluable patients will be defined as patients with measurable and/or evaluable lesions who receive at least cycle 1 doses of study treatment (one dose of IV bevacizumab and 21 days of rucaparib, PO, BID) and complete the first post-treatment CT or MRI for tumor assessment. Patients who discontinued study treatment due to toxicity incurred by previous therapy will still be evaluated but will be replaced by additional patients for the efficacy analysis.

Patients removed from study for early withdraw or hypersensitivity reactions will be replaced if they have received less than one cycle of study treatments during cycle 1, but will be included in the safety analysis.

Patients who do not receive at least one cycle doses of study treatment will be considered unevaluable for efficacy analysis and will be replaced unless the missed doses were due to development of grade 3-4 adverse events related to study treatment. Patient who missed doses but have more than 80% total drug accountability will still be considered evaluable. The dose adjustment of rucaparib will follow after adjustment of SOC per protocol as described in Section 6.3.

9 STUDY MONITORING AND REPORTING PROCEDURES

9.1 Adverse Event Monitoring and Management

9.1.1 Definition of an Adverse Event (AE)

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

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

9.1.2 Definition of a Serious Adverse Event (SAE)

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

- Results in death. Any event resulting in death during the reporting period (from date of first

dose of rucaparib through 30 days after last dose) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing, that results in death must also be reported as an SAE.

- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly or birth defect
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

9.1.3 Definition of an Adverse Events of Special Interest (AESIs)

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

Details on Clovis' currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to Clovis **within 24 hours** of knowledge of the event.

9.1.4 Events or Outcomes Not Qualifying as Serious Adverse Events

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

- Pre-planned or elective hospitalization including social and/or convenience situations (e.g., respite care)
- Hospital visits of less than 24 hours duration (e.g., patient presents to the emergency room, but is not admitted to a ward)
- Overdose of either rucaparib, bevacizumab or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as a non-serious AE on the appropriate eCRF page.
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an AE/SAE; and
- Events that meet the SAE criteria and occur after informed consent, but before the first dose of rucaparib, which are considered unrelated to screening procedures.

9.1.5 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant

changes in lab values within the normal range will require similar judgment. An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

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

9.1.6 Pregnancy or Drug Exposure during Pregnancy

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

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

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

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

Events that occur after signing of informed consent, but prior to initiation of rucaparib, unless serious and due to a protocol-mandated procedure, should be recorded. Any serious event related to a protocol-mandated procedure should be reported as an SAE during the screening period. Any AE that occurs after first dose of rucaparib through 30 days after receiving the last dose of rucaparib will be recorded on the AE eCRF.

In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis, if appropriate. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

SAEs and AESIs that occur during the study or within 30 days after receiving the last dose of rucaparib, whether or not related to rucaparib, must be reported immediately (i.e., within 24 hours of knowledge of the event) to the sponsor/ SAE designee. The contact information for reporting of SAEs/AESIs can be found on the SAE/AESI Reporting Form. After the 30-day reporting window after discontinuation of rucaparib treatment, only SAEs assessed as related to rucaparib and all AESIs, irrespective of causality, need to be reported. Information on the follow-up of AEs, SAEs, and AESIs is provided below.

The contact information for reporting of SAEs/AESIs to Clovis include email: drugsafety@clovisoncology.com or Fax: 1-303-261-8319, which can be found on the SAE/AESI Reporting Form.

The contact information for reporting of SAEs/AESIs to Sponsor:

E-mail: SCCIIReporting@ouhsc.edu or via fax at 1-405-271-1416.

Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE V4.0 grading scale (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Severity is not the same as Serious.

For AEs not covered by NCI CTCAE V4.0, the severity will be characterized as mild, moderate, severe, life-threatening, or fatal according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required
- Life-threatening events require urgent intervention to prevent death
- Fatal events are those events that led to the patient's death

Causal Relationship of Adverse Events to Rucaparib

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

Not Related To Rucaparib	<ul style="list-style-type: none"> • An AE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medications, disease under study, etc.) • It does not follow a reasonable temporal sequence from administration of rucaparib • It does not follow a known pattern of response to rucaparib • It does not reappear or worsen when rucaparib is restarted • An alternative explanation is likely, but not clearly identifiable
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Related to Rucaparib	<ul style="list-style-type: none"> • An AE that is difficult to assign to alternative causes • It follows a strong or reasonable temporal sequence from administration of rucaparib • It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient • It follows a known response pattern to rucaparib • It is confirmed with a positive re-challenge or supporting laboratory data
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Outcome and Action Taken

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

Action Taken with Study Drug (note all that apply)

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

Outcome

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

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

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 30 days after the last dose of rucaparib. Any SAEs, AESIs, and treatment-related Grade 3/4 AEs must be followed until resolution or stabilization, death, or until lost to follow-up. After the 30-day window, treatment-related SAEs and all AESIs, irrespective of causality, need to be reported.

9.1.9 Regulatory Aspects of Serious Adverse Event and Adverse Events of Special Interest Reporting

All SAEs and AESIs, regardless of relationship to the study drugs, must be reported to the sponsor/SAE designee **within 24 hours** of knowledge of the event, during the study through 30

days after receiving the last dose of study treatment, according to the procedures below. After the 30-day specified window, only SAEs considered to be treatment-related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report. The Clovis study-specific Serious Adverse Event (SAE)/Adverse Events of Special Interest (AESI) Report Form must be used for reporting SAEs and AESIs to Clovis. The contact information for reporting of SAEs and AESIs can be found on the SAE/AESI Reporting Form and Pregnancy Report Forms. In addition, the Sponsor SAE/UP form must be used for reporting SAEs to the Sponsor.

The Sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drugs that are both serious and unexpected to the U.S. Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32

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

9.2 Reporting of Serious Adverse Events

All SAEs should be recorded on Clovis study-specific SAE/AESI Report Forms and faxed or emailed to:

Clovis Oncology, Inc.
Drug Safety Department
Fax: 1-303-261-8319

(Please use the safety reporting fax cover sheet attached to the SAE reporting form for your fax transmission)

Email: drugsafety@clovisoncology.com

In addition, all SAEs should be recorded on the Sponsor SAE/UP form together with the MedWatch Form 3500A and sent to SCC IIT Office through:

E-mail: SCCIITreporting@ouhsc.edu or via fax at 1-405-271-1416

9.3 MED WATCH 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500a form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Clovis or the Sponsor may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

Assessing Causality: Investigators are required to assess whether there is a reasonable possibility that rucaparib combined treatment caused or contributed to an adverse event. The general guidance is described in section 9.1.

9.4 Safety Reporting Requirements for IND Holders

In accordance with 21 CFR 212.32, IND safety reporting requirements will be followed:

9.4.1 Expedited IND Safety Reports:

9.4.1.1 7 Calendar-Day Telephone or Fax Report:

The Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of rucaparib combined with bevacizumab. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Clovis Oncology, Inc., within 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

9.4.1.2 15 Calendar-Day Written Report:

The Sponsor is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of rucaparib. An unexpected adverse event is one that is not already described in the list of expected events in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Clovis Drug Safety, and all participating investigators within 15 calendar days of first learning of the

event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

9.4.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size

The study hypothesis will be evaluated in a 2-stage design, a method provided by Sill et al. [77]. This will be used to decide whether there are sufficient numbers of patients progression-free at 6 months or with objective responses to continue study in a second stage (at the interim analysis) or deem the drug worthy of further investigation in a phase III study (at the end of the study). In particular, the null hypothesis is $H_0: \pi_r \leq 11\%$ and $\pi_s \leq 24\%$ and the alternative hypothesis is $H_0: \pi_r \geq 31\%$ ($=11\%+20\%$) or $\pi_s \geq 44\%$ ($=24\%+20\%$), where π_r is the objective response rate, π_s is the PFS rate at 6 months, 11% and 24% are the response rate and PFS rate at 6 months respectively from a previous study [58]. The following decision rule will be applied where $X_s(1)$ is the number of patients progression-free at 6 months after the first stage, $X_r(1)$ is the number of patients with objective tumor responses (partial or complete) after the first stage, X_s is the cumulative number of patients progression-free at 6 months after stage 2, X_r is the cumulative number of patients with responses after stage 2, $C_s(1)$ is the critical value for $X_s(1)$, $C_r(1)$ is the critical value for $X_r(1)$, C_s is the critical value for X_s , and C_r is the critical value for X_r : Decision Rule: If either $X_s(1) > C_s(1)$ or $X_r(1) > C_r(1)$ after the first stage, then the study will open to a second stage of accrual to further evaluate the activity of the drug. If either $X_s > C_s$ or $X_r > C_r$ after the second stage and clinical judgment indicates, then the agent will be deemed clinically interesting and worthy of further investigation.

For a flexible design with 0.1 alpha level and at least 90% power, the targeted accrual for the first stage (denoted by $n_{(1)}$) will be 28 eligible and evaluable patients, but is permitted to range from 24 to 31. The cumulative targeted accrual for the first and second stage combined (denoted by n) will be 50 eligible and evaluable patients, but is permitted to range from 46 to 53. Critical values for each stage are provided below:

Stage 1									Stage 1 + Stage 2								
$n_{(1)}$	24	25	26	27	28	29	30	31	n	46	47	48	49	50*	51**	52	53
$C_r(1)$	3	4	4	4	4	4	5	4	C_r	9	9	9	9	10	10	10	10
$C_s(1)$	6	6	7	7	7	8	8	9	C_s	15	15	16	16	16	16	17	17

*(C_r, C_s) = (9, 16) when $n_{(1)} = 25$ or 26; **(C_r, C_s) = (10, 17) when $n_{(1)} = 24, 28$ or 30; (C_r, C_s) = (9, 17) when $n_{(1)} = 25$

To account for up to 50% dropout and non-evaluable patients, up to 100 patients may be accrued to the clinical trial. Patient evaluability will be determined per Section 8.3.

Following first stage accrual, an interim analysis will be performed to assess activity as well as interest in proceeding with the second stage and/or to a randomized study design.

10.2 Data Analysis Plan

10.2.1 Patient Disposition

Patient disposition will be summarized and include the number dosed, the number in each patient population for analysis, the number who withdrew prior to completing the study and reason(s) for withdrawal.

10.2.2 Demographic and Baseline Characteristics

Patient demographic and characteristics at study entry will be summarized with frequency tables for categorical variables, and with descriptive statistics such as the mean, standard deviation, median, and range as appropriate, for quantitative variables.

10.2.3 Medical History and Cancer History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The count and percentage of subjects under each history term, coded by system organ class (SOC) and preferred term (PT), will be summarized.

Cancer history data will also be summarized, including the primary site of cancer, the stage and grade of cancer at study entry, time from initial diagnosis of cancer to Day 1 of the study in days, duration of metastatic disease in days (first dose date – date of diagnosis of metastatic disease + 1), the extent of metastatic disease, and the histology.

10.2.4 Study Drug Administration and Compliance

Study drug administration, both rucaparib and bevacizumab, will be summarized in terms of the actual doses administered and the proportion of drug actually taken relative to the amount that should have been taken; these data will be summarized in frequency distributions by cycle. The total number of cycles administered; the median (range) of cycles administered; dose modifications, dose delays, and dose omissions; and reasons for deviations from planned therapy will be summarized.

10.2.5 Safety Analyses

10.2.5.1 Adverse Events

Adverse events will be tabulated using MedDRA. The severity of the AE will be graded by the Investigator using the NCI CTCAE v4.0. The frequency of patients experiencing a specific AE will be tabulated by dose level, cycle, system organ class, preferred term, seriousness, worst severity, timing of occurrence, outcome, and relationship to study drugs. In addition, the number and percentage of patients experiencing a specific AE will be tabulated similarly.

10.2.5.2 Laboratory Abnormalities

The severity of laboratory abnormalities will be graded using the NCI CTCAE v4.0 whenever possible. The frequency of patients experiencing a specific laboratory abnormality will be tabulated by dose level, cycle, worst severity, and timing of occurrence. In addition, the number and percentage of patients experiencing a specific laboratory abnormality will be summarized similarly.

10.2.5.3 Other Safety Assessments

The results of vital sign measurements, body weight assessments, ECOG performance status determinations, physical examinations, and ECGs will be summarized by cycle and dose level, using appropriate descriptive statistics.

The baseline QT interval value will be the mean QT interval obtained from three ECGs in the hour just prior to first dose.

10.2.6 Biomarkers

Pre-dose assessments of biomarkers from tumor biopsies, such as level of DNA damage, PARP and BRCA in tumor, will be summarized for each patient at each dose level.

10.2.7 Antitumor Evaluation

The objective tumor response (complete and partial response) will be summarized as the proportion (and 95% CI based on Clopper-Pearson method) of patients with a tumor response. The duration of response will be summarized descriptively by Kaplan-Meier method. These assessments will be performed by CT or MRI every 2 cycles and for all patients treated in the study. Results will be presented in tabular and graphic form, as appropriate.

Progression-Free Survival (PFS) rate at six month or EOS is defined as the percentage of patients who are alive and progression-free at six months or EOS (estimated by the Kaplan-Meier method). Patients who are still alive without progression at EOS will be censored on the date of the last evaluable response assessment that is not progressive disease (PD). Median PFS together with a 95% CI will also be provided.

Primary efficacy endpoints (objective response and six month PFS rates) of rucaparib and bevacizumab combination will be compared with those in patients previously treated with bevacizumab single agent (retrospective data) via Chi-square or log-rank test.

Overall survival (OS) rate is defined as the percentage of patients who are alive at End of Study (EOS) and 2 years follow-up. Patients who are still alive at EOS or 2 years post EOS are censored on the date they were last known to be alive. An exploratory analysis to determine OS at EOS will be estimated by the Kaplan-Meier method.

Analyses involving translational research endpoints will be considered exploratory and will be carried out with notable associations highlighted as being worthy of further follow-up and possible confirmation. Associations between marker expressions levels (alone or in combination) and efficacy endpoints (objective response, PFS and OS) will be assessed by Chi-square or log-rank test as appropriate.

11 DATA AND SAFETY MONITORING PLAN

Safety oversight will be performed by Stephenson Cancer Center's (SCC) internal Data and Safety Monitoring Committee (DSMC). The DSMC is composed of individuals with the appropriate expertise in adult and pediatric hematology and medical oncology, radiation oncology, translational and correlative science, pharmacy, nursing and biostatistics. The DSMC operates under the rules of an approved data safety monitoring plan which complies with the National Cancer Institute (NCI) guidelines published as *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by NCI* as of January 2005 and the "NIH Policy for Data and Safety Monitoring," NIH Guide for Grants and Contracts, <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.

The Data Safety Monitoring Committee is charged with oversight of participant safety, study conduct and the validity and integrity of data for clinical trials at SCC. While the focus of the DSMC is to monitor interventional investigator initiated trials (IITs) that are not subject to external monitoring, it has the authority to monitor any SCC protocol when potential concerns are identified. The DSMC also has the authority to suspend or close a study until the principal investigator addresses any issues that may cause harm or increase risks to subjects. The DSMC reports all findings to the Institutional Review Board (IRB).

Under the direction of the DSMC chair, a full board meeting is convened on a biannual basis to review the accumulated safety data, accrual information, and additional information as stated in the DSMC plan.

11.1 DSMC Auditing

In addition to monitoring, the DSMC oversees an internal auditing process to ensure subject safety and data quality. All cancer-related clinical trials active at the SCC are eligible for audit; however, priority is placed on those clinical trials that are not monitored or audited by an outside entity. If an external entity conducts an audit of a clinical trial at the SCC, then the findings of that audit are reported to the DSMC, either through the formal audit report provided by the external auditing entity, if available, or from the PI, who will report any findings communicated during the audit process.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Quality Assurance

Stephenson Cancer Center (SCC) will be responsible for clinical monitoring of data for this study.

12.2 Electronic Case Report Forms

The Principal Investigator will develop electronic case report forms for study data entry. All study data will be stored in a 21 CFR 11-compliant database. Only Investigator and assigned research staff will have access to study data. The electronic case report forms will be available to sponsor, IRB or regulatory authorities in case of an audit or inspection. Site staff should contact the Sponsor for information regarding access to the electronic data capture system.

12.3 Record Retention

Investigator will retain all research documents and case report forms at study site for at least five years after study closure. The site must notify the Sponsor Institute prior to record destruction to store study records at Sponsor Institute's expense.

13 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572. Study medication may be administered only under the supervision of the Investigators listed on this form. Curriculum vitae must be provided to the Sponsor for the site Principal Investigator and made available for upon request for the sub-Investigators.

13.2 Ethical Conduct of the Study

The study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki in addition to the requirements of the ICH E2A guidelines. This study will also comply with U.S. FDA regulations under a U.S. Investigational New Drug (IND) application in addition to local, state, and federal laws.

13.3 Informed Consent

The informed consent document will be in compliance with ICH GCP, local regulatory requirements, and legal requirements. A model informed consent document will be provided for this study. The informed consent document used in this study, and any changes made during the course of the study, will be prospectively approved by the Sponsor and then submitted for approval to the IRB of record for approval.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The study site will retain the original of each patient's signed consent document.

13.4 Institutional Review Board or Ethics Committee

This protocol, the Informed Consent document, any information to be given to the patient, and relevant supporting information must be submitted to the IRB by the Principal Investigator and reviewed and approved by the IRB before the study is initiated.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB. Investigators are also responsible for promptly informing the IRB of any protocol amendments.

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB of record per institutional standards and federal regulations.

13.5 Confidentiality

The Sponsor and site will maintain confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent document (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

13.6 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/EC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.

When immediate deviation from the protocol is required to eliminate an immediate hazard to patients, the Investigator will contact the Sponsor or its designee if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation.

14 REFERENCES

1. Hanahan, D. and R.A. Weinberg, *The hallmarks of cancer*. Cell, 2000. **100**(1): p. 57-70.
2. Drew, Y., et al., *Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer*. Br J Cancer, 2016. **114**(7): p. 723-30.
3. Swisher, E.M., et al., *Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial*. Lancet Oncol, 2017. **18**(1): p. 75-87.
4. Tentori, L., et al., *Poly(ADP-ribose) polymerase (PARP) inhibition or PARP-1 gene deletion reduces angiogenesis*. Eur J Cancer, 2007. **43**(14): p. 2124-33.
5. Lim, J.J., et al., *VEGFR3 inhibition chemosensitizes ovarian cancer stemlike cells through down-regulation of BRCA1 and BRCA2*. Neoplasia, 2014. **16**(4): p. 343-53 e1-2.
6. Wei, W., et al., *PARP-1 may be involved in angiogenesis in epithelial ovarian cancer*. Oncol Lett, 2016. **12**(6): p. 4561-4567.
7. Moore, D.H., et al., *Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study*. J Clin Oncol, 2004. **22**(15): p. 3113-9.
8. Long, H.J., 3rd, et al., *Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study*. J Clin Oncol, 2005. **23**(21): p. 4626-33.
9. Tewari, K.S., et al., *Improved survival with bevacizumab in advanced cervical cancer*. N Engl J Med, 2014. **370**(8): p. 734-43.
10. D'Onofrio, G., et al., *Poly(ADP-ribose) polymerase signaling of topoisomerase 1-dependent DNA damage in carcinoma cells*. Biochem Pharmacol, 2011. **81**(2): p. 194-202.
11. Shunkwiler, L., G. Ferris, and C. Kunos, *Inhibition of Poly(ADP-Ribose) Polymerase Enhances Radiochemosensitivity in Cancers Proficient in DNA Double-Strand Break Repair*. Int J Mol Sci, 2013. **14**(2): p. 3773-85.
12. Kunos, C., et al., *A phase I-II evaluation of veliparib (NSC #737664), topotecan, and filgrastim or pegfilgrastim in the treatment of persistent or recurrent carcinoma of the uterine cervix: an NRG Oncology/Gynecologic Oncology Group study*. Int J Gynecol Cancer, 2015. **25**(3): p. 484-92.
13. Thaker, P.H., et al., *A Phase I Trial of Paclitaxel, Cisplatin and Veliparib in the Treatment of Persistent or Recurrent Carcinoma of the Cervix: An NRG Oncology Study (NCT#01281852)*. Ann Oncol, 2016.
14. Scanlon, S.E. and P.M. Glazer, *Hypoxic stress facilitates acute activation and chronic downregulation of fanconi anemia proteins*. Mol Cancer Res, 2014. **12**(7): p. 1016-28.
15. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2016*. CA Cancer J Clin, 2016. **66**(1): p. 7-30.
16. Lincoln, S., et al., *Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study*. Gynecol Oncol, 2003. **88**(3): p. 277-81.
17. Thigpen, J.T., et al., *Phase II trial of cisplatin as first-line chemotherapy in patients with*

- advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study.* Gynecol Oncol, 1989. **33**(1): p. 68-70.
18. Thigpen, J.T., et al., *Phase II trial of cisplatin as second-line chemotherapy in patients with advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group study.* Am J Clin Oncol, 1984. **7**(3): p. 253-6.
 19. Thigpen, J.T., et al., *Phase II trial of adriamycin in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study.* Cancer Treat Rep, 1979. **63**(1): p. 21-7.
 20. McMeekin, S., et al., *Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer.* Gynecol Oncol, 2015.
 21. Aghajanian, C., et al., *Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study.* J Clin Oncol, 2011. **29**(16): p. 2259-65.
 22. Alvarez, E.A., et al., *Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study.* Gynecol Oncol, 2013. **129**(1): p. 22-7.
 23. Aghajanian C, F.V., Dizon DS, Carlson J, Powell MA et al. , *A randomized phase II study of paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus and ixabepilone/carboplatin/bevacizumab as initial therapy for measurable stage III or IVA, stage IVB or recurrent endometrial cancer, GOG 86P.* . J Clin Oncol **33**(suppl: abstr 5500).
 24. Lorusso, D., Ferrandina G, Colombo N, Pignata S et al. , *Randomized phase II trial of carboplatin-paclitaxel (CP) compared to carboplatin-paclitaxel-bevacizumab (CP-B) in advanced (stage III-IV) or recurrent endometrial cancer: The MITO END-2 trial.* J Clin Oncol, 2015. **33**(suppl; abstr 5502).
 25. Salmena, L., A. Carracedo, and P.P. Pandolfi, *Tenets of PTEN tumor suppression.* Cell, 2008. **133**(3): p. 403-14.
 26. Gupta, A., et al., *Cell cycle checkpoint defects contribute to genomic instability in PTEN deficient cells independent of DNA DSB repair.* Cell Cycle, 2009. **8**(14): p. 2198-210.
 27. Shen, W.H., et al., *Essential role for nuclear PTEN in maintaining chromosomal integrity.* Cell, 2007. **128**(1): p. 157-70.
 28. Farmer, H., et al., *Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy.* Nature, 2005. **434**(7035): p. 917-21.
 29. McCabe, N., et al., *Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition.* Cancer Res, 2006. **66**(16): p. 8109-15.
 30. Mendes-Pereira, A.M., et al., *Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors.* EMBO Mol Med, 2009. **1**(6-7): p. 315-22.
 31. Dedes, K.J., et al., *PTEN deficiency in endometrioid endometrial adenocarcinomas predicts sensitivity to PARP inhibitors.* Sci Transl Med, 2010. **2**(53): p. 53ra75.
 32. Forster, M.D., et al., *Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer.* Nat Rev Clin Oncol, 2011. **8**(5): p. 302-6.
 33. Clovis Oncology Inc. *RUBRACA (rucaparib) Prescribing Information.* April 2018];

- Available from:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209115s003lbl.pdf.
34. Oza, A.M., et al., *Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2*. Gynecologic Oncology, 2017. **147**(2): p. 267-275.
 35. Coleman, R.L., et al., *Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial*. The Lancet, 2017. **390**(10106): p. 1949-1961.
 36. Ménissier de Murcia, J., et al., *Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse*. The EMBO Journal, 2003. **22**(9): p. 2255-2263.
 37. Schreiber, V., et al., *Poly(ADP-ribose) Polymerase-2 (PARP-2) Is Required for Efficient Base Excision DNA Repair in Association with PARP-1 and XRCC1*. Journal of Biological Chemistry, 2002. **277**(25): p. 23028-23036.
 38. Dantzer, F., et al., *Poly(ADP-ribose) polymerase-2 contributes to the fidelity of male meiosis I and spermiogenesis*. Proceedings of the National Academy of Sciences of the United States of America, 2006. **103**(40): p. 14854-14859.
 39. Joshi, A., et al., *PARP1 during embryo implantation and its upregulation by oestradiol in mice*. Reproduction, 2014. **147**(6): p. 765-80.
 40. O'Malley, D.M., et al., *Abstract LB-A12: Results from the phase 3 study ARIEL3: mutations in non-BRCA homologous recombination repair genes confer sensitivity to maintenance treatment with the PARP inhibitor rucaparib in patients with recurrent platinum-sensitive high-grade ovarian carcinoma*. Molecular Cancer Therapeutics, 2018. **17**(1 Supplement): p. LB-A12.
 41. Abida, W., et al., *Preliminary Results from TRITON2: A Phase 2 Study of Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Associated with Homologous Recombination Repair (HRR) Gene Alterations [poster 793PD]*, in *ESMO Annual Congress*. Munich, Germany.
 42. Kristeleit, R., et al., *A Phase I-II Study of the Oral Poly(ADP-ribose) Polymerase Inhibitor Rucaparib in Patients with Germline BRCA1/2-mutated Ovarian Carcinoma or Other Solid Tumors*. Clin Cancer Res, 2017.
 43. Shroff, R.T., et al., *Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation*. JCO Precision Oncology, 2018. **2018**: p. 10.1200/PO.17.00316.
 44. Reiss Binder, K.A., et al., *A Phase II, single arm study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic mutation in BRCA1, BRCA2 or PALB2 [abstract CT234]*, in *AACR Annual Meeting*. 2019: Atlanta, GA.
 45. US Department of Health and Human Services, F.D.A., CDER, CBER, *Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, F.D.A. US Department of Health and Human Services, CDER, CBER, Editor. 2009.
 46. Temple, R., *Hy's law: predicting serious hepatotoxicity*. Pharmacoepidemiology and Drug Safety, 2006. **15**(4): p. 241-243.

47. Clovis Oncology UK Ltd. *RUBRACA (rucaparib) SmPC*. February 2019]; Available from: https://www.ema.europa.eu/documents/product-information/rubraca-epar-product-information_en.pdf.
48. Fulcher, N., et al., *Incidence of secondary myelodysplastic syndrome and acute myeloid leukemia in patients with ovarian and breast cancer in real-world setting in the U.S.* Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 5574.
49. Friedenson, B., *The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers.* BMC Cancer, 2007. **7**(1): p. 152.
50. Plummer, R., et al., *Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors.* Clin Cancer Res, 2008. **14**(23): p. 7917-23.
51. Plummer, R., et al., *A phase II study of the potent PARP inhibitor, Rucaparib (PF-01367338, AG014699), with temozolomide in patients with metastatic melanoma demonstrating evidence of chemopotentiality.* Cancer Chemother Pharmacol, 2013. **71**(5): p. 1191-9.
52. National Cancer Institute. *Common Terminology Criteria for Adverse Events, Version 4.03.* 14 June 2010 [cited 19 November 2014]; Available from: http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
53. Hurwitz, H., et al., *Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.* N Engl J Med, 2004. **350**(23): p. 2335-42.
54. Keefe, D., et al., *Noncardiac vascular toxicities of vascular endothelial growth factor inhibitors in advanced cancer: a review.* Oncologist, 2011. **16**(4): p. 432-44.
55. Abdel-Qadir, H., et al., *Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: A systematic review and meta-analysis.* Cancer Treat Rev, 2017. **53**: p. 120-127.
56. Sliesoraitis, S. and B. Tawfik, *Bevacizumab-induced bowel perforation.* J Am Osteopath Assoc, 2011. **111**(7): p. 437-41.
57. Eremina, V., et al., *VEGF inhibition and renal thrombotic microangiopathy.* N Engl J Med, 2008. **358**(11): p. 1129-36.
58. Scappaticci, F.A., et al., *Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab.* J Surg Oncol, 2005. **91**(3): p. 173-80.
59. Monk, B.J., et al., *Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study.* J Clin Oncol, 2009. **27**(7): p. 1069-74.
60. Bizzarri, N., et al., *Bevacizumab for the treatment of cervical cancer.* Expert Opin Biol Ther, 2016. **16**(3): p. 407-19.
61. Ganapathy, V., et al., *Detection of In Vivo DNA Damage Induced by Very Low Doses of Mainstream and Sidestream Smoke Extracts Using a Novel Assay.* American Journal of Preventive Medicine, 2015. **48**(1, Supplement 1): p. S102-S110.
62. Ames, B.N., *Endogenous DNA damage as related to cancer and aging.* Mutat Res, 1989. **214**(1): p. 41-6.
63. Hasty, P., et al., *Aging and Genome Maintenance: Lessons from the Mouse?* Science, 2003.

- 299**(5611): p. 1355-1359.
64. Cooke, M.S., et al., *Oxidative DNA damage: mechanisms, mutation, and disease*. FASEB J., 2003. **17**(10): p. 1195-1214.
 65. Nadin, S.B., et al., *DNA damage and repair in peripheral blood lymphocytes from healthy individuals and cancer patients: a pilot study on the implications in the clinical response to chemotherapy*. Cancer Lett, 2006. **239**(1): p. 84-97.
 66. Grimaldi, K.A., et al., *PCR-based methods for detecting DNA damage and its repair at the sub-gene and single nucleotide levels in cells*. Mol Biotechnol, 2002. **20**(2): p. 181-96.
 67. Pfeifer, G.P., et al., *Chromatin structure analysis by ligation-mediated and terminal transferase-mediated polymerase chain reaction*. Methods Enzymol, 1999. **304**: p. 548-71.
 68. Dai, S.M., et al., *Ligation-mediated PCR: robotic liquid handling for DNA damage and repair*. Biotechniques, 2002. **33**(5): p. 1090-7.
 69. Ayala-Torres, S., et al., *Analysis of gene-specific DNA damage and repair using quantitative polymerase chain reaction*. Methods, 2000. **22**(2): p. 135-47.
 70. McGurk, C.J., et al., *Measurement of covalent drug-DNA interactions at the nucleotide level in cells at pharmacologically relevant doses*. Methods Enzymol, 2001. **340**: p. 358-76.
 71. Mills, W.K., et al., *In vivo detection of nucleotide lesions preceding mutation fixation*. Cancer Research, 2010. **70**.
 72. Reis, A.M., et al., *Targeted detection of in vivo endogenous DNA base damage reveals preferential base excision repair in the transcribed strand*. Nucleic Acids Res, 2012. **40**(1): p. 206-19.
 73. Alshareeda, A.T., et al., *Clinical and biological significance of RAD51 expression in breast cancer: a key DNA damage response protein*. Breast Cancer Res Treat, 2016. **159**(1): p. 41-53.
 74. Chen, X., et al., *High expression of Rad51c predicts poor prognostic outcome and induces cell resistance to cisplatin and radiation in non-small cell lung cancer*. Tumour Biol, 2016. **37**(10): p. 13489-13498.
 75. Liu, Y., et al., *RAD51 Mediates Resistance of Cancer Stem Cells to PARP Inhibition in Triple-Negative Breast Cancer*. Clin Cancer Res, 2017. **23**(2): p. 514-522.
 76. Gachechiladze, M., et al., *RAD51 as a potential surrogate marker for DNA repair capacity in solid malignancies*. Int J Cancer, 2017.
 77. Sill, M.W., et al., *A method for utilizing co-primary efficacy outcome measures to screen regimens for activity in two-stage Phase II clinical trials*. Clinical Trials, 2012. **9**(4): p. 385-395.