Clinical Trial Protocol

Study Title	**Phase 2 Trial of Niraparib or Niraparib and Bevacizumab Combination in Patients with Recurrent Endometrial Cancer and/or Ovarian Cancer with ARID1A Mutation (OU-SCC-ARID1A)**
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Contents

1 PROTOCOL SUMMARY 6
1.1 Synopsis 6
1.2 Schema 9
1.3 Schedule of Activities 10
2 BACKGROUND AND STUDY RATIONALE 12
2.1 Disease background 12
2.1.1 Endometrial cancer 12
2.1.2 Ovarian cancer 14
2.2 Emerging roles of PARP inhibitors on cancer treatment 14
2.2.1 Rationale for PARP inhibitors in ARID1A mutated endometrial and ovarian cancer 14
2.3 Combination niraparib and bevacizumab 15
2.4 Summary of study medications 15
2.5 Rationale for this study 17
2.5.1 Rationale for randomized study 18
2.5.2 Rationale for correlative studies 18
2.6 Risks and benefit assessment 19
2.6.1 Known potential risks for niraparib 19
2.6.2 Known potential benefits for niraparib 19
2.6.3 Assessment of potential risks and benefits 19
3 STUDY OBJECTIVES AND ENDPOINTS 19
3.1 Primary objectives 20
3.2 Secondary objectives 20
3.3 Translational objectives 20
3.4 Study endpoints 20
4 STUDY POPULATION 21
4.1 Inclusion criteria 21
4.2 Exclusion criteria 22
5 SUBJECTS REGISTRATION RANODMIZATION AND ENROLLMENT 23
5.1 Required protocol specific regulatory documents 23
5.2 Patients registration randomization and enrollment 23
6 STUDY DESIGN AND TREATMENT PLAN 24
6.1 Study design 24

6.2 Treatment plan 24
6.2.1 Niraparib administration 26
6.2.2 Bevacizumab administration 26
6.3 Dose modification or discontinuation for adverse reactions 26
6.3.1 Dose modification for niraparib 26
6.3.2 Dose modification for bevacizumab 29
6.4 Precaution for concomitant medication during the Study 31
6.4.1 Non-study anti-cancer agent 31
6.4.2 Hematopoietic growth factors and blood products 32
6.5 Supportive care 32
6.6 Duration of therapy 32
6.7 Duration of follow-up 32
7 STUDY PARAMETERS 32
7.1 Therapeutic parameters 32
7.2 Biological Sample Collection for Correlative Studies 32
7.2.1 Instruction for tumor tissue collection 33
7.2.2 Instruction for Blood sample collection and processing 33
7.2.3 Sample shipping 34
7.3 Follow up Parameter 34
8 EVALUATION CRITERIA 34
8.1 Parameters of Outcome –RECIST 1.1 Criteria 34
8.1.1 Definition of Measurable Lesions 34
8.1.2 Baseline Documentation of “Target” and “Non-Target” lesions 35
8.1.3 Response Criteria 35
8.1.4 Definition of Disease Progression 35
8.1.5 Evaluation of Non-Target Lesions 36
8.1.6 Evaluation of New Lesions 36
8.1.7 Survival 36
8.1.8 Progression-Free Survival 36
8.2 Subjective Parameters 36
8.3 Definition of Evaluable Patients 36
9 SAFETY MONITORING AND REPORTING PROCEDURES 37
9.1 Adverse Event Reporting Period 37

9.1.1 Reporting Abnormal Labs ... 37
9.1.2 Reporting to Sponsor ... 37
9.1.3 Reporting to GlaxoSmithKline (GSK) ... 37
9.1.4 Reporting Suspected Unexpected Serious Adverse Reactions ... 39
9.1.5 Reporting Guidelines ... 39
9.2 Adverse Event Monitoring ... 40
9.2.1 Definitions (per 21 CFR 312.32(a)) ... 40
9.2.2 Definition of an Adverse Events of Special Interest (AESIs) ... 42
9.2.3 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events ... 42
9.2.4 Pregnancy or Breastfeeding ... 42
9.3 Documenting Adverse Events ... 43
9.3.1 Specific Instructions for Recording Adverse Events ... 43
9.4 Causality Assessment of Adverse Events ... 44
9.5 Severity Assessment of Adverse Events ... 45
9.6 Study Monitoring ... 45
9.7 Reporting Product Complaints for GSK Products ... 45
9.8 Data Disclosure and Patient Confidentiality ... 46
10 STATISTICS ... 46
10.1 Sample size justification ... 46
10.2 Data analysis plan ... 47
10.3 Accrual goal ... 47
11 DATA AND SAFETY MONITORING PLAN ... 48
11.1 DSMC Auditing ... 48
12 DATA HANDLING AND RECORD KEEPING ... 48
12.1 Data Quality Assurance ... 48
12.2 Electronic Database and Case Report Forms ... 48
12.3 Record Retention ... 49
13 ETHICAL AND REGULATORY CONSIDERATIONS ... 49
13.1 Investigators and Study Administrative Structure ... 49
13.2 Ethical Conduct of the Study ... 49
13.3 Informed Consent ... 49
13.4 Institutional Review Board or Ethics Committee ... 49
13.5 Drug Accountability ... 50

13.6 Confidentiality 50
13.7 Protocol Violations/Deviations 50
14 REFERENCES 50

1 PROTOCOL SUMMARY

1.1 Synopsis

Study Title	Phase 2 Trial of Niraparib or Niraparib and Bevacizumab Combination in Patients with Recurrent Endometrial Cancer and/or Ovarian Cancer with ARID1A Mutation (OU-SCC-ARID1A)
Overview/ Hypothesis	ARID1A mutations have been found in endometrial cancer and endometriosis-associated ovarian cancer [1], which may be used as a therapeutic target for cancer treatment. Clinical studies demonstrated that niraparib plus bevacizumab combination significantly improved clinical outcomes in platinum-sensitive ovarian cancer [2, 3]. We hypothesize that niraparib and bevacizumab combination may produce a synergistic anticancer effect in patients with advanced and/or recurrent endometrial cancer and/or ovarian cancer with an *ARID1A* mutation. This hypothesis is supported by the preliminary data of a phase II trial conducted in our research group. We found that rucaparib and bevacizumab combination demonstrated clinical benefit in patients with recurrent endometrial cancer with *ARID1A* mutations. The rate of objective response (33%) and 6-month PFS (66.7%) was higher among 6 subjects with *ARID1A* mutations as compared to the entire study population (10.7% and 21%, respectively). These data suggest that patients with *ARID1A* mutated endometrial or ovarian cancer may be more sensitive to niraparib (PARP inhibitor) and bevacizumab combination therapy. This randomized, phase 2 basket trial will investigate the efficacy and safety of niraparib single agent or niraparib plus bevacizumab in 92 eligible and evaluable subjects with recurrent and/or advanced endometrial cancer or ovarian cancer with *ARID1A* tumor mutations.
Objectives	**Co-Primary Objectives** • To estimate the proportion of patients with recurrent endometrial cancer with mutated *ARID1A*, who have objective tumor response (complete or partial), to the combination treatment of niraparib and bevacizumab and to monotherapy niraparib • To estimate the proportion of patients with recurrent ovarian cancer with mutated *ARID1A*, who have objective tumor response (complete or partial), to the combination treatment of niraparib and bevacizumab and to monotherapy niraparib **Secondary Objectives** • To determine the nature and degree of toxicity of each regimen in study subjects. • To estimate the proportion of subjects with recurrent

	endometrial cancer or ovarian cancer with mutated *ARID1A*, who survive progression-free for at least 6 months, treated with each regimen. • To estimate the progression-free survival (PFS) of subjects with recurrent endometrial cancer or ovarian cancer with mutated *ARID1A* treated with each regimen.
Endpoints	**Translational Objectives** • To obtain fresh tumor tissue pre-dose in a subset of patients to determine whether patient-derived organoid (PDO) response after treatment correlates with patient response and PFS. • To determine the degree of and ability to respond to DNA damage by analyzing both HR and NHEJ pathways, including RAD51 foci formation, Gamma *H2AX* staining and a 53BP1 foci assay in PDOs. • To evaluate correlation between tumor ARID1A protein expression by IHC and tumor *ARID1A* mutation determined by next generation sequencing • To obtain a serum sample for exosome isolation to determine miRNA signatures that predict response to therapy. • To correlate mutations in DNA damage repair pathway genes (somatic and germline) with tumor response. **Primary endpoint** • Objective response rate as measured by RECIST version 1.1 for each individual patient defined as best response with disease assessments every 8 weeks prior to disease progression or unacceptable toxicity.
	Secondary Endpoints • Toxicity as defined by incidence of patients with ≥grade 3 adverse events. • PFS, as determined by the number of days from the start of study treatment to date of progression or death or last time of follow up. • Rate of 6-month PFS. **Translational Endpoint** • Correlate patient derived organoid response to therapy with tumor response.
Study Population	**Key eligibilities include:** a) Female, at least 18 years of age b) Histologically confirmed progressive or recurrent endometrial cancer or ovarian cancer with previously identified *ARID1A* tumor mutations

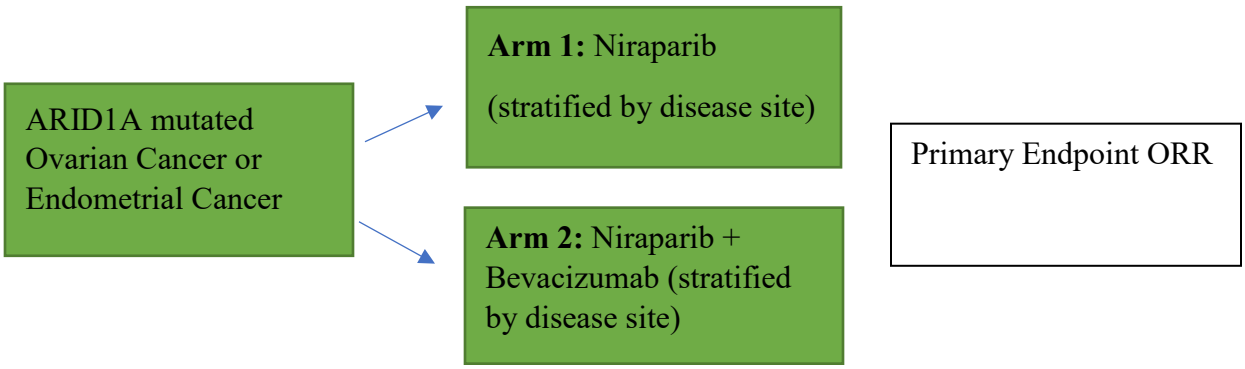
	c) Archival tumor tissue specimen must be available. Otherwise, if unavailable then patient should agree to have tumor biopsy to obtain sufficient tissue for histological assessment. If unable to be safely biopsied and patient desires enrollment, patient may be enrolled per Medical Monitor (MM) discretion. d) Patient must agree to have blood draw at pre- and post-treatment for correlative studies. e) Patients must have an ECOG performance status of 0 or 1 f) Patients should have no major existing co-morbidities or medical conditions that will preclude therapy in the view of the principal investigator Please see Section 4 for full eligibilities.

Phase	Phase 2 randomized trial
Study Design	This is a multicenter, two arm, open label, randomized phase II clinical trial evaluating the efficacy and safety of niraparib monotherapy or niraparib combined with bevacizumab in patients with recurrent endometrial cancer and/or ovarian cancer with *ARID1A* mutation.
Description of Sites/Facilities Enrolling Participants	This study will enroll eligible subjects at four medical centers including the Stephenson Cancer Center University Oklahoma Health Sciences Center as the coordinating Center, and 3 additional sites (names of participating institutes and PIs are to be determined)
Description of Study Intervention	**Arm 1 Niraparib single agent** • Niraparib (200mg or 300 mg based on body weight and blood platelet count), oral, once daily **Arm 2 Niraparib plus Bevacizumab** • Niraparib (200mg or 300 mg based on body weight and blood platelet count), oral, once daily • Bevacizumab (15 mg/kg, IV on day 1 of each cycle) One cycle = 21 days. Patients will be treated until disease progression or toxicity unless patient withdraws consent.
Study Duration	This randomized phase 2 basket trial will take up to 48 months for accrual, study treatment, post-treatment follow-up and data analysis. The planned sample size is 46 evaluable patients in each of Arm 1 (niraparib single agent) and Arm 2 (niraparib plus bevacizumab). It is anticipated that this study will require approximately 24 months of accrual assuming an accrual rate of 4~5 patients per month across four sites.

Participant Duration	Eligible subjects will be treated until disease progression or toxicity unless patient withdraws consent. It is estimated that a median of 8 months will be needed for treatment and post-dose follow-up to observe safety/adverse events.

1.2 Schema

Study design is summarized in schema below:



1.3 Schedule of Activities

The schedule of events to be performed during the study is provided in table 1.

Table 1 Study calendar

Parameter	Screening		Day 1 or Prior to each cycle	Every 8 weeks	End of treatment	Follow up
	Within 28 days of C1D1	Within 14 days of C1D1	(-/+ 3 days)	(-/+ 7 days)	(30 days post the last dose) [i]	(Q3M for 3 years)
Inclusion /exclusion	x		x			
Demographics	x					
History / Physical [a]	x		x		x	
ECOG PS	x				x	
Vital signs / weight [b]	x		x [b]		x	
CT CAP or / MRI [c]	x			x	x	x
RECIST				x	x	
CBC/Diff/ platelets [d]		x	x		x	
Chemistries [e]		x	x		x	
PT/PTT/INR		x	x			
Urinalysis [f]		x	x		x	
Toxicity assessment [g]			x		x	

Parameter	Screening		Day 1 or Prior to each cycle	Every 8 weeks	End of treatment	Follow up
	Within 28 days of enrollment	Within 14 days of enrollment	(-/+ 3 days)	(-/+ 7 days)	(30 days post the last dose) [i]	(Q3M for 3 years)
Urine / serum Pregnancy Test [h]		x	x		x	
12-lead ECG [j]	x				x	
Concomitant Medications	x		x		x	
Blood sample for correlative study		x			x	
Tumor tissue	x [k]					
Niraparib dispensed /collected			x			
Bevacizumab infusion [l]			x			
Survival						x

a. Complete physical examination will be performed during screening, at each study visit during the Treatment Phase and at treatment discontinuation. Focused physical exam, including a pelvic exam and an assessment of the major body systems at other times are as clinically indicated.
b. Vital signs will include blood pressure, pulse, respiration and body temperature and will be taken ideally 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. For niraparib, blood pressure and heart rate should be monitored at least weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with niraparib. For bevacizumab, blood pressure should be monitored every two to three weeks during treatment with bevacizumab; continue to monitor blood pressure at regular intervals in patients with bevacizumab-induced or -exacerbated hypertension after discontinuing bevacizumab. For blood pressure and heart rate monitoring scheduled on dates when the patient is otherwise not scheduled to be in clinic, home monitoring is acceptable with use of provided patient logs. Patient logs must be returned to record results for investigator review and clinical management to ensure patient safety. 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.

c. Imaging should be completed prior to Cycle 4 and every 8 weeks (±7 days) thereafter (prior to even cycles). Follow up CT scans performed Q3M for 3 years, as clinically indicated following SOC.
d. CBCs weekly x 4 weeks after initiating niraparib or during any dose change of niraparib, including at end of treatment, to ensure stability of platelets and other hematologic parameters.
e. 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 niraparib and ongoing at times testing occurs. Additional and more frequent tests may be performed at the investigator's discretion.
f. 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. If bevacizumab is discontinued, then urinalysis can be discontinued if clinically indicated.
g. Any SAEs, AESIs, and treatment related Grade 3/4 AEs must be followed until resolution or stabilization, or until lost to follow-up.
h. For women of childbearing potential only. A serum or urine pregnancy test must be performed ≤ 3 days prior to first dose of niraparib (a negative result is required before dosing can begin) and at the End of Treatment Visit. A serum or urine 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 and to GSK.
i. With a window of +/- 7 days.
j. 12-lead ECGs to be performed at screening (within 28 days prior to enrollment) and at the End of Treatment Visit; and any time if clinical indicated during study treatment. 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).
k. Archival tumor tissue specimen must be available for histological research. If unavailable, then patient should agree to have fresh tumor biopsy unless not medically eligible or biopsy is not able to be obtained safely. Fresh biopsy will be taken from patients for translational research until 15 evaluable samples per arm (15 endometrial and 15 ovarian samples each) are obtained. If unable to be safely biopsied and patient desires enrollment, they may be enrolled per MM.
l. Only for subjects randomized to enroll in the arm of niraparib plus bevacizumab. Bevacizumab infusion performed on the same day that niraparib is dispensed.

2 BACKGROUND AND STUDY RATIONALE

2.1 Disease background

2.1.1 Endometrial cancer

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States with an estimated 65,620 new cases in 2020 and resulting in 12,590 deaths [4]. Although the vast majority of patients present with early-stage disease, treatment options for advanced or recurrent

endometrial cancer are limited. Current standard of care cytotoxic chemotherapy in the advanced and recurrent setting includes agents such as doxorubicin and carbo- or cisplatin and paclitaxel however response rates are generally poor, particularly in the recurrent setting [5-9]. Globally, the current first line chemotherapy for advanced or recurrent endometrial cancer is carboplatin and paclitaxel, however this regimen only demonstrates a median progression free survival of 13 months [10]. 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 [11, 12]. 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 progression free survival (PFS) was 4.2 months, and the median overall survival (OS) was 10.5 months [11].

Recently, recurrent endometrial cancer has 2 new FDA approvals: pembrolizumab for recurrent endometrial cancer with mismatch repair deficiency or microsatellite instability-high status (based on the tissue agnostic FDA approval granted in May 2017) (refer to link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf) and pembrolizumab/lenvatinib for recurrent endometrial cancer without microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) (July 2021) [13]. While all of these new approvals are welcome additions to options for patients with recurrent endometrial cancer following disease progression through first line systemic chemotherapy, additional active regimens are urgently needed to prolong PFS and OS which are unacceptably short in both disease settings.

Based on molecular characterization of endometrial tumors by the Cancer Genome Atlas Research Network, endometrial cancers can be classified into one of four subgroups: POLE ultramutated, microsatellite instability hypermutated, copy number low, and copy number high. While most endometrial tumors have few copy number or TP53 mutations, they frequently demonstrate mutations in *PTEN* and *ARID1A* [14]. Researchers have further investigated the association of molecular markers and disease prognosis in endometrial cancer including markers such as p53 mutation, p16 overexpression, *PTEN* mutations, microsatellite instability, and *PI3K/AKT* [15-17].

In addition, epigenetic defects in the tumor suppressor gene, AT-rich interaction domain 1A (*ARID1A*) leading to reduced *ARID1A* expression is associated with shorter PFS and may be used as prognostic marker for patients with endometrial cancer [18, 19].

Clear cell (CC) carcinoma of the endometrium, while rare, frequently demonstrates *ARID1A* mutations and is generally accepted to carry a poor prognosis with decreased response to chemotherapy. Because of its relative rarity, this histology is frequently combined with all other histologies of EC and therefore little to no prospective data exists to guide the management of CC endometrial tumors. A pooled analysis of advanced or recurrent EC Gynecologic Oncology Group trials demonstrated decreased response rates to chemotherapy and PFS as well as increased risk of death for CC histology. Overall response rates to chemotherapy for CC histology was 32% as compared to 44% for serous or endometrioid histologies. Tumors with at least 10% of CC histology demonstrate an estimated odds of response of 0.52 ($p<0.05$). This same decrease in response is not seen when considering mixed tumors with small proportions of serous histology highlighting the poor prognosis of clear cell tumors and need for therapies targeted to improve outcomes in this population [20].

2.1.2 Ovarian cancer

Epithelial ovarian cancer (EOC) traditionally demonstrates exquisite chemo-sensitivity in the front line setting and results in the majority of patients experiencing a complete response at the conclusion of planned cytotoxic chemotherapy and surgery. Despite this, approximately 80% of patients will recur within the first 3 years of diagnosis and once recurred, their disease is no longer curable. In addition, EOC consists of multiple histologic subtypes, including high-grade serous (70-80%), endometrioid (10%), clear cell (10%), and mucinous (3%); and these subtypes usually have different patterns of molecular biology, response to therapy, and prognosis [21]. New and more targeted approaches to the treatment of recurrent ovarian cancer are desperately needed to improve outcomes.

Historically, less common epithelial ovarian cancer histologic subtypes, such as clear cell and endometrioid demonstrate decreased responsiveness to standard cytotoxic chemotherapy. Due to their infrequent numbers, these tumor subtypes are commonly grouped into clinical trials with predominately high-grade serous histology making evaluation of optimal regimens for these selected subtypes of EOC difficult. In a study evaluating molecular profiles of ovarian tumors, *ARID1A* mutations occurred in 46% of clear-cell and 30% of endometrioid ovarian carcinomas, but none of the high-grade serous ovarian carcinomas [22]. Similarly, researchers found that *ARID1A* mutations could be identified in only 10 out of 154 (~6%) patients with high-grade serous ovarian carcinomas [23]. Treatment strategies targeted to *ARID1A* mutated tumors have not been reported and further investigation is warranted [24]. As in endometrial cancer, ovarian clear cell carcinoma (OCCC), particularly OCCC harboring *ARID1A* mutation carries a poor prognosis. In the frontline setting, OCCC demonstrates a response rate of only 30% to platinum-based chemotherapy as compared to approximately 70% seen in high grade serous tumors [25].

2.2 Emerging roles of PARP inhibitors on cancer treatment

Robust data exists demonstrating survival benefit of PARP inhibitors in cancers, particularly ovarian cancer, with defects in the homologous recombination DNA repair system, regardless of the *BRCA* mutational status [26, 27].

2.2.1 Rationale for PARP inhibitors in ARID1A mutated endometrial and ovarian cancer

ARID1A is a subunit of highly conserved SWI/SNF chromatin remodeling complex responsible for repositioning nucleosomes to modulate DNA accessibility to cellular processes involved in chromatin structure. It functions as a tumor suppressor gene by interacting with ATR at sites of double stranded DNA breaks. If *ARID1A* function is lost, it leads to impaired G2/M checkpoint activation and renders cells sensitive to double stranded break-inducing therapies, i.e. PARP inhibitors [28-30]. Prior preclinical studies correlate *ARID1A* mutations with increased sensitivity of cancer cells to PARP inhibitors [31].

Endometrial cancer frequently shows defects in the homologous recombination pathway including mutated *ARID1A*, somatic mutations in *PTEN*, TP53 genes, and PI3K-AKT pathway, especially in EC with POLE-ultramutated, MSI-hypermutated, and copy-number low tumors, indicating the therapeutic potential of PARP inhibitors on EC [18, 32]. Preclinical studies have shown promising anticancer activity of PARP inhibitors against endometrial cancer cell growth [33-35]. An *in vivo* study in animal model demonstrated the therapeutic efficacy of PARP inhibitors in mice bearing human endometrial cancer. The study found that a low estrogen environment could compromise the homologous recombination DNA repair pathway and enhance anticancer effect of olaparib in

mice model bearing *PTEN*-null EC [36]. Furthermore, case reports showed clinical benefit of PARP inhibitor in patients with metastatic and recurrent EC with *PTEN*-deficient or *BRCA* mutation [37, 38]. These data suggest that endometrial cancer with defects in DNA repair, such as *ARIDA* mutations, may be more sensitive to PARP inhibitors.

The clinical benefit of PARP inhibition on ovarian cancer have been reported in multiple landmark trials particularly among patients with *BRCA1/2* germline or somatic mutations or HRD tumors. In the PRIMA study comparing maintenance niraparib vs placebo, maintenance treatment with niraparib resulted in an improvement in median progression-free survival (mPFS) of 10.4 to 21.9 among HRD patients and 8.2 to 13.8 among the overall patients, comparing to placebo control [39]. In PAOLA-1/ENGOT-ov 25 trial, all patients received paclitaxel, carboplatin and bevacizumab and if they were in response following 6 cycles they were randomized to bevacizumab + placebo or bevacizumab + olaparib. The results showed that the median PFS was 22.1 months with olaparib plus bevacizumab vs 16.6 months with placebo plus bevacizumab [40, 41]. In VELIA (GOG 3005) trial comparing veliparib maintenance vs placebo, the benefit of veliparib led to an improved mPFS from 22 to 34.7 months among the *BRCA* associated cancers; and 17.3 to 23.5 months among the overall population [42].

2.3 Combination niraparib and bevacizumab

Cancers with *ARID1A* mutation have also have increased sensitivity to anti-angiogenic therapy [28] *ARID1A* deficient hepatocellular carcinoma has been shown to have higher vessel density and enhanced angiogenesis by virtue of ectopic Ang2 production, leading to profound sensitivity to Ang2 specific inhibitors such as sorafenib [43] *ARID1A* loss may regulate other oncogenic pathways such as increased PD-L1, PIK-3CA activating mutations, or DNA methylation [30] Overexpression of VEGF, which is commonly observed in endometrial and cervical cancers, may lend to further sensitivity to bevacizumab and other anti-angiogenic therapies.

In order to induce sensitivity to PARP inhibition, strategies are needed to induce HRD within tumors. One demonstrated mechanism of turning an HR proficient tumor into an HRD tumor is via induction of chronic hypoxia with anti-angiogenic agents such as bevacizumab. Induced chronic hypoxia causes translational downregulation of DNA repair which may increase susceptibility to DNA damaging or synthetically lethal agents, like PARP inhibitors, in these hypoxic cells [44]. Based on these rationales and the known efficacy of single agent bevacizumab treatment in both recurrent ovarian and endometrial cancer, this study proposes to evaluate the combination in *ARID1A* mutant recurrent ovarian and endometrial cancer.

2.4 Summary of study medications

Niraparib is a potent, orally active PARP1 and PARP2 inhibitor with FDA approval for maintenance treatment regardless of *BRCA* mutation status for adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Additionally, there is an FDA approval for women with recurrent ovarian cancer that harbors defects in the HR DNA repair pathway or that are driven by PARP-mediated transcription factors. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf).

Previous clinical studies have reported the safety and anti-cancer activity of niraparib monotherapy or combined with VEGF inhibitor bevacizumab on patients with advanced ovarian cancer [2, 3, 45].

AVANOVA (NCT02354131) is phase I/II trial of niraparib versus niraparib-bevacizumab combination in patients with platinum-sensitive epithelial ovarian cancer. Data from phase I dose

escalation study showed that the recommended phase II dose (RP2D) was bevacizumab 15 mg/kg with niraparib 300 mg. The objective response rate was 50%; median PFS was 11.6 (95% confidence interval 8.4-20.1) months [3]. AVANOVA part-2 is a randomized, phase 2, superiority trial comparing niraparib and bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer [2]. A total of 97 patients were randomly assigned 1:1 with 48 to niraparib (300 mg, by mouth, once daily) plus bevacizumab (15 mg/kg, IV, once every 3 weeks) and 49 to single-agent niraparib. The results showed that niraparib plus bevacizumab significantly improved PFS compared with niraparib alone (median PFS 11.9 months vs 5.5 months, respectively; adjusted hazard ratio [HR] 0.35 [95% CI 0·21-0.57], p<0·0001). Grade 3 or worse adverse events occurred in 31 (65%) of 48 patients who received niraparib plus bevacizumab and 22 (45%) of 49 who received single-agent niraparib. The most common grade 3 or worse adverse events in combination group were anemia (15%), thrombocytopenia (10%), and hypertension (21%). Niraparib plus bevacizumab was associated with increased incidence of any-grade proteinuria (21% vs 0) and hypertension (56% vs 22%) compared with niraparib alone [2].

Additional data for safety of niraparib and bevacizumab comes from the OVARIO trial (NCT03326193) which was a phase 2 trial of bevacizumab and niraparib in maintenance therapy following front line platinum based therapy for ovarian cancer [46]. This single arm study of 105 patients has reported promising results of efficacy as well as safety. Of the 105 patients with advanced ovarian cancer who achieved complete or partial response to platinum-based chemotherapy, 49% had a history of hypertension – which is the toxicity most likely to overlap. The 12-month PFS rate was 75% in the intention to treat cohort, 88% in HRD and 66% in HR proficient patients. Twenty-five percent of patients had treatment emergent adverse events requiring treatment discontinuation, 71% with dose reduction and 81% with interruption. Treatment emergent adverse events in ≥10% of grade 3 or 4 included thrombocytopenia (37%), anemia (32%), hypertension (25%) and neutropenia (12%) [46]. These AEs are primarily niraparib driven with the exception of hypertension which can be managed with medication adjustment.

The TOPACIO/KEYNOTE-162 trial (NCT02657889) are phases 1 and 2 studies of niraparib plus pembrolizumab in patients with advanced or metastatic triple-negative breast cancer (TNBC) or recurrent ovarian carcinoma, irrespective of BRCA mutation status [26]. The recommended phase 2 dose was 200 mg of oral niraparib once daily and 200 mg of intravenous pembrolizumab on day 1 of each 21-day cycle. Among 60 evaluable patients with ovarian cancer, the objective response rate (ORR) was 18% (90% CI, 11%-29%), including 3 (5%) with confirmed complete responses and 8 (13%) with confirmed partial responses. The ORRs were consistent across subgroups based on platinum-based chemotherapy sensitivity, previous bevacizumab treatment, or tumor BRCA or homologous recombination deficiency (HRD) biomarker status. However, median duration of response was not reached (range, 4.2 to ≥14.5 months) [26].

The benefit of niraparib treatment has not been limited to ovarian cancer. In a phase I dose-escalation study (NCT00749502), 100 patients with advanced solid tumors were treated with niraparib single agent (30mg~400mg, by mouth, once daily). Antitumor activity was also reported in breast cancer with BRCA1/2 mutation carriers and sporadic high-grade serous ovarian cancer, non-small-cell lung cancer, and prostate cancer [47]. A phase II trial of niraparib single agent maintenance therapy on advanced endometrial cancer (NCT04080284) is currently

ongoing.

2.5 Rationale for this study

This randomized, Phase II basket trial proposes to evaluate the efficacy and safety of niraparib and niraparib + bevacizumab combination in patients with recurrent and advanced endometrial and/or ovarian cancer with mutated *ARID1A*. Studies reported that *ARID1A* mutation was identified in 27.45% of endometrial cancer tumor tissues [48], and 30%~46% of endometriosis associated and clear cell ovarian carcinomas [22]. A meta-analysis demonstrated the clinical significance of *ARID1A* in endometrium-related gynecological cancers; negative *ARID1A* expression predicted shorter PFS (HR, 1.84; 95%CI, 1.32-2.57, P = 0.000) in patients with endometrium related gynecological cancers [19]. ARID1A genes encode DNA-targeting subunits and play important role in regulating the DNA damage checkpoint [49]. ARID1A deficiency impairs DNA repair and sensitizes cancer cells to PARP inhibitors *in vitro* in cell culture and *in vivo* in animal model bearing various types of malignancies including endometrial cancer and ovarian cancer [28, 31]. These data suggest a potential therapeutic strategy and biomarker for using PARP inhibitors in patients with *ARID1A*-mutant tumors.

Both niraparib and bevacizumab are FDA approved agents for treatment of various types of malignancies, but endometrial cancer is not yet in the indication list although bevacizumab is NCCN listed for endometrial cancer. Research is needed to explore the novel strategy of combining niraparib and bevacizumab in patients with endometrial cancer. Pre-clinical studies found that PARP inhibitors can inhibit tumor angiogenesis by decreasing the activity of critical pro-angiogenic factors such as vascular endothelial growth factor (VEGF) [50]. The combination of PARP inhibitors and anti-VEGF agent bevacizumab has potential to produce a synergistic anticancer effect in cancer treatment [51]. Indeed, the FDA has recently approved PARP inhibitor olaparib plus bevacizumab as maintenance treatment for patients with ovarian cancer with homologous recombination deficiency (HRD) (refer to link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf). However, the benefit of niraparib and bevacizumab combination on ovarian cancer with *ARID1A* mutation remains unknown and needs further investigation.

In a phase II study of bevacizumab monotherapy, 56 patients with recurrent or persistent endometrial cancer were enrolled and treated with bevacizumab 15 mg/kg intravenously every 3 weeks [11]. Among evaluable 52 patients, 7 patients (13.5%) achieved objective tumor responses (one complete response and six partial responses; median response duration, 6.0 months), and 21 patients (40.4%) survived progression free for at least 6 months. Median PFS and overall survival times were 4.2 and 10.5 months, respectively [11]. The additional benefit of bevacizumab combined with chemotherapy for advanced or recurrent endometrial cancer was observed in a randomized phase II trial (NRG Oncology/GOG 86P); median overall survival (OS) was significantly improved in patients receiving paclitaxel and carboplatin plus bevacizumab compared with historic control treated with paclitaxel and carboplatin (36 versus 23 months) [52]. We hypothesize that niraparib and bevacizumab combination may produce a synergistic anticancer effect in patients with advanced and/or recurrent endometrial and ovarian cancer with an *ARID1A* mutation.

Our research group has generated early data to support this concept. In a single arm, phase 2 of rucaparib and bevacizumab in recurrent endometrial cancer, eligible patients were treated with rucaparib 600mg PO BID and bevacizumab 15mg/kg IV once every 3 weeks. The ORR in all comers was less than the preset bar to proceed from first to second stage accrual. (Unpublished data). However, the patients who had clinical benefit almost all had *ARID1A* mutations. The

preliminary data showed that the rate of *ARID1A* mutation in recurrent endometrial cancer was 33% (6 of 18 patients tested). The rate of objective response (33%) and 6-month PFS (66.7%) was higher among 6 subjects with *ARID1A* mutations as compared to the entire study population (10.7% and 21%, respectively). These data suggest that patients with *ARID1A* mutated endometrial cancer may be more sensitive to niraparib (PARP inhibitor) and bevacizumab combination therapy. Because ARID1A mutations are common in endometriosis associated ovarian cancer, we hypothesize that niraparib and bevacizumab combination may improve clinical benefit in patients with endometriosis associated ovarian cancer as well. We aim to investigate preliminary anti-cancer response of single agent niraparib and niraparib + bevacizumab combination in patients with endometrial cancer or ovarian cancer with *ARID1A* mutation in this phase 2 basket trial. Our long-term goal is to conduct a phase 3 study to further confirm the efficacy of niraparib and niraparib + bevacizumab in a large patient population.

2.5.1 Rationale for randomized study

Clinical studies in platinum-sensitive recurrent ovarian cancer with high-grade serous or endometrioid histology showed that niraparib plus bevacizumab significantly improved PFS and objective response compared with niraparib alone. However, combination of niraparib and bevacizumab was associated with increased incidences of adverse events, especially proteinuria and hypertension [2]. In addition, ovarian clear cell carcinoma (OCCC) harboring *ARID1A* mutation demonstrates a low response rate of only 30% to platinum-based chemotherapy as compared to approximately 70% seen in high grade serous tumors [25]. These data suggested that the benefit and risk of niraparib plus bevacizumab on endometrioid or OCCC harboring *ARID1A* mutation remains unclear.

This open label, randomized phase II basket trial aims to evaluate the benefit and safety of niraparib single agent or niraparib plus bevacizumab in patients with endometrial and/or ovarian cancer with mutated *ARID1A*. Eligible subjects will be enrolled by randomized allocation to receive either niraparib single agent or niraparib plus bevacizumab.

2.5.2 Rationale for correlative studies

We will assess PDO response to DNA damage induced by study treatment. Both HR and non-homologous end-joining (NHEJ) pathways will be analyzed. Because all patients will receive niraparib, we have chosen to focus primarily on HR and NHEJ rather than Alt. NHEJ. Gamma H2AX foci serve as an indication of DNA double-strand breaks (DSB's) [53], RAD51 foci serve as an indicator of HR, and a p53-binding protein 1 (53BP1) foci assay will serve as a potential indicator of NHEJ [54]. While more specific assays for NHEJ exist, they are particularly difficult to perform in primary human cells, particularly PDOs. As such, we will also use therapeutic interrogation to decipher DNA damage deficiencies including Carbo/Pac and inhibitors of CHK1, EZH2, and ATR. PDO mRNA expression levels of all proteins involved in both HR and NHEJ will be analyzed as will results from any genetic testing performed on patients enrolled is this study.

The study of the balance between HR and NHEJ is important for the prediction of treatment response upon inhibition of these pathways in various genetic backgrounds – it is important to ensure that this balance is tipped in favor of tumor response, particularly when investigating synthetic lethal combination therapy. The overall hypothesis is that PDOs can be used to rapidly screen for these synthetic lethal combinations to predict response while providing insight into the molecular crosstalk between HR and NHEJ. In addition, using PDO response itself as a

functional assay has been shown to more accurately predict response to PARPi when compared to NGS measures of HRD. We hypothesize that this is likely to be true regardless of the type of DNA damage response deficiency that exists, HR or NHEJ.

2.6 Risks and benefit assessment

2.6.1 Known potential risks for niraparib

Most common adverse reactions (incidence ≥10%) in patients who received niraparib monotherapy were nausea, thrombocytopenia, anemia, fatigue, constipation, musculoskeletal pain, abdominal pain, vomiting, neutropenia, decreased appetite, leukopenia, insomnia, headache, dyspnea, rash, diarrhea, hypertension, cough, dizziness, acute kidney injury, urinary tract infection, and hypomagnesemia.

Most common adverse reactions incidence (incidence >10%) in patients who received bevacizumab monotherapy include epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

As reported in a randomized phase 2 study, niraparib plus bevacizumab was associated with increased incidences of any-grade proteinuria (21% vs 0) and hypertension (56% vs 22%) compared with niraparib alone [2].

2.6.2 Known potential benefits for niraparib

Niraparib is a PARP1/2 inhibitor with FDA approval for maintenance treatment of adult patients with epithelial ovarian cancer. Bevacizumab is a VEGF inhibitor with FDA approval for the treatment of adult patients with various types of malignancies. In Feb 2021, FDA approved niraparib combined with chemotherapy drugs for the treatment of adult patients with epithelial ovarian cancer. A randomized phase 2 trial showed that niraparib plus bevacizumab significantly improved progression-free survival compared with niraparib alone (median progression-free survival 11.9 months vs 5.5 months) in patients with high-grade serous or endometrioid platinum-sensitive recurrent ovarian cancer [2]. The benefit of niraparib and bevacizumab combination on endometrial cancer and/or ovarian cancer with *ARID1A* mutation remains unknown and will be investigated in this study.

2.6.3 Assessment of potential risks and benefits

Patients with endometrial cancer or ovarian cancer harboring *ARID1A* mutation have early recurrence of tumor with a poor prognosis [20, 55]. Treatment strategies targeting to ARID1A have not been reported [24]. Our preliminary data indicated that PARP inhibitor combined with bevacizumab could improve anticancer efficacy in patients with recurrent endometrial cancer with *ARID1A* mutations. The investigators in this study will closely monitor and manage the potential adverse events associated with niraparib and bevacizumab combination. We anticipate that niraparib and bevacizumab combination treatment will have tolerable safety and bring benefit to patients with endometrial cancer or ovarian cancer with *ARID1A* mutation.

3 STUDY OBJECTIVES AND ENDPOINTS

This is a two-arm, randomized, phase 2 basket study of niraparib (arm 1) and niraparib + bevacizumab combination (arm 2) in patients with advanced or recurrent endometrial or ovarian cancer with mutated *ARID1A*. Enrollment in each arm will be stratified by disease site.

3.1 Primary objectives

- To estimate the proportion of patients with recurrent endometrial cancer with mutated *ARID1A*, who have objective tumor response (complete or partial), to the combination treatment of niraparib and bevacizumab and to monotherapy niraparib
- To estimate the proportion of patients with recurrent ovarian cancer with mutated *ARID1A*, who have objective tumor response (complete or partial), to the combination treatment of niraparib and bevacizumab and to monotherapy niraparib

3.2 Secondary objectives

- To determine the nature and degree of toxicity of each regimen in study subjects.
- To estimate the proportion of subjects with recurrent endometrial cancer or ovarian cancer with mutated *ARID1A*, who survive progression-free for at least 6 months, treated with each regimen.
- To estimate the progression-free survival (PFS) of subjects with recurrent endometrial cancer or ovarian cancer with mutated *ARID1A* treated with each regimen.

3.3 Translational objectives

- To obtain fresh tumor tissue pre-dose in a subset of patients to determine whether patient-derived organoid (PDO) response after treatment correlates with patient response and PFS.
- To determine the degree of and ability to respond to DNA damage by analyzing both HR and NHEJ pathways, including RAD51 foci formation assay, Gamma *H2AX* staining and a 53BP1 foci assay in PDOs.
- To evaluate correlation between tumor ARID1A protein expression by IHC and tumor *ARID1A* mutation determined by next generation sequencing.
- To obtain a serum sample for exosome isolation to determine miRNA signatures that predict response to therapy.
- To correlate mutations in DNA damage repair pathway genes (somatic and germline) with tumor response.

3.4 Study endpoints

Primary endpoint

- Objective response rate as measured by RECIST version 1.1 for each individual patient as measured by best response with disease assessments every 8 weeks prior to disease progression or unacceptable toxicity.

Secondary endpoints

- Number and percentage of patients with ≥grade 3 adverse events.
- PFS, as determined by the number of days from the start of study treatment to date of progression or death or last time of follow up.
- Rate of 6-month PFS.

Translational endpoints

- Correlate patient derived organoid response to therapy with tumor response.

4 STUDY POPULATION

4.1 Inclusion criteria

1. Histologically confirmed progressive or recurrent endometrial cancer or ovarian cancer
    - Patients with previously identified *ARID1A* tumor mutations.
        - Note: Any *ARID1A* mutation is eligible and any CLIA Next generation sequencing test is allowable for eligibility.
2. Histological tissue specimen (tissue block or 8-10 unstained slides) must be available (specimen can be the sample at diagnosis or taken at relapse). If unavailable, then patient should agree to have fresh tumor biopsy for histological assessment unless not medically eligible. If unable to be safely biopsied and patient desires enrollment, patient may be enrolled per MM discretion.
3. A subset of patients (15 ovarian samples and 15 endometrial samples) should agree to have tumor biopsy for translational studies assessment. If unable to be safely biopsied and patient desires enrollment, they may be enrolled per medical monitor discretion. Tissue collection for the translational biopsies will continue until a total of 30 viable samples have been collected (15 endometrial and 15 ovarian). Patient agrees to have blood draw at pre-treatment and post-treatment (end of study) for translational studies assessment.
4. Patients who have progressed after ≥1 prior platinum containing regimen.
5. Measurable disease by RECIST criteria v1.1.
6. ECOG performance status 0 or 1.
7. Life expectancy > 12 weeks.
8. Adequate bone marrow, hepatic and renal function as defined by the following values within 14 days prior to starting treatment:
    - Hemoglobin ≥ 9 g/dL Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
    - Platelet count ≥ 100 x 10^9/L with no platelet transfusion in the past 28 days.
    - Creatinine clearance ≥50 mL/min (estimated using Cockcroft-Gault equation).
    - Total bilirubin ≤1.5 x institutional upper limit (ULN) (where bilirubin rise > 1.5 x ULN due to Gilbert's syndrome a conjugated bilirubin ≤1.5 x ULN is required).
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5 x ULN if no demonstrable liver metastases or ≤5 times ULN if patient has documented liver metastases.
9. No significant medical illness which in the opinion of the Investigator would preclude entry to study treatment.
10. Women of child-bearing potential who are confirmed NOT to be pregnant. This should be evidenced by a negative urine or serum pregnancy test within 72 hours prior to start of trial treatment. Patients will be considered to be not of child-bearing potential if they are:
    - Post-menopausal - defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments, OR women under 50 years old who have been amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments and have serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and plasma estradiol levels in the post-menopausal range for the institution.
    - Able to provide documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
    - Radiation or chemotherapy-induced oophorectomy or menopause with > 1 year since

last menses.

11. Patient is willing and able to comply with the protocol for the duration of the study. including undergoing treatment and scheduled visits and examinations.
12. Able to swallow, absorb, retain oral medication.
13. Able to provide written, informed consent.
14. Patients must have recovered from any effects of any major surgery and not have an open wound, active ulcer, or fistula.

4.2 Exclusion criteria

1. Patients with localized advanced disease without other measurable lesion and could be treated with curative intent.
2. Other malignancy within the last 5 years that would be expected to impact on overall survival. Prior malignancy with no expected impact on overall survival are allowed.
3. Patients with myelodysplastic syndrome/acute myeloid leukemia history or with features suggestive of MDS/AML.
4. Patients receiving radiotherapy within 2 weeks prior to study treatment.
5. Major surgery within 4 weeks of starting study treatment.
6. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
7. Any previous treatment with PARP inhibitor, including niraparib.
8. Clinically significant (e.g. active) cardiovascular disease, uncontrolled high blood pressure. Uncontrolled high blood pressure defined as values ≥160/100 or symptomatic, refer to CTCAE.
9. Previous Cerebro-Vascular Accident (CVA), Transient Ischemic Attack (TIA) or Sub-Arachnoids Hemorrhage (SAH) within 6 months prior to study treatment.
10. Patients with increased risk of bleeding or history or evidence of hemorrhagic disorders within 6 months prior to study treatment.
11. Resting ECG with QTc > 470 msec on 2 or more time points within a 24-hour period or family history of long QT syndrome
12. Persistent toxicities (Common Terminology Criteria for Adverse Event (CTCAE) > grade 2) caused by previous cancer therapy, excluding alopecia.
13. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
14. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.
15. Pregnant or lactating woman
16. Participation in another clinical study with an investigational product during the chemotherapy course within 30 days prior to study treatment.
17. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

18. Patients with a known hypersensitivity to investigational drugs or excipients.
19. Clinical/radiological evidence of bowel obstruction (e.g. hospitalization) or symptoms of sub-acute bowel obstruction within 6 weeks prior to trial entry

5 SUBJECTS REGISTRATION RANODMIZATION AND ENROLLMENT

Study participants will be recruited from the Gynecologic Oncology clinical practices of four medical centers, including the Stephenson Cancer Center. Patients with progressive or recurrent endometrial cancer or ovarian cancer with previously identified genetic aberrations in ARID1A will be asked by their clinician whether they are interested in speaking with the research team regarding participation in clinical research after discussing plan of regular cancer care. If they agree to the discussion, a research team member will discuss the study and go through the consent form with them. Non-English-speaking patients will have this discussion with an approved medical translator in their primary language. The patients will be given a consent form with adequate time to review and afforded the opportunity to discuss the study with friends and/or family. The participant will be provided a signed copy of the consent for their records.

5.1 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 activated.

5.2 Patients registration randomization and enrollment

Patients must have signed and dated all applicable consents and authorization forms to be registered in the Clinical Trial Management System (CTMS) database, which is sponsored by The University of Oklahoma Stephenson Cancer Center (OUSCC).

Sites must confirm with The University of Oklahoma Stephenson Cancer Center (OU-SCC) that a slot is available before proceeding with consenting any patient by contacting DataIntegrity@ouhsc.edu. A Screening identification (Screening ID) number will be provided by OU-SCC research staff after the patient has been consented. After all screening procedures and assessments have been completed, the study site should complete the Subject Enrollment Form and send along with the required documentation to DataIntegrity@ouhsc.edu, for confirmation of eligibility. The Study ID number will be generated by OU-SCC once eligibility has been confirmed. Once the patient has been provided a Study ID number, only the Study ID number should be used.

Randomization will occur in a 1:1 ratio with the use of a computer-based program.
After all screening procedures and assessments have been completed, and eligibility has been established, the subject will be randomized to receive study treatment of either niraparib monotherapy in Arm 1 or niraparib plus bevacizumab in Arm 2. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm; and patients in each arm will be stratified by disease site of origin (endometrial or ovarian).

Patients must not start protocol treatment prior to registration and enrollment. Patient will start protocol treatment only after pre-treatment evaluation is complete, eligibility criteria have been met and they have been enrolled on the study.

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 study treatment. Evaluable patients are defined in protocol Section 8.3.

6 STUDY DESIGN AND TREATMENT PLAN

6.1 Study design

This is a phase 2 trial of single agent niraparib or niraparib + bevacizumab in patients with recurrent and/or advanced endometrial cancer or ovarian cancer with *ARID1A* mutation. Patients in each arm will be stratified by disease site of origin (endometrial or ovarian). All patients signed informed consent will have baseline CT scan/MRI of the pelvis and abdomen as part of staging. Patients will have baseline laboratory work including CBC, CMP, INR (PT) and urine analysis. ECOG performance score will be calculated at base line.

Eligible subjects will receive study treatment niraparib (200mg or 300 mg based on body weight and blood platelet count, oral, once daily; refer to FDA label at link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf). If enrolled in niraparib + bevacizumab arm they will receive bevacizumab (15 mg/kg, IV on day 1 of each cycle) as described in Section 6.2. The primary endpoint (proportion of ORR) will be evaluated in a Simon's optimum 2-stage design [56].

For the exploratory objectives, 15 endometrial and 15 ovarian baseline tumor tissues at pre-dose will be collected in eligible patients to generate PDOs for evaluation of drug response and response to DNA damage via RAD51 foci formation and H2AX staining as predictive biomarkers for tumor response. In addition, ARID1A level in tumor tissue will be tested by Immunohistochemistry (IHC) staining to correlate to ARID1A mutation identified by NGS. Exosomes will be isolated from patient serum to determine miRNA signatures that predict response to therapy. In addition, the molecular profile by Foundation-One may be standard of care in clinical setting; the aberrant p53 expression, somatic and germline mutations in DNA damage response pathways genes, and mutation in PTEN pathway, and loss of heterozygosity (LOH) will be analyzed and correlated with the clinical outcome if optional data from Foundation-One is available.

6.2 Treatment plan

Study treatment plan are summarized in Table 2.

Table 2 Dose regimen for Niraparib plus Bevacizumab combination therapy in recurrent endometrial cancer or ovarian cancer with mutated ARID1A.

<table>
<tr><th>Arm</th><th>Number of Patients</th><th>Dose of Niraparib</th><th>Dose of Bevacizumab</th></tr>
<tr><td>1
(Single Agent Niraparib)</td><td>14~46 evaluable subjects
(Stratified by endometrial, ovarian cancer)</td><td rowspan="2">200 mg, PO, QD for patients weighing <77 kg (<170 lbs) OR with a platelet count < 150,000/μL.
OR
300 mg, PO, QD for patients weighing ≥77 kg (≥170 lbs) AND a platelet count ≥150,000/μL.</td><td>N/A</td></tr>
<tr><td>2
(Niraparib + Bevacizumab)</td><td>14~46 evaluable subjects
(Stratified by endometrial, ovarian cancer)</td><td>15mg/kg, IV, day 1 every 21 days</td></tr>
<tr><td colspan="4">One cycle = 21 days. Patients will be treated until disease progression or toxicity unless patient withdraws consent.</td></tr>
</table>

Arm 1
The treatment regimen for niraparib single agent is as below.

- Niraparib 200 or 300 mg taken orally, once daily for 21 days per cycle

Arm 2
The treatment regimen for niraparib and bevacizumab is as below.

- Niraparib 200 or 300 mg taken orally, once daily for 21 days
- Bevacizumab 15 mg/kg, IV infusion, on day 1 of each cycle when niraparib is dispensed, once every 3 weeks

One cycle is equal to 21 days.

According to FDA label, the dose of niraparib can be based on body weight and blood platelet count as below:

- For patients weighing <77 kg (<170 lbs) OR with a platelet count < 150,000/μL, the recommended dose is 200 mg taken orally once daily.
- For patients weighing ≥77 kg (≥170 lbs) AND a platelet count ≥150,000/μL, the recommended dose is 300 mg taken orally once daily.

The study treatment will continue unless patients have tumor progression or experience intolerant side effects. The anticancer efficacy including ORR and PFS will be assessed by RECIST v.1.1. The safety of the study treatment will be monitored according to CTCAE v5. Based on FDA label, niraparib and bevacizumab have overlapping toxicity for Hypertension. It

is recommended to monitor blood pressure and heart rate at least weekly for the first two months, then every 3 weeks-cycle during treatment.

6.2.1 Niraparib administration

Patients will be instructed to take their niraparib dose at approximately the same time each day. Niraparib can be taken with or without food. Patients will be advised to swallow each capsule whole and not to chew, crush, or split niraparib prior to swallowing. Bedtime administration may be a potential method for managing nausea.

Doses are considered missed if greater than 12 hours from the normal dosing time. In the case of a missed dose of niraparib, instruct patients to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of niraparib, an additional dose should not be taken.

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 modification or discontinuation for adverse reactions

Study treatment dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., surgery, unrelated medical events, patient vacation, and/or holidays). Re-escalation with niraparib is permitted. Patients should be placed back on study therapy within 28 days of the scheduled interruption for niraparib or bevacizumab, unless otherwise discussed with the Lead Principal Investigator.

Dose interruption or discontinuation of niraparib does not preclude continuation of bevacizumab and vice versa. For instance, if an AE is attributed to niraparib during the study treatment, then bevacizumab will be continued while the niraparib held. While niraparib is held, the patient will continue to receive bevacizumab, be monitored for safety, and will resume niraparib only if toxicity is less than or equal to Grade 1 prior to resuming. If the AE is immune related and attributed to bevacizumab; then niraparib will be continued while the bevacizumab is held.

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

6.3.1 Dose modification for niraparib

Dose interruption of niraparib may be implemented by the Investigator or treating physician at any time, when deemed in the best interest of the patient. See the following sections for permitted duration of interruption prior to required discontinuation from treatment.

6.3.1.1 Niraparib dose modifications for non-hematologic toxicity

Treatment with niraparib must be interrupted for any treatment-related non-hematologic CTCAE Grade 3 or 4 event. Once resolved to baseline (or Grade ≤ 1 if previously normal), the patient may restart treatment with niraparib with a dose level reduction (see **Table 3**) unless prophylaxis is considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made to a

lower dose level, if available, or niraparib dosing should be discontinued. If the toxicity requiring dose interruption has not resolved to baseline or CTCAE Grade ≤ 1 during a maximum 4-week (28- day) dose interruption period, and/or the patient has already undergone a dose reduction to 100 mg QD, the patient must permanently discontinue treatment with niraparib. ***Note that treatment with bevacizumab may continue if discontinuation criteria as outlined in Section 6.3.2 have not been met***.

Table 3: Recommended Dose Modifications for Adverse Reactions

Starting Dose level	**200 mg**	**300 mg**
First dose reduction	100 mg/day (one 100-mg capsule once daily)	200 mg/day (two 100-mg capsules once daily)
Second dose reduction	Discontinue medication.	100 mg/day (one 100-mg capsule once daily)

Table 4: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

Abnormality	**Intervention**
Non-hematologic CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. Resume niraparib at a reduced dose.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue niraparib.
Posterior Reversible Encephalopathy Syndrome (PRES), symptoms include but not limit to headache, vision changes, confusion or seizure with or without high blood pressure)	Discontinue niraparib.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

6.3.1.2 Niraparib Dose Modifications for Hematologic Toxicity

The dose interruption/modification criteria for niraparib for hematologic toxicities will be based on blood counts and are outlined in **Table 5**.

For thrombocytopenia, patients with a platelet count < 100,000/μL must have niraparib interrupted and have blood counts monitored weekly until recovery to ≥ 100,000/μL; upon recovery, niraparib can be resumed at a reduced dose for the first occurrence with once weekly monitoring for 4 weeks to confirm no recurrence of thrombocytopenia.

For Grade 3 or 4 neutropenia or anemia, treatment with niraparib must be interrupted with blood counts monitored at minimum weekly for neutropenia but up to twice weekly if clinically

indicated, and weekly for anemia until recovery to ≤ Grade 1. Niraparib dosing should be resumed with a dose level reduction (see **Table 3**) at that time and the patient monitored once weekly for 4 weeks to ensure the safety of the new dose level. If clinically indicated, use of G-CSF is allowed according to current American Society of Clinical Oncology (ASCO) guidelines [57].

If the hematologic toxicity does not recover to the specified level within 4 weeks (28 days) of dose interruption and/or the patient has already undergone a dose reduction to a minimum dose of 100 mg QD, then niraparib should be discontinued.

Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed.

It is strongly recommended that the patient be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE ≤ Grade 1 within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue niraparib. Note that treatment with bevacizumab may continue following discussion with the Principal Investigator and MM if discontinuation criteria as outlined in Section 6.3.2 have not been met.

The reason for interruption, reduction, or discontinuation of niraparib should be recorded in the eCRF.

Table 5. Management of Hematologic Toxicities

Test complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. Medical and supportive therapy should be optimized for management of toxicities.	
Platelet count < 100,000/μL[b]	First occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. • Resume niraparib at same or reduced dose per Table 3. • If platelet count is <75,000/μL, resume at a reduced dose.
	Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. • Resume niraparib at a reduced dose per Table 3. • Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily. [a]

Neutrophil <1,000/μL or Hemoglobin <8 g/dL	• Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/μL or hemoglobin returns to ≥9 g/dL. • Resume niraparib at a reduced dose per Table 3. • Discontinue niraparib if neutrophils and/or hemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.[a]
Hematologic adverse reaction requiring transfusion or hematopoietic growth factor support	• For patients with platelet count ≤10,000/μL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and /or transfusion at a higher platelet count. • Resume niraparib at a reduced dose.
Confirmed diagnosis of MDS* or AML†	Permanently discontinue niraparib.
*MDS = myelodysplastic syndrome †AML = acute myeloid leukemia	

Abbreviations: CBC = complete blood count.
* If blood counts do not recover within 28 days to normal values (ie, platelets ≥ 100,000/μL, hemoglobin ≥ 9 g/dL, neutrophils ≥ 1,500/μL) niraparib should be discontinued.
a. Dose not to be decreased below 100 mg daily.
b. For patients with platelet count ≤ 10,000/μL, prophylactic platelet transfusion per guidelines should be considered [58, 59]. For patients taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤ 20,000/μL.

6.3.2 Dose modification for bevacizumab

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 per institutional standards. 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, niraparib may be continued if at the discretion of the treating physician, it can be safely done so knowing the possible side effect profile of niraparib. Niraparib may be continued if all treatment parameters have been met, and if side effects of bevacizumab have resolved to baseline or </= grade 1 within 3 weeks and all other treatment parameters have been met. Once bevacizumab is

held, it cannot start until the next cycle of niraparib 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, clinically significant hypotension, or if otherwise clinically indicated. Subjects who experience an NCI CTCAE V5.0 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 ≥ Grade 2: Bevacizumab should be discontinued
- Venous thromboembolic event ≥ grade 4: Bevacizumab should be discontinued
- Venous thromboembolic event ≤ 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≥160 mmHg or DBP ≥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

Ovarian Failure:

- Advise females of reproductive potential of the risk of ovarian failure prior to initiating bevacizumab.

Congestive Heart Failure (CHF):

- Discontinue bevacizumab in patients who develop CHF.

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 ≤ Grade 1 and unlikely to recur with retreatment.

Please refer to bevacizumab FDA label for more detailed information about safety management (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761099s004lbl.pdf).

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 cytopenia should be administered according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

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 (such as reduction in symptoms) with disease progression, the patient may continue treatment after consulting with the Principal Investigator.

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 3 years from the date of enrollment. All patients must also be followed through completion of all protocol therapy.

7 STUDY PARAMETERS

7.1 Therapeutic parameters

All required pretreatment laboratory studies should be done as outlined in the study calendars in Table 1 of Section 1.3.

1. Pre-study scans should be performed within the screening window of 28 days prior to C1D1 to be used in screening assessment.
2. All patients must have a pre-dosing weight taken at every visit, as appropriate.
3. Initial history / physical (H&P) exam and laboratory tests can be used for cycle 1 day 1 (C1D1) if done within 72 hours. The laboratory tests include mandatory tumor sample if no archival sample is available, mandatory pre- and post- blood samples, and an optional tumor pre-treatment sample.

7.2 Biological Sample Collection for Correlative Studies

ARID1A IHC staining will be performed by the SCC Tissue Pathology Core without charge.

For correlative study to be performed by Dr. Andrade's research lab, the tumor tissues at pre-dose in a subset of patients will be collected for generation of PDOs and correlation with patient response post-drug treatment. Both pre-dose and end of study treatment serum samples will be collected from all patients for exosome isolation to identify miRNA's that predict patient response to therapy.

- If an archival tumor tissue sample is not present, patients must agree to have a pre-dose fresh tumor biopsy, after a written consent and prior to study treatment.

- Peripheral blood must be collected at pre- and post- study treatment.

7.2.1 Instruction for tumor tissue collection

For pre-treatment baseline tumor tissue: the tissues need to be retrieved from a fresh biopsy and frozen viably. The fresh biopsy will be taken on patients for translational evaluation until 15 evaluable samples per arm (15 endometrial and 15 ovarian) are obtained. Once this criterion is fulfilled then no further fresh biopsies will be required. It is not mandatory for every participant on study as archival tumor if present will suffice. The patient number, protocol number, specimen code, and collection date (dd/mon/year) should be written on the sample label.

For the fresh tumor biopsy samples, four cores are preferred using the following guidelines:

- The needle used to obtain the core biopsies should be 14-16 gauge.
- It is strongly suggested that core biopsies be image-guided.
- If samples are collected during surgery, rather than by image-guided biopsy, please always be aware that it is important to keep fresh tissues on ice and process them within 2-5 minutes of devascularization to well preserve the nucleic acids and proteins in the fresh tissue samples.
- The required biopsies include at least two core biopsies to be viably frozen. Tissues should be collected at bedside in a 15 mL conical tube containing DMEM/F12 cell culture media supplemented with 10% fetal bovine serum and 5% Penicillin-Streptomycin and immediately placed on ice (to preserve cell survival).

The cores should then be cut into equal sized pieces of approximately $5mm^3$ in size and placed in separate polypropylene cryovials (1 to 2 milliliters in size) containing DMEM/F12 with 10% fetal bovine serum and 10% dimethlysulfoxide (DMSO). The vials should then be placed in a slow freezing container (allowing for a cooling rate of -1 degree Celsius per minute) and placed in a -80 degree Celsius freezer overnight. Vials should then be stored at -190 degrees Celsius (LN_2) until transport to the SCC Biospecimen Core for further processing and distribution.

For *ARID1A* IHC staining to be performed in the SCC Tissue Pathology Core, 3 unstained slides prepared by freshly cut serial sections at 4 to 5 micron thickness per patient are required. Whenever possible, these should be cut from the same block as the slides that are cut and sent to for NGS testing.

For archival FFPE tumor tissue, at least 16 unstained slides will be prepared by freshly cut serial sections at 4~5 micron thickness. Each slide should contain ≥ 100 viable tumor cells plus one original (not recut) H&E Slide for each block used.

7.2.2 Instruction for Blood sample collection and processing

Peripheral blood (one 10-milliliter red-top tube, BD367820 or equivalent) should be collected prior to treatment and at the end of treatment (or after tumor progression) for biomarker assessment. After collection, the whole blood must be allowed to clot for 30 minutes at room temperature, spun at 1,000 to 2,000 x g in a 4-degree Celsius centrifuge for 10 minutes to allow for serum separation and collection. Serum should then be transferred into 2 milliliter screw cap microcentrifuge tubes and immediately frozen at -80°C. The patient number, protocol number, specimen code, and collection date (dd/mon/year) should be written on the sample label.

7.2.3 Sample shipping

Please plan to schedule shipping during weekday from Monday to Wednesday. If you want to ship on Thursday, please check with the shipping company and confirm with the receiver for the arrival time. No packages will be accepted during weekends.

Specimens to be Shipped to SCC Biospecimen Core

Shipping address:

Biospecimen Acquisition Core and Bank
3rd floor, Room 372
Biomedical Research Building,
975 NE 10th Street, Oklahoma City, OK 73104
P: (405) 271-1688
E: scc-biospecimen-core@ouhsc.edu

Required Specimen	Collection Time Point	Shipping comments
Tumor tissue	Fresh, viably frozen pre-treatment biopsy	Ship overnight in dry ice
Tumor tissue	Archival or at pre-treatment biopsy (FFPE specimens)	Ship overnight at room temperature

7.3 Follow up Parameter

Follow-up is required as outlined in Sections 1.3 (Table 1) and 6.7. 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 every 8~9 weeks prior to every odd cycle. Patients will also be seen within 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 28 days prior. Required study procedures are based on the presence or absence of bevacizumab or niraparib related cardiovascular or other toxicities. At the EOT, information collected for subsequent treatments 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 niraparib.

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 every 3 months to be collected for up to 3 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 ≥ 10 mm based on caliper measurement by clinical exam, CT or MRI, or ≥ 20 mm when measured by chest X-ray.

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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 Response Criteria

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. To be assigned a status of complete response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than four weeks after the criteria for response is met.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. To be assigned a status of partial response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than four weeks after the criteria for response is met.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease). To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks.

8.1.4 Definition of Disease Progression

At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

8.1.5 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Principal Investigator.

8.1.6 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

8.1.7 Survival

Survival is the observed length of life from the date of patient enrollment/randomization to death or the date of last contact. Participants without events reported will be censored at the last date patient is known to be alive.

8.1.8 Progression-Free Survival

Progression free survival is defined as the period from the date of patient randomization /enrollment until disease progression, death, or date of last contact. Participants without events reported will be censored at the last disease. Progression will be evaluated by RECIST v1.1 [60].

8.2 Subjective Parameters

The performance status, specific symptoms, and side effects are graded according to the CTCAE V5.0. Of particular interest will be ≥grade 3 adverse events.

8.3 Definition of Evaluable Patients

Per NCI definition, patients whose response to a treatment can be measured because enough information has been collected. In this study, 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 at least 80% of intended 21 days of niraparib, PO, once daily) and complete the first post-treatment CT or MRI for tumor assessment.

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 niraparib will follow after adjustment of SOC per protocol as described in Section 6.3.

9 SAFETY MONITORING AND REPORTING PROCEDURES

The safety plan for patients in this study is based on clinical experience with niraparib and bevacizumab in completed and ongoing studies.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study drugs will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. At-home administration of oral drugs dispensed to patient will be confirmed via pill diary. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in section 6.3.

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern.

9.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment. Guidance for toxicity management are defined in section 6.3 and Tables 3-5.

9.1.1 Reporting Abnormal Labs

Any abnormal labs that are deemed clinically significant by the treating physician must be reported.

9.1.2 Reporting to Sponsor

The principal investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the appropriate IRB(s) and sponsor institute in accordance with CFR 312.32 (IND Safety Reports). All SAEs should be reported on the REDCap database for the study and the MedWatch 3500A form should be attached.

The Sponsor is responsible for reporting to the regulatory authorities per CFR 312.32 (IND Safety Reports).

9.1.3 Reporting to GlaxoSmithKline (GSK)

The Sponsor Institution must report all Serious Adverse Events (SAEs) (serious AESI by default) and all follow up information to GSK on a GSK-specific SAE Report Form with

accompanying coversheet within 24 hours of becoming aware of the initial event or clinically significant follow-up information. The Sponsor Institution must provide a causality assessment and must sign and date all SAE Report Forms. If supporting documentation is included in the submission to GSK (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), Sponsor will redact any patient identifiers (including Medical Record number).

The following reportable events must be submitted to GSK:

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Pregnancies

The Sponsor has the responsibility to monitor the outcome of all pregnancies reported during the Investigator Sponsored Trial. The Sponsor must report all pregnancies associated with GSK product including follow up outcomes to GSK within 24 hours of awareness. Each pregnancy must be reported within 24 hours of becoming aware of the pregnancy using the GSK pregnancy notification form. Pregnancy is not an AE, and therefore does not need to be reported as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported and as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy follow up is reported using the GSK pregnancy follow up form. Any SAE that occurs during pregnancy must be recorded, reported as an SAE (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect), and reported to the Sponsor Institution and GSK within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Contact information for submission of reportable events to GSK:

- Fax: +44-20-8754 7822
  - OR
- E-mail: OAX37649@gsk.com

Post-Study Adverse Events: The sponsor institute / principal investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior study drug exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

Aggregate Reports: The Sponsor will forward a copy of the Final Study Report to GSK upon completion of the Study. The Sponsor will forward a copy of the Publication to GSK upon completion of the Study.

Note: For any aggregated reports, if there were safety concerns associated with GSK products,

the sponsor will provide the draft reports for GSK review and comments prior to submission. For publication, GSK should review the manuscript before submission for publication per contract.

9.1.4 Reporting Suspected Unexpected Serious Adverse Reactions

In compliance with FDA regulations, as contained in 21 CFR 312.64, all Suspected Unexpected Serious Adverse Reactions (SUSARs) must be immediately reported to Stephenson Cancer Center, University of Oklahoma Health Sciences Center (the sponsor for this study) within 24 hours of awareness via the REDCap study database.

The Sponsor is responsible for notifying GSK within 24 hours of awareness of the event to the Sponsor Institute.

Contact information for submission of reportable events to GSK's Case Management Group (Global):

Fax:

+44(0)2081814780OR

E-mail: OAX37649@gsk.com

Specifying:

- PROTOCOL Number and/or Title
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

All SUSARs must be reported to the FDA by the Sponsor within 7 (serious criteria of death or life threatening) or 15 (all other seriousness criteria) days of awareness per 21 CFR 312.32.

Supporting and follow up data: Any supporting or follow up documentation must be sent to Stephenson Cancer Center, University of Oklahoma Health Sciences Center, IRB (as applicable) and FDA when available. The Sponsor is also responsible for notifying GSK about the supporting or follow up data.

9.1.5 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, as applicable:

- Treatment regimen
- 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

MedWatch 3500A is available at
http://www.fda.gov/medwatch/getforms.html

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 patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally GSK team may contact the sponsor/principal investigator for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, site investigators may contact the sponsor at SCC-IIT-Office@ouhsc.edu. Relevant follow-up information should be reported to the sponsor/principal investigator as soon as it becomes available and/or upon request.

9.2 Adverse Event Monitoring

9.2.1 Definitions (per 21 CFR 312.32(a))

Adverse event: "Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with study treatment that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as tumor biopsy).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Life-threatening adverse event or life-threatening suspected adverse reaction: "An adverse event or suspected adverse reaction is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death."

Serious adverse event or serious suspected adverse reaction: "An adverse event or suspected

adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

Suspected adverse reaction: "Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."

Unexpected adverse event or unexpected suspected adverse reaction: "An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation."

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCA version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

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
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward)
- Overdose of study drugs (niraparib or bevacizumab) or concomitant medication

unless the event meets SAE criteria (eg, hospitalization). However, overdose should be recorded and reported as overdose, if associated with adverse events, the AEs should be reported as AEs or SAEs per AE and SAE definition.

- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event.
- Events that meet the SAE criteria and occur after informed consent, but before the first dose of niraparib, which are considered unrelated to screening procedures.

9.2.2 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 a product or program, for which ongoing monitoring and rapid communication can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor to other parties (eg, regulators) might also be warranted.

Serious AESIs and follow up information must be reported to GSK within 24 hours of becoming aware of the initial event or follow-up information. Others shall be sent within thirty (30) calendar days.

Adverse Events of Special Interest for Niraparib

The adverse events of special interest for niraparib are summarized in tables 2-4 and detailed information can be found in niraparib Investigator's Brochure.

9.2.3 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

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

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

9.2.4 Pregnancy or Breastfeeding

If a patient becomes pregnant or breastfeeding while receiving study drugs or within 5 months after the last dose of study treatment, a report should be completed and expeditiously report to sponsor/principal investigator. Follow-up to obtain the outcome of the pregnancy should also occur.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported to sponsor/principal investigator, as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the niraparib or bevacizumab should be reported to sponsor/principal investigator as an SAE.

Pregnancy reports: While such reports are not serious AEs or ADRs (Adverse Drug Reactions) per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Sponsor/Principal investigator within 24 hours of the awareness date using the applicable safety report form provided. Meantime, the sponsor must

report all pregnancies associated with GSK product including follow up outcomes to GSK within 24 hours of awareness. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

9.3 Documenting Adverse Events

All AEs information must be documented on the case report form. Additional follow-up information (e.g., test results, autopsy, and discharge summary) may be obtained to supplement AE reports. A copy of all initial and follow-up reports will be included with the patient's study files.

9.3.1 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis versus Signs and Symptoms: If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths: All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

Preexisting Medical Conditions: A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Hospitalizations for Medical or Surgical Procedures: Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

9.4 Causality Assessment of Adverse Events

The relationship between an AE and the study drug will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions.

An AE will be considered associated with the use of study drug if there is a reasonable possibility that the AE may have been caused by the study drug. This definition applies to those AEs that are considered definitely, probably, and possibly related to the use of the study drug:

Definitely Related: An AE that follows a temporal sequence from administration of the study drug; follows a known response pattern to the study drug; improves after stopping the study drug (positive dechallenge) and reappears after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the patient's clinical state or by other therapies

Probably Related: An AE that follows a reasonable temporal sequence from administration of the study drug; follows a known response pattern to the study drug; improves after dechallenge; and cannot be reasonably explained by the known characteristics of the patient's clinical state or by other therapies.

Possibly Related: An AE that follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug but could have been produced by the patient's clinical state or by other therapies.

An AE may be considered not associated with the use of study drug if there is not a reasonable possibility that the AE may have been caused by the study drug. This definition applies to those AEs that are considered not related to the use of the study drug:

Not Related: An AE assessed as not related to study drug is defined as an AE for which sufficient information exists to indicate that the etiology is unrelated to the study drug. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence after administration of the study drug.
- The AE is readily explained by the patient’s clinical state or other therapies.
- Negative dechallenge—the AE does not abate upon dose reduction or cessation of therapy (assuming that it is reasonable to expect abatement of the AE within the observed interval).

In addition, the relationship between an AE and the study drug may be determined by the Investigator on the basis of his or her clinical judgment and the definitions using GSK reporting guidelines:

Related: There is a reasonable possibility of a causal relationship between the medicinal product and AE, i.e. there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated

Not Related: A causal relationship between the medicinal product and the AE cannot be established, based on consideration of factors described above.

If a site is using 5 categories, the AEs must be grouped into one of two categories for reporting purposes. An AE considered definitely related, probably related, or possibly related will be reported under related. If an AE is considered unlikely related or unrelated, it will be reported as unrelated.

9.5 Severity Assessment of Adverse Events

Severity of AEs will be graded according to the CTCAE Version 5.0.

Adverse events not included in the CTCAE, Version 5.0 must be graded as follows: Mild, Moderate, Severe, Life-threatening, and Fatal according to the following definitions:

- Mild: The AE is noticeable to the patient but does not interfere with routine activity.
- Moderate: The AE interferes with routine activity but responds to symptomatic therapy or rest.
- Severe: The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- Life-threatening: The AE places the patient at risk of death at the time of the event.
- Fatal: The AE results in the death of the patient.

9.6 Study Monitoring

All aspects of the study will be carefully monitored at periodic intervals throughout the study per FDA/ICH guidance "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry" dated March 2018". All Case Report Forms (CRFs) will be up to 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for a select group of patients per the study-specific monitoring plan. The monitoring visits provide the PI with the opportunity to evaluate the progress of the study, to verify appropriate consent form procedures, review drug accountability and to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records and to assure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

Furthermore, this study will fall under the purview of the Stephenson Cancer Center Data Safety Monitoring Committee (DSMC).

9.7 Reporting Product Complaints for GSK Products

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the Sponsor Institution or qualified designee to GSK within 1 working day of first becoming aware of the possible defect to GSK QA at gsk-rd.complaints@gsk.com . The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product and batch number quality complaint.

9.8 Data Disclosure and Patient Confidentiality

Patient medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to patients in this study will identify each patient only by their initials and number. Medical information resulting from a patient's participation in this study may be given to the patient's personal physician or to the appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency inspectors, the clinical trial office auditors and monitors, and the Institutional Review Board (IRB).

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain patient confidentiality. All study records will be kept in a locked file cabinet or other secured area. All computer entry and networking programs will be identifiable only by coded numbers. Patient personal medical information may be reviewed by representatives of the Sponsor, of the IRB, or of regulatory authorities in the course of monitoring the progress of the clinical trial. Every reasonable effort will be made to maintain such information as confidential.

10 STATISTICS

10.1 Sample size justification

The primary endpoint for this phase 2 trial is to estimate the objective response rate (complete or partial) in subjects with recurrent and/or advanced endometrial cancer or ovarian cancer with mutated ARID1A, who receive combination treatment of niraparib and bevacizumab as compared to monotherapy niraparib.

There is no published clinical data available for tumor response of niraparib monotherapy in EC. The published data from GOG -229E will be used as historical control for bevacizumab monotherapy in EC, which revealed an ORR of 13.5% [11]. Based on the preliminary data from our group, a phase II trial of rucaparib (PARP inhibitor) and bevacizumab in recurrent endometrial cancer showed the ORR is 33.3%. These rates will be used in the sample size calculation.

AVANOVA part-2 trial evaluated the effect of niraparib 300 mg alone or combined with bevacizumab in patients with platinum-sensitive recurrent ovarian cancer of high-grade serous or endometrioid histology [2]. In the intention-to-treat population, the proportion of patients achieving a confirmed objective response was higher with combination therapy (60%; 95% CI 45–74) than with niraparib alone (27%, 95% CI 1.79–9.97), p=0·001). In the frontline setting, OCCC demonstrates response rates of only approximately 30% [25]. It is to be expected that the response rate in the recurrent setting is lower [61]. However, the anticancer effect of niraparib combined with bevacizumab in patients with recurrent ovarian cancer with mutated ARIDIA remains unknown and is to be investigated in this study. The published data from TOPACIO/KEYNOTE-162 trial showed that the ORR of niraparib plus pembrolizumab was 13% in patients with platinum-refractory ovarian cancer [62]. These data may also be used in the sample size calculation for this basket trial.

The study hypothesis will be evaluated in a Simon's optimum 2-stage design [56]. This will be used to decide whether there are sufficient numbers of patients with objective responses to continue the 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).

The study is a, phase 2 trial, with 80% power, a one-sided level of significance equal to 0.05, a historical RR of 13%, and a hypothesized improvement to 30% RR with either single agent niraparib or combination niraparib and bevacizumab. We will use a Simon's two-stage design for both treatment arms. In the first stage of both treatment groups, we will enroll 14 evaluable patients and will terminate the study early for futility if 2 or fewer patients experience a response. Otherwise, we will enroll an additional 32 evaluable patients for a total of 46 evaluable per group. At the end of the trial, we will conclude this combination is better than historical controls if 10 or more have a response. Allowing for up to 15% dropout and non-evaluable patients, we will enroll up to 55 patients for 46 evaluable patients per treatment arm for a total enrollment of 110. Patients warranting replacement are those who are not evaluable (refer to section 8.3 for Definition of Evaluable Patients).

10.2 Data analysis plan

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, quantile, and range as appropriate, for continuous variables.

Toxicities and adverse events will be summarized by attribution and grade using frequencies and relative frequencies.

The primary outcome, ORR (complete and partial response for at least 8 weeks) will be summarized as the proportion (and 95% CI based on Clopper-Pearson method) of patients with a tumor response. Unadjusted and adjusted logistic regression will be used to analyze ORR.

The assessments for tumor response will be performed by CT or MRI every 8 weeks and for all patients treated in the study.

PFS is defined as the period from the date of study randomization until objective disease progression, or death, or date of last contact or to the date of censoring (dropout, end of study or death). The proportion of evaluable subjects with PFS for at least 6 months will be calculated and compared between each treatment arm. Unadjusted and adjusted analysis will be conducted for all outcomes. For PFS, Kaplan Meier and Cox proportional hazards regression analysis will be conducted. Demographic variables will be used in the adjusted analysis.

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 (ORR and PFS) will be assessed by Chi-square or log-rank test as appropriate.

10.3 Accrual goal

This is a two-arm, multi-center, phase II study. A total of 92 evaluable patients stratified by disease site will be enrolled, with 46 in each arm within 4 medical centers including the Stephenson Cancer Center as the primary site. Based on our previous experience with a similar patient population, we anticipate enrollment of 1~2 patients in arm 1, and 1~2 patients in arm 2, per month in our site and additional 2~3 eligible patients per month in other participating sites.

The planned sample size is 46 evaluable patients in arm 1, and 46 patients in arm 2. To account

for non-evaluable patients, the study may enroll up to a maximum of 55 patients in each arm to obtain an evaluable 46 patients. It is anticipated that this study will require approximately 24 months of accrual assuming an accrual rate of 4~5 patients per month in four sites. It is estimated that 48 months of post accrual follow-up will be necessary to observe the minimum number completed cycles and to assess the time-to-event variables, including duration of response and PFS.

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 auditing all data for this study.

12.2 Electronic Database and Case Report Forms

The Principal Investigator and designated team developed an electronic database (REDCap) and case report forms for study data entry. All study data is recorded into REDCap database

sponsored by OU-SCC and 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 even of an audit.

12.3 Record Retention

Investigator will retain all research documents and case report forms at study site per institutional policy.

13 ETHICAL 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 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 follow ICH GCP, local regulatory requirements, and legal requirements. 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, GSK, and IRB.
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. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

13.4 Institutional Review Board or Ethics Committee

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already

identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by GSK per their institutional standards (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

13.5 Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

13.6 Confidentiality

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, GSK representatives, and the IRB for each study site, if appropriate.

13.7 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 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. Any deviation from the protocol must be important for the rights, safety, and well-being of the trial participants and reliability of the results.

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