STATISTICAL ANALYSIS PLAN

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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Abbreviations

AE	Adverse event
CR	Complete response
PFS	Progression free survival
PR	Partial response
SAP	Statistical analysis plan

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1. **Objectives**
    a. **Primary Objectives**
        i. To estimate the proportion of patients with recurrent endometrial cancer with mutated ARID1A, who have objective tumor response (complete or partial response (CR or PR)), to the combination treatment of niraparib and bevacizumab and to monotherapy niraparib
        ii. 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

    b. **Major Secondary Objectives**
        i. To determine the nature and degree of toxicity of each regimen in study subjects.
        ii. 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.
        iii. To estimate the progression-free survival (PFS) of subjects with recurrent endometrial cancer or ovarian cancer with mutated ARID1A treated with each regimen.

    c. **Translational Objectives**
        i. 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.
        ii. 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.
        iii. To evaluate correlation between tumor ARID1A protein expression by IHC and tumor ARID1A mutation determined by next generation sequencing
        iv. To obtain a serum sample for exosome isolation to determine miRNA signatures that predict response to therapy.
        v. To correlate mutations in DNA damage repair pathway genes (somatic and germline) with tumor response.

2. **Endpoints**
    a. **Primary Endpoint**
        i. 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.
    b. **Secondary Endpoints**
        i. Toxicity as defined by incidence of patients with ≥grade 3 adverse events.
        ii. 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.
        iii. Rate of 6-month PFS.
    c. **Translational Endpoint**
        i. Correlate patient derived organoid response to therapy with tumor response.

3. Design information

a. **General design considerations**

i. 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.

ii. Study Interventions

1. Arm 1 Niraparib single agent
    a. Niraparib (200mg or 300 mg based on body weight and blood platelet count), oral, once daily
2. Arm 2 Niraparib plus Bevacizumab
    a. Niraparib (200mg or 300 mg based on body weight and blood platelet count), oral, once daily
    b. Bevacizumab (15 mg/kg, IV on day 1 of each cycle)
3. One cycle = 21 days. Patients will be treated until disease progression or toxicity unless patient withdraws consent.

iii. Study Duration

1. 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.

iv. Participant Duration

1. 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.

b. **Sample size**

i. 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.

4. Study Populations

Inclusion and exclusion criteria are sometimes modified during the duration of the protocol. Before beginning analysis, the statistical team will review the criteria in the SAP to confirm it is up to date with the current criteria.

a. **Inclusion criteria**
   i. Histologically confirmed progressive or recurrent endometrial cancer or ovarian cancer
      1. Patients with previously identified ARID1A tumor mutations.
      2. Note: Any ARID1A mutation is eligible and any CLIA Next generation sequencing test is allowable for eligibility.
   ii. 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.
   iii. 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.
   iv. Patients who have progressed after ≥1 prior platinum containing regimen.
   v. Measurable disease by RECIST criteria v1.1.
   vi. ECOG performance status 0 or 1.
   vii. Life expectancy > 12 weeks.
   viii. Adequate bone marrow, hepatic and renal function as defined by the following values within 14 days prior to starting treatment:
   ix. Hemoglobin ≥ 9 g/dL Absolute neutrophil count (ANC) ≥ 1.5 x 109/L.
   x. Platelet count ≥ 100 x 109/L with no platelet transfusion in the past 28 days.
   xi. Creatinine clearance ≥50 mL/min (estimated using Cockcroft-Gault equation).
   xii. 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).
   xiii. 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.
   xiv. No significant medical illness which in the opinion of the Investigator would preclude entry to study treatment.
   xv. 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:
   xvi. 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.
   xvii. Able to provide documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
   xviii. Radiation or chemotherapy-induced oophorectomy or menopause with > 1 year since last menses.

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

b. **Exclusion Criteria**

i. Patients with localized advanced disease without other measurable lesion and could be treated with curative intent.
ii. 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.
iii. Patients with myelodysplastic syndrome/acute myeloid leukemia history or with features suggestive of MDS/AML.
iv. Patients receiving radiotherapy within 2 weeks prior to study treatment.
v. Major surgery within 4 weeks of starting study treatment.
vi. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
vii. Any previous treatment with PARP inhibitor, including niraparib.
viii. 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.
ix. Previous Cerebro-Vascular Accident (CVA), Transient Ischemic Attack (TIA) or Sub-Arachnoids Hemorrhage (SAH) within 6 months prior to study treatment.
x. Patients with increased risk of bleeding or history or evidence of hemorrhagic disorders within 6 months prior to study treatment.
xi. Resting ECG with QTc > 470 msec on 2 or more time points within a 24-hour period or family history of long QT syndrome
xii. Persistent toxicities (Common Terminology Criteria for Adverse Event (CTCAE) > grade 2) caused by previous cancer therapy, excluding alopecia.
xiii. 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.
xiv. 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.
xv. Pregnant or lactating woman
xvi. Participation in another clinical study with an investigational product during the chemotherapy course within 30 days prior to study treatment.

xvii. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
xviii. Patients with a known hypersensitivity to investigational drugs or excipients.
xix. Clinical/radiological evidence of bowel obstruction (e.g. hospitalization) or symptoms of sub-acute bowel obstruction within 6 weeks prior to trial entry

5. Analysis Populations

The analysis populations are defined as below.

a. Safety population:

All patients who receive at least one dose of bevacizumab will be included in the analyses of compliance and safety.

b. **Evaluable population:** 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. Patients who missed doses but have more than 80% total drug accountability will still be considered evaluable.

6. Primary Objective Evaluation

a. 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.

7. Secondary Objective Evaluation

a. Progression free survival (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.
b. Toxicity
    i. The severity of the AE will be graded by the Investigator using the NCI CTCAE, version 5.0.
    ii. Toxicities and adverse events will be summarized by attribution and grade using frequencies and relative frequencies.

8. Translational Objectives

a. 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.

9. Handling of Missing Data

Every effort will be made to collect information at all defined visits including at early withdrawal or dropout. Reasons for missing data will be summarized. However, there will be no imputation of missing data.