STATISTICAL ANALYSIS PLAN

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

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Study Products:	Rucaparib Bevacizumab

Abbreviations

CR	Complete response
EOS	End of study
OS	Overall survival
PFS	Progression free survival
PR	Partial response
SAP	Statistical analysis plan

Contents

1. **Objectives**
    a. **Primary Objectives**
        i. To estimate the proportion of patients with persistent or recurrent cervical or endometrial cancer, who survive progression-free for at least 6 months, treated with combination bevacizumab and rucaparib.

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

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

2. **Study End Points**
    a. **Primary endpoint**
        i. PFS rate at 6 months
    b. **Secondary endpoints**
        i. Objective response rate
        ii. Incidence and severity of adverse events
        iii. PFS
        iv. OS
    c. **Translational endpoints**:
        i. MSI
        ii. HRD status
        iii. Degree of DNA damage

3. **Design Information**
    a. **General statistical considerations**

The study hypothesis will be evaluated in a 2-stage design. This will be used to decide whether there are sufficient numbers of patients progression free at 6 months or with objective responses to continue study in a second stage (at the interim analysis) or deem the drug worthy of further investigation in a phase III study (at the end of the study).

Null hypothesis is H_0: $\pi_r \leq 11\%$ and $\pi_s \leq 24\%$
Alternative hypothesis is H_a: $\pi_r \geq 31\%$ (=11%+20%) or $\pi_s \geq 44\%$ (=24%+20%),

where π_r is the objective response rate, π_s is the PFS rate at 6 months, and 11% and 24% are the response rate and PFS rate at 6 months respectively from a previous study.

The following decision rule will be applied where $X_{s(1)}$ is the number of patients progression-free at 6 months after the first stage, $X_{r(1)}$ is the number of patients with objective tumor responses (partial or complete) after the first stage, X_s is the cumulative number of patients progression-free at 6 months after stage 2, X_r is the cumulative number of patients with responses after stage 2, $C_{s(1)}$ is the critical value for $X_{s(1)}$, $C_{r(1)}$ is the critical value for $X_{r(1)}$, C_s is the critical value for X_s, and C_r is the critical value for X_r. Decision Rule: If either $X_{s(1)} > C_{s(1)}$ or $X_{r(1)} > C_{r(1)}$ after the first stage, then the study will open to a second stage of accrual to further evaluate the activity of the drug. If either $X_s > C_s$ or $X_r > C_r$ after the second stage and clinical judgment indicates, then the agent will be deemed clinically interesting and worthy of further investigation.

b. Sample Size and Power

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

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

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

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 (current version 5.0) to confirm it is up to date with the current criteria.

a. Inclusion Criteria

i. Patients with histologically-documented carcinoma of the cervix or endometrium.
ii. Patients with measurable and/or evaluable lesions as defined by RECIST 1.1.
iii. Women at least 18 years of age.
iv. Patient with persistent or recurrent squamous cell or adenocarcinoma of the cervix, or any carcinoma or carcinosarcoma of the endometrium who has undergone at least one prior line of systemic therapy. Prior bevacizumab is allowed. (Note: previous cisplatin during radiation therapy should NOT count as a prior line of systemic therapy).
v. ECOG performance status of 0, 1, or 2.

vi. Patient should agree to have tumor biopsy and baseline blood draw for correlative studies. If unable to be safely biopsied and patient desires enrollment, may be enrolled per principal investigator discretion.
vii. Adequate organ function should be confirmed by the following laboratory values obtained ≤ 14 days prior to first dose of rucaparib. Suggested criteria for adequate organ function include:
    1. Bone Marrow Function
        a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
        b. Platelets > 100 x 10^9/L
        c. Hemoglobin ≥ 9 g/dL independent of transfusion ≤ 14 days prior to screening hemoglobin assessment
    2. Hepatic Function
        a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN); if liver metastases, then ≤ 5 x ULN
        b. Bilirubin ≤ 1.5 x ULN; < 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome
        c. Serum albumin ≥ 30 g/L (3.0 g/dL)
    3. Renal Function
        a. Serum creatinine ≤ 1.5 x ULN
        b. Measured or calculated creatinine clearance (CrCL) ≥ 30 ml/min. For calculated CrCL, the Cockcroft Gault formula or institutional standard formula can be used. Patients must have a life expectancy of at least 3 months (to be able to complete one cycle of study treatment).
viii. Patients must have a life expectancy of at least three months (to be able to complete one cycle of study treatment).
ix. Patients should have no major existing co-morbidities or medical conditions that will preclude therapy in the view of the principal investigator.
x. Prior bevacizumab is allowed if off drug ≥ 28 days prior to study enrollment.
xi. Ability to understand and the willingness to sign a written informed consent document.
xii. Women of childbearing potential must not be considering getting pregnant and must avoid pregnancy during the study and for at least six months after the last dose of rucaparib or longer if requested by local authorities.

b. Exclusion Criteria

i. Have active second malignancy, i.e., patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment; However patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed >6 months prior and/or bone marrow transplant (BMT) >2 years prior to first dose of rucaparib.
ii. Prior treatment with any PARP inhibitor.
iii. Untreated or symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.

iv. Received treatment with chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C); or radiation, biologic/targeted agents, experimental drugs within 3 weeks prior to first dose of rucaparib; and/or ongoing adverse effects from such treatment > NCI CTCAE V5.0 Grade 1 (Grade 2 non-hematologic toxicity to most recent treatment may be permitted with prior advanced approval from Sponsor).
v. Hospitalization for bowel obstruction within 3 months prior to enrollment.
vi. Patients must have no history of gross hemoptysis (defined as bright red blood of a ½ teaspoon or more) or coagulopathy. Patients with history of major tumor-related bleeding that is not controlled despite locoregional treatment or at high risk of recurrent tumor related bleeding will be excluded.
vii. Patients with history of hypertension must be well-controlled (≤150/100) on a stable regimen of anti-hypertensive therapy.
viii. Patients with tumors that invaded major vessels (e.g. the carotid) as shown unequivocally by imaging studies will be excluded due to the possibility of increased risk for tumor bleeding with bevacizumab therapy.
ix. Patients should not have a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study enrollment, or anticipation of need for major surgical procedure during the course of the study. No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to registration. No serious non-healing wound, ulcer, or bone fracture.
x. Patients should not have unstable angina or myocardial infarction within the previous 6 months; no uncontrolled hypertension; no symptomatic congestive heart failure; no serious cardiac arrhythmia requiring medication; no clinically significant peripheral vascular disease; no history of any CNS cerebrovascular ischemia or stroke within the last 6 months; no active serious infection.
xi. Patients should not have other coexisting medical condition that would preclude full compliance with the study.
xii. Patients may not be receiving any other investigational agents.
xiii. Patients should not have a history of prior severe infusion reaction to a monoclonal antibody. Patients with known hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies.
xiv. Pregnant women are excluded from this study because rucaparib and bevacizumab have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with rucaparib and bevacizumab, breastfeeding should be discontinued if the mother is treated with rucaparib and bevacizumab. Should a woman become pregnant or suspect she is pregnant while in this study, she should inform her treating physician immediately.
xv. HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible drug interactions with rucaparib and bevacizumab.

5. Analysis Populations

The analysis populations are defined as below.

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

- **Safety population:** All patients who receive at least one dose of combination bevacizumab and rucaparib will be included in the analyses of compliance and safety. For efficacy analysis, patients removed from study for early withdraw or hypersensitivity reactions will be replaced if they have received less than one cycle of study treatments during cycle 1, but will be included in the safety analysis.

- **Biomarker population:** Patients with sufficient pre-dose biomarker data will be included in biomarker analysis.

6. Summary of Study Population

a. Patient Disposition

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

b. Demographic and Baseline Characteristics

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

c. Medical History and Cancer History

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

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

d. Study Drug Administration and Compliance

i. Study drug administration, both rucaparib and bevacizumab, will be summarized in terms of the actual doses administered and the proportion of drug actually taken relative to the amount that should have been taken; these data will be summarized in frequency distributions by cycle. The total number of cycles administered; the

median (range) of cycles administered; dose modifications, dose delays, and dose omissions; and reasons for deviations from planned therapy will be summarized.

7. Antitumor Evaluation

i. The objective tumor response (complete and partial response) will be summarized as the proportion (and 95% CI based on the Clopper-Pearson exact method) of evaluable patients with a tumor response. The duration of response will be calculated as time from the date of first response (complete response (CR), or partial response (PR)) to the date of disease progression. Duration of response will be summarized using the Kaplan-Meier method. Median duration of response with 95% CI will be computed if data allows. The disease assessments will be performed by CT or MRI every 2 cycles using RECIST 1.1. Results will be presented in tabular and graphic form, as appropriate.

ii. Progression-Free Survival (PFS) rate at 6 months is defined as the proportion of evaluable patients who were progression free 6 month after study enrollment. 95% CI based on the Kaplan-Meier method will be reported.

iii. Progression-Free Survival (PFS) is defined as the time in months from date of enrollment to the date of death or the first documented date of progression, whichever comes first. For patients who did not die and did not have progression, the PFS is censored at the last documented tumor assessment.
Survival curve for PFS will be generated using the Kaplan-Meier method. Median PFS with 95% CI will be computed.

iv. Overall survival (OS) is defined as time in months from date of enrollment to the date of death. Patients who are still alive at EOS or 2 years post EOS are censored on the date they were last known to be alive.
Survival curve for OS will be generated using the Kaplan-Meier method. Median OS with 95% CI will be computed.

8. Safety Analyses

The safety population will be used.

a. Adverse Events

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

b. Laboratory Abnormalities

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

c. Other Safety Assessments

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

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

9. Biomarkers

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

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

10. 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.