IISR GUIDE STUDY INFORMATION Date: (07/02/23) Protocol Version: 1.44	
Country(s) the study will be conducted in:	Korea
Compound/Product:	Niraparib
Study Type :	Clinical interventional
Study Title:	A single-arm phase II study of niraparib and bevacizumab maintenance therapy in platinum-sensitive recurrent ovarian cancer patients previously treated with a PARP inhibitor
Indication:	Ovarian cancer

INVESTIGATOR CONTACT INFORMATION	
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RESOURCES REQUESTED	
Resource Requested:	Drug & Funding
Estimated Study Budget: *(Enter total here – including direct, indirect cost and institutional overhead)*	250,071,071(KRW)
Do you have additional funding sources for this project? *(If yes, please explain)*	No
Dosage and Formulation:	100mg, capsule
Estimated Total Drug Supply for Study: *(number of tablets, capsules, vials)*	(100mg x 2 x 30 x 12 x 44) capsules
Total # of Subjects:	44
Study Timeline: *Planned Study Activation: (month/year)* *Study activation is final regulatory authority approved protocol and fully executed contract*	*Dec 2020*
Study Activation to First Patient In (days, weeks, months):	*May 2021*
First Patient In to Last Patient In	*30 months*

Last Patient In to Last Patient Out (days,weeks, months)	*6 months*
Monthly enrollment rate: (days)	*3 pts/ month*
Treatment duration: (in months)	*Till PD (expected median PFS 12 months)*
Number of Study Sites/Depots: (depots are defined as shipment facilities for sites)	*8 sites*
Completion of Data Analysis: (# months)	*3 months*
Completion of Final Study Report/Manuscript: (month/year)	*Jul 2024*
Publication Plan: (target journal, target conference)	*Journal of Clinical Oncology, ASCO*

STUDY PROPOSAL

Background:

PARP inhibitors represent a major breakthrough in ovarian cancer care.

In 2014, FDA approved olaparib for the treatment of patients with germline BRCA mutation who have been treated with three or more prior lines of chemotherapy.

Niraparib showed activity regardless of BRCA status based on the phase III ENGOT-OV16/NOVA trial.

AVANOVA trial showed a significant activity with niraparib and bevacizumab compared to niraparib even in HRD negative / BRCA wt patients groups.

PRIMA trial showed a significant benefit with niraparib maintenance compared to placebo in front-line setting.

Rationale:

Unmet needs in Platinum-sensitive recurrent ovarian cancer previously treated with a PARP inhibitor

Based on study 19, Korean FDA has permitted the use of olaparib for maintenance therapy in platinum-sensitive recurrent ovarian cancer with BRCA mutation since 2017. Recently, Korean FDA has permitted the use of niraparib for maintenance therapy in platinum-sensitive recurrent ovarian cancer based on NOVA study.
In addition, clinical trials using PARP inhibitors for front-line maintenance therapy (DUO-O, KEYLINK-001, ATHENA) has been performed, are ongoing in Korea. More ovarian cancer patients are expected to have opportunities to use PARP inhibitors for front-line or second-line therapy.
Given the expanding clinical use of PARP inhibitors and the high likelihood of acquired resistance, there is a significant need for clinical strategies to overcome PARP inhibitors resistant disease. Platinum-based chemotherapy is considered as current standard of care for platinum sensitive recurrent ovarian cancer previously treated with a PARP inhibitor. However, information regarding re-challenging patients with PARP inhibitor is very limited. It is unknown whether PARP inhibitor re-treatment as maintenance therapy is beneficial or not.

Rationale for combination

Acquired resistance with use of PARP inhibitors comes from homologous recombination repair restoration. Therefore, induction of BRCAness offer a clinical approach for PARP inhibitor resistant disease. Hypoxia induced by anti-angiogenic agent may create homologous recombination repair deficiency, thus enhancing the effect of PARP inhibitor retreatment. NRG GY-004 (olaparib+cediranib) shows activity even in BRCA wt patients [Liu et al., 2014]. AVANOVA (niraparib+bevacizumab) shows activity even in BRCA wt or HRD negative patients [Mirza et al., 2019]. PAOLA randomized phase III study is evaluating synergistic effects of olaparib and bevacizumab [Ray-Coquard et al., 2019].
In addition, safety was established for following combinations: olaparib+cediranib, olaparib+bevacizumab, niraparib+bevacizumab

There is a strong unmet need for PARP inhibitor re-treatment in platinum sensitive recurrent ovarian cancer previously treated with a PARP inhibitor. To date, no robust data exist to suggest that re-treatment with a different PARP inhibitor would be effective. The question of retreatment is being evaluated in the phase IIIb OReO trial (NCT03106987). It is unknown whether such patients could derive clinical benefit from PARP inhibitor re-treatment with other novel agent. We suggest niraparib re-treatment with bevacizumab to show synergistic effects in platinum-sensitive recurrent ovarian cancer previously treated with a PARP inhibitor.

Hypothesis:

Niraparib re-treatment with Bevacizumab is synergistic in patients previously treated with a PARP inhibitor

Primary Aim/Objective:

To determine the efficacy of niraparib re-treatment with bevacizumab by assessment of Progression-free survival (PFS)..

Secondary Aim/Objective:

- To determine the efficacy of niraparib re-treatment with bevacizumab by assessment of *Overall survival, Time to progression, Time to first subsequent treatment (or death), Time to second subsequent treatment, PFS2*
- To evaluate the safety and tolerability of niraparib re-treatment with bevacizumab

Primary Endpoint(s):

6-months PFS rate

Secondary Endpoint(s):

OS, Time to progression, TFST, TSST, PFS2, safety

Study Plan:

Type and design of study : a single-arm phase II

Requirements for run-in or washout of medication : NA

Description of population to be studied : Recurrent epithelial ovarian cancer with prior PARP inhibitor treatment.

- Inclusion Criteria.

1. Participant has histologically confirmed diagnosis of high-grade predominantly serous, endometrioid, carcinosarcoma, mixed mullerian with high-grade serous component, clear cell, or low-grade serous OC, primary peritoneal cancer, or fallopian tube cancer will be enrolled in this study (only up to 4 patients with clear cell carcinoma will be included and mucinous carcinoma will not be included).
2. Participant has received at least 2 previous courses of platinum-containing therapy, and has disease that was considered platinum sensitive following the penultimate (next to last) platinum course (more than 12 months' period between penultimate platinum regimen and progression of disease)
   Note: The last platinum regimen does not necessarily have to immediately follow the next to last (penultimate) platinum regimen. For example, if a patient received a non-platinum regimen between the penultimate platinum regimen and last platinum regimen, they could be eligible, so long as they meet all entry criteria.
3. Participant has responded to last the platinum regimen (complete or partial response), remains in response and is enrolled on study within 8 weeks of completion of the last platinum regimen
4. Participant had prior treatment with PARP inhibitor
5. Participant is able to provide a newly obtained core or excisional biopsy of a tumor lesion for prospective testing of BRCA 1/2 and PD-L1 status prior to enrollment.
6. Female participants who are at least 20 years of age on the day of signing informed consent with.
7. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 10 days prior to enrollment.
8. A female participant is eligible to participate if she is not pregnant (see Appendix 2), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 2
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 during the treatment period and for at least 180 days following the last dose of niraparib and at least 180 days following the last dose of chemotherapy or bevacizumab
9. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial. The participant may also provide consent for future biomedical research; however, the participant may participate in the main study without participating in future biomedical research.
10. Participant has adequate organ function as defined in the following table (Table 1).; all screening laboratory tests should be performed within 10 days prior to the start of study treatment

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

- Exclusion Criteria.

1. Participant has mucinous, germ cell, or borderline tumor of the ovary.
2. Participant has a history of non-infectious pneumonitis that required treatment with steroids or currently has pneumonitis.
3. Participant either has myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) or has features suggestive of MDS/AML.
4. Participant has a known additional malignancy that is progressing or has required active treatment within the past 2 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ, endometrial carcinoma) that have undergone potentially curative therapy are not excluded.

   Note: Participants with synchronous primary endometrial cancer or a past history of primary endometrial cancer that met the following conditions are not excluded: Stage not greater than IA: no more than superficial myometrial invasion.

5. Drainage of ascites during last 2 cycles of last chemotherapy.
6. Palliative radiotherapy within 1 week encompassing >20% of the bone marrow.
7. Persistent > grade 2 toxicity from prior cancer therapy.
8. Symptomatic uncontrolled brain or leptomeningeal metastases. A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days.
9. Known hypersensitivity to the components of niraparib and bevacizumab.
10. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
11. 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 below.
    - Uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction and congestive cardiac failure
    - Uncontrolled hypertension, defined as systolic > 140 mmHg or diastolic > 90 mmHg documented by 2 blood pressure readings taken at least 1 hour apart
    - Thromboembolism of ateries and veins
    - Uncontrolled cerebrovascular disease or prone to bleeding
    - Clinically significant intestinal obstruction, abdominal fistula, or gastrointestinal perforation
    - Uncontrolled major seizure disorder
    - Unstable spinal cord compression
    - Superior vena cava syndrome
    - Any psychiatric disorder that prohibits obtaining informed consent
12. History or current evidence of any condition, therapy, or lab abnormality that might confound the results of the study, interfere with the patient‘s participation for the full duration of the study treatment, or is not in the best interest of the patient to participate.
13. Immunocompromised patients
14. Patients with known active hepatic disease (i.e. , Hepatitis B or C).

Study Drug(s):

Product names, doses, dose form, dosing schedules, route and mode of administration treatment periods, follow-up periods (per group or arm) (can be shown as table and/or narrative,). These would include placebo, active comparator, challenge agent or companion medication administration , when applicable.

Maintenance :

niraparib po 200mg or 300mg QD*

bevacizumab iv15mg/kg every 3 weeks (Q3W)

*The recommended starting dosage of niraparib is 200mg QD. For patients who weigh ≥77 kg and have baseline platelet count ≥150,000/μL, the recommended starting dosage is 300 mg QD.

Estimated number of subjects to be treated (or for open-label studies use appropriate term, eg, treated).

44

Expected duration and sequence of all study periods, including follow-up.

24 months

Timing of the first dose.

May 2021

Number of visits (or telephone interviews), whether inpatient or outpatient, and other scheduled visits (laboratory tests between visits).

Refer to 6.1 study flow chart

If a defined post-intervention follow-up period is required, specify observations or tests to be performed. Define the length and purpose of the follow-up period.

Include supporting tables, graphs and schematics.

Refer to 6.1 study flow chart

Safety Reporting (please do not change the safety section of the template)

Refer to 7.2.

Statistical Analysis:

Study Design/Description – single-arm ph2

This is a hypothesis generating study to determine the efficacy of niraparib retreatment with bevacizumab

Randomization/Stratification – N/A

Accrual and Feasibility - planned sample size (44 pts) and accrual rate (3/months)

Sample size justification.

The rate of patients with progression-free state at 6 months is expected as 50% without maintenance (current SOC, results from GOG 213 & SOLO-2), and HR of adding maintenance therapy of niraparib retreatment with bevacizumab was assumed to 0.5, which was equivalent to 70.7% of PFS rate. When applying the same expected efficacy (HR=0.5) with PAOLA study (PARP inhibitor+ anti-angiogenic therapy), the null hypothesis for this study will be 50% of 6 month PFS rate, and alternative hypothesis of interest will be 70% of 6 month PFS rate.

Using Simon's two stage optimal design at a one-sided 5% level of significant and 80% power, totally 39 patients are required in this study. In 1st stage, 22 patients will be enrolled and followed up for 6 months, then if 10 or more PD are observed, the trial will be terminated. If not, the trial continues to the 2nd stage, a total of 39 patients will be studies. If the total number of PD is less than 15 or equal to , the null hypothesis is rejected.Considering 10% follow-up loss, the sample size will be 44 patients.

Efficacy Analysis.

- Efficacy analyses are based on the modified intent-to-treat (ITT) approach (patients should receive at least one treatment dose).
- The primary analysis of the primary endpoint of 6 months-PFS rate will be performed when all enrolled patients have completed 6 months of follow-up and/or investigator-assessed response assessments have been completed for all patients. All secondary endpoints will be evaluated at this time. Additional updated analyses of efficacy and safety may be conducted at later times if deemed appropriated.
- Interim After recruiting 22 patients, interim analysis to determine futility of the treatment will be conducted.
- Missing data will not be replaced by other data, and if tumor imaging assessment was missed, disease progression or death, if new anticancer therapy has been initiated, the data will be censored at the last assessment prior to initiation of new anticancer treatment.
- Descriptive statistics will be used to summarize the characteristics of the study patients.
- Survival analyses are performed using Kaplan-Meier method.

Primary Objective, Endpoint(s), Analysis Plan.

(1) **Objective:** To determine the efficacy of Niraparib re-treatment with Bevacizumab by assessment of progression-free survival (6 months PFS rate)

(2) **Hypothesis:** Niraparib re-treatment with Bevacizumab is synergistic in patients previously treated with a PARP inhibitor

Secondary Objectives, Endpoints, Analysis Plans.

(1) **Objective**: To determine the efficacy of Niraparib re-treatment with Bevacizumab by assessment of Overall survival, Time to progression, Time to first subsequent treatment (or death), Time to second subsequent treatment, PFS2

(2) Safety objective: To evaluate the safety and tolerability of Niraparib re-treatment with Bevacizumab

Safety analysis.

- Safety analyses are based on the safety population (at least one dose of study drug). Adverse events are graded according to CTCAE version 5.0.

Data Management Plan:

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the eCRF should be consistent with the data recorded on the source documents.
Clinical data and clinical laboratory data will be entered into eCRF. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.
In addition, all data in the eCRF will be backed up in a separate server to prevent damage to the data due to system failures, disasters, etc. At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with other essential documents.

Ethical and Regulatory Considerations:

Prior to initiating the study, the Investigator must obtain written approval to conduct the study from appropriate institutional ethical and/or regulatory committee and send a copy to Takeda (gma.externalresearch@takeda.com). Should changes to the study become necessary, copies of written approvals from appropriate institutional ethical and/or regulatory committees must be sent to Takeda (gma.externalresearch@takeda.com).

If research involves human subjects, the Investigator must register the study with clinical trials.gov and other appropriate entities, as necessary.

An IND or CTA may be required. The investigator is responsible to work with regulatory authority to obtain or prove exemption

References:

Gonzalez-Martin, A, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med, 2019. 381(25): p. 2391-2402.

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum sensitive relapsed ovarian cancer. N Engl J Med. 2012 Apr 12;366(15):1382-92.

Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. The Lancet Oncology 2014;15:1207-14.

Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med*. 2016;375(22):2154-2164.

Mirza, M.R, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol, 2019. 20(10): p. 1409-1419.

Ray-Coquard, I, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med, 2019. 381(25): p. 2416-2428.

Supporting documentation/tables and graphs: *Refer to protocol*
Detailed Budget for all study related costs: *Please refer to the budget template*

1.0 TRIAL SUMMARY

Abbreviated Title	NIRVANA
Trial Phase	*Phase II*
Clinical Indication	Platinum-sensitive recurrent ovarian cancer patients previously treated with a PARP inhibitor
Trial Type	Single arm
Type of control	n/a
Route of administration	Niraparib for po / bevacizumab for iv
Trial Blinding	n/a
Treatment Groups	Maintenance : Niraparib 200mg or 300mg (once daily [QD])* Bevacizumab 15mg/kg every 3 weeks (Q3W) *The recommended starting dosage of niraparib is 200mg QD. For patients who weigh ≥77 kg and have baseline platelet count ≥150,000/µL, the recommended starting dosage is 300 mg QD.
Number of trial participants	44
Estimated enrollment period	*30 months*
Estimated duration of trial	*48 months*
Duration of Participation	36 months
Estimated average length of treatment per patient	12 months

2.0 TRIAL DESIGN

2.1 Trial Design

The study design is depicted in Figure 1.

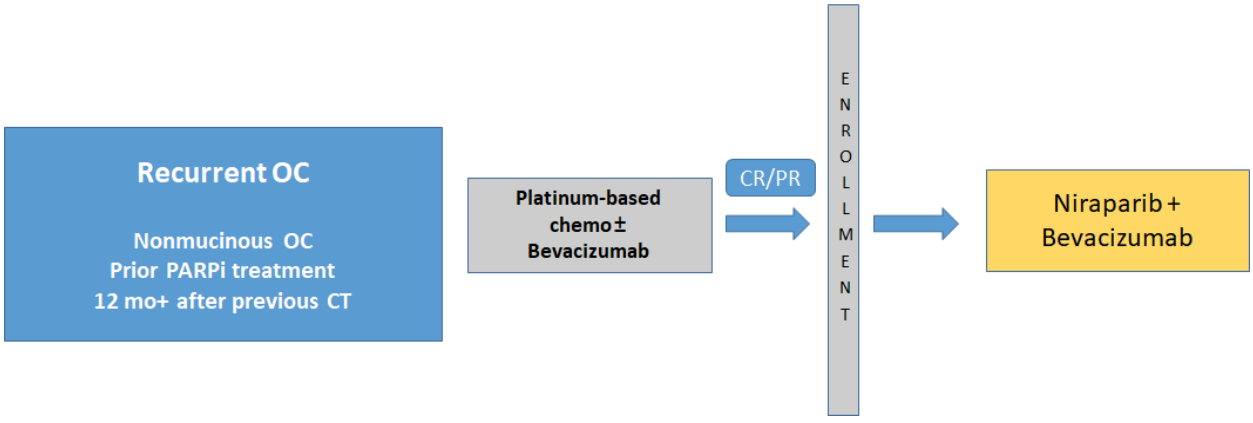

Figure 1. Study diagram

Abbreviations: OC, ovarian cancer; CT, chemotherapy; CR, complete remission; PR, partial remission

2.2 Trial Diagram

The study diagram is depicted in Figure 2.

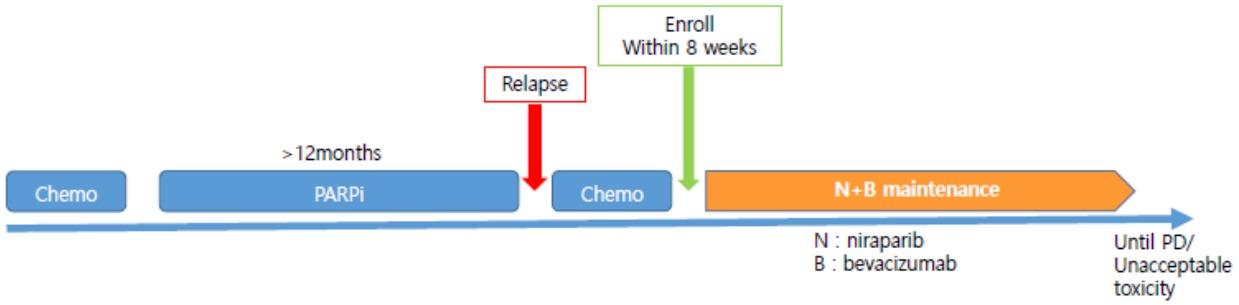

Figure 2. Study diagram

Abbreviations: Chemo, Chemotherapy; CR, complete remission; PR, partial remission; N, Niraparb; B, bevacizumab; PD, progressive disease

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(3) **Objective:** To determine the efficacy of Niraparib re-treatment with Bevacizumab by assessment of progression-free survival (6 months PFS rate)

(4) **Hypothesis:** Niraparib re-treatment with Bevacizumab is synergistic in patients previously treated with a PARP inhibitor

3.2 Secondary Objective(s) & Hypothesis(es)

(3) Objective: To determine the efficacy of Niraparib re-treatment with Bevacizumab by assessment of Overall survival, Time to progression, Time to first subsequent treatment (or death), Time to second subsequent treatment, PFS2

(4) **Safety objective**: To evaluate the safety and tolerability of Niraparib re-treatment with Bevacizumab

3.3 Exploratory Objective

(1) **Objective:** To identify molecular biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of Niraparib and Bevacizumab

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Niraparib

Niraparib is an orally active PARP1/2 inhibitor with nanomolar potency being developed

as a monotherapy agent for tumors with defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors.

4.1.2 Preclinical and Clinical Trial Data

In preclinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with homologous recombination defects. In a BRCA1-mutant xenograft study, niraparib dosed orally caused tumor regression, which was mirrored by >90% reduction in tumor weight compared with the control; in a BRCA2-mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Utilizing patient-derived ovarian xenografts, niraparib previously demonstrated response in both BRCA mutation and BRCA wild-type(wt) tumors.[1] BRCA mutation status alone was insufficient to predict response to niraparib. To understand the selectivity observed, samples from a collection of high-grade ovarian tumors were subjected to homologous recombination deficiency (HRD) analysis to determine the frequency of BRCA mutation and BRCA hypermethylation. In addition, the HRD assay determines a comprehensive signature for HRD by analyzing single nucleotide polymorphism data to measure loss of heterozygosity (LOH), tumor telomeric allelic imbalance (TAI), and large-scale state transitions (LST) within a tumor. The final HRD score is the sum of the LOH+TAI+LST scores with numerical outputs ranging from 0 to 100.

Collectively, there was 25% BRCA deficiency in this primary tumor collection, consistent with previous studies in high-grade ovarian cancer.[2] In vivo response to niraparib monotherapy was demonstrated in BRCA mutation and BRCA wild-type models, with all sensitive models found to be HRD-positive (HRDpos). In addition, niraparib resistance or lack of in vivo efficacy was demonstrated in tumors with low HRD scores. Therefore, the HRD score has been shown to be an excellent predictor of lack of response to niraparib, and tumors with non-HRDpos scores are significantly less likely to respond to niraparib than tumors with HRDpos scores. Collectively, HRD testing of ovarian cancer is predictive of BRCA mutation status and relative responsiveness to niraparib.

As a monotherapy, the efficacy of niraparib was evaluated in a PRIMA study, a phase 3 clinical trial, in patients with high-risk ovarian cancer, fallopian tube cancer, and primary peritoneal cancer who responded to primary platinum-based chemotherapy. The PRIMA study satisfied the primary efficacy evaluation variable by demonstrating that the median progression-free survival period was longer and the risk of death or disease progression was significantly reduced in patients with niraparib compared to the placebo-administered group.

- This study met the primary efficacy evaluation variables in HRD-positive patients. The median progression-free survival period evaluated using RECIST (Version 1.1) was 21.9 months in niraparib group and 10.4 months in placebo group (HR 0.43 [95% CI: 0.310 to 0.588]; p<0.0001). Depending on the HRD test results, the primary evaluation variables were sequentially tested for the entire population. In this study, the median progression-free survival period was 13.8 months in the niraparib randomized patient group and 8.2 months in the placebo group, meeting the primary evaluation variables in this study (HR 0.62 [95% CI: 0.502 to 0.755]; p<0.0001).
- Patients were given niraparib regardless of tumor HRD status. The median progression-free survival period of patients with positive HRD was 8.1 months in niraparib group and 5.4 months in placebo group (HR 0.68 [95% CI: 0.492 to 0.944]; p=0.0203).
- Although not complete, the overall survival duration for all subjects was numerically better niraparib (HR 0.70 [95% CI: 0.442 to 1.106]; p=0.1238)

4.2 Rationale

4.2.1 Unmet needs in Platinum-sensitive recurrent ovarian cancer previously treated with a PARP inhibitor

Based on study 19, Korean FDA has permitted the use of olaparib for maintenance therapy in platinum-sensitive recurrent ovarian cancer with BRCA mutation since 2017 [Ledermann et al., 2012]. Recently, Korean FDA has permitted the use of niraparib for maintenance therapy in platinum-sensitive recurrent ovarian cancer based on NOVA study In addition, Korean FDA has permitted the use of niraparib maintenance therapy in front-line ovarian cancer based on PRIMA. In addition, clinical trials results using PARP inhibitors for front-line maintenance therapy (PRIMA, SOLO-1, PAOLA-1, VELIA) has been published and PARP inhibitor combination trials (DUO-O, KEYLINK-001, ATHENA) are ongoing in Korea. More ovarian cancer patients are expected to have opportunities to use PARP inhibitors for front-line or second-line therapy. Given the expanding clinical use of PARP inhibitors and the high likelihood of acquired resistance, there is a significant need for clinical strategies to overcome PARP inhibitors resistant disease. Platinum-based chemotherapy is considered as current standard of care for platinum sensitive recurrent ovarian cancer previously treated with a PARP inhibitor. However, information regarding re-challenging patients with PARP inhibitor is very limited. It is unknown whether PARP inhibitor re-treatment as maintenance therapy is beneficial or not.

4.2.2 Rationale for combination

Acquired resistance with use of PARP inhibitors comes from homologous recombination repair restoration. Therefore, induction of BRCAness offer a clinical approach for PARP inhibitor resistant disease. Hypoxia induced by anti-angiogenic agent may create homologous recombination repair deficiency, thus enhancing the effect of PARP inhibitor retreatment. NRG GY-004 (olaparib+cediranib) shows activity even in BRCA wt patients [Liu et al., 2014]. AVANOVA (niraparib+bevacizumab) shows activity even in BRCA wt or HRD negative patients [Mirza et al., 2019]. PAOLA randomized phase III study is evaluating synergistic effects of olaparib and bevacizumab [Ray-Coquard et al., 2019].
In addition, safety was established for following combinations: olaparib+cediranib, olaparib+bevacizumab, niraparib+bevacizumab

There is a strong unmet need for PARP inhibitor re-treatment in platinum sensitive recurrent ovarian cancer previously treated with a PARP inhibitor. To date, no robust data exist to suggest that re-treatment with a different PARP inhibitor would be effective. The question of retreatment is being evaluated in the phase IIIb OReO trial (NCT03106987). It is unknown whether such patients could derive clinical benefit from PARP inhibitor re-treatment with other novel agent. We suggest niraparib re-treatment with bevacizumab to show synergistic effects in platinum-sensitive recurrent ovarian cancer previously treated with a PARP inhibitor.

4.3 Justification for Dose

4.3.1 Rationale for Niraparib Dosing Regimen

4.3.2 The recommended starting dosage of niraparib is 200mg QD. For patients who weigh ≥77 kg and have baseline platelet count ≥150,000/μL, the recommended starting dosage is 300 mg QD.Rationale for Bevacizumab Dosing Regimen

The dose of bevacizumab is allowed as per the local SOC and approved product label.

4.4 Rationale for Endpoints

4.4.1 Efficacy Endpoints

This study will use primary endpoint of 6 months PFS rate as in figure 1.

This study will use PFS based on RECIST 1.1 criteria as assessed by the investigator as the primary endpoint. PFS is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy. For clinical trials that have settings with a long postprogression survival and/or involve multiple rounds of postprogression therapy, a primary endpoint of PFS supported by intermediate clinical endpoints (ex: TSST, PFS2) and OS may provide a more comprehensive approach for evaluating efficacy [Matulonis et al. 2015].

4.4.2 Biomarker Research

To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)
This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.
The Sponsor will collect tissue from archival samples, pre-treatment sample, and post-treatment sample. The Sponsor will get blood samples every 6 weeks during treatment period. The clinical trial co-investigator (Hyun-Woong Cho, Korea University Guro Hospital) will collect blood samples a total of two times (before the C1D1 and after the end of the test). This research will include exome sequencing, RNA sequencing, and immunohistochemistry.
Comprehensive genomic profiling & immune biomarker exploration will be performed for all samples to find the predictive biomarkers for combination therapy of niraparib and bevacizumab.

1) DNA/ RNA analyses from tumor/blood
Tumor and blood samples from this study will be examined to identify BRCA reversion mutation and HRD status changes. The application of next generation sequencing has provided scientists the opportunity to identify tumor-specific DNA changes. RNA sequencing will be performed to identify immune dynamic changes between pre-treatment and progression
2) Analysis of immune marker using FACS from tumor/blood

We will Examine the phenotypic characteristics of CD4 and CD8 T cells in terms of various immune check points (PD-1, CTLA4, TIM3, LAG3) and memory markers (CD45RO+CCR7+) in fresh tissue and PBMC by FACS on pre-treatment & at progression.

We will examine the tumor infiltrating immune cells including Treg cells and MDSCs on pre-treatment & at progression.

3) PD-L1 testing and multiplex IHC from tumor/blood

Tumor samples from this study may undergo protemic analyses (eg. PD-L1 IHC). PD-L1 expression level at pre-treatment and at progression will be checked. Using established platform of Vectra, multispectral imaging will be performed to identify tumor microenvironment comprehensively.

ctDNA, PBMCs and plasma will also be isolated and stored for exploratory biomarker analysis.

5.0 METHODOLOGY

5.1 Study Population

Female participants of at least 20 years of age with EOC, fallopian tube cancer, or primary peritoneal cancer will be enrolled in this study.

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Participant has histologically confirmed diagnosis of high-grade predominantly serous, endometrioid, carcinosarcoma, mixed mullerian with high-grade serous component, clear cell, or low-grade serous OC, primary peritoneal cancer, or fallopian tube cancer will be enrolled in this study (only up to 4 patients with clear cell carcinoma will be included and mucinous carcinoma will not be included).
2. Participant has received at least 2 previous courses of platinum-containing therapy, and has disease that was considered platinum sensitive following the penultimate (next to last) platinum course (more than 12 months' period between penultimate platinum regimen and progression of disease)
   Note: The last platinum regimen does not necessarily have to immediately follow the next to last (penultimate) platinum regimen. For example, if a patient received a non-platinum regimen between the penultimate platinum regimen and last platinum regimen, they could be eligible, so long as they meet all entry criteria.
3. Participant has responded to last the platinum regimen (complete or partial response), remains in response and is enrolled on study within 8 weeks of completion of the last platinum regimen
4. Participant had prior treatment with PARP inhibitor
5. Participant is able to provide a newly obtained core or excisional biopsy of a tumor lesion for prospective testing of BRCA 1/2 and PD-L1 status prior to enrollment

Demographics

6. Female participants who are at least 20 years of age on the day of signing informed consent with

7. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 10 days prior to enrollment.

Female participants:

8. A female participant is eligible to participate if she is not pregnant (see Appendix 2), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 2
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 during the treatment period and for at least 180 days following the last dose of niraparib and at least 180 days following the last dose of chemotherapy or bevacizumab.

Informed Consent

9. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial. The participant may also provide consent for future biomedical research; however, the participant may participate in the main study without participating in future biomedical research.

Laboratory Values

10. Participant has adequate organ function as defined in the following table (Table 1).; all screening laboratory tests should be performed within 10 days prior to the start of study treatment.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	

International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant has mucinous, germ cell, or borderline tumor of the ovary.
2. Participant has a history of non-infectious pneumonitis that required treatment with steroids or currently has pneumonitis
3. Participant either has myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) or has features suggestive of MDS/AML.
4. Participant has a known additional malignancy that is progressing or has required active treatment within the past *2* years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ, endometrial carinoma) that have undergone potentially curative therapy are not excluded.

   Note: Participants with synchronous primary endometrial cancer or a past history of primary endometrial cancer that met the following conditions are not excluded: Stage not greater than IA: no more than superficial myometrial invasion.
5. Drainage of ascites during last 2 cycles of last chemotherapy.
6. Palliative radiotherapy within 1 week encompassing >20% of the bone marrow.
7. Persistent > grade 2 toxicity from prior cancer therapy.
8. Symptomatic uncontrolled brain or leptomeningeal metastases. A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days.
9. Known hypersensitivity to the components of niraparib and bevacizumab.
10. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
11. 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 below.

- Uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction and congestive cardiac failure
- Uncontrolled hypertension, defined as systolic > 140 mmHg or diastolic > 90 mmHg documented by 2 blood pressure readings taken at least 1 hour apart
- Thromboembolism of ateries and veins
- Uncontrolled cerebrovascular disease or prone to bleeding
- Clinically significant intestinal obstruction, abdominal fistula, or gastrointestinal perforation
- Uncontrolled major seizure disorder
- Unstable spinal cord compression
- Superior vena cava syndrome
- Any psychiatric disorder that prohibits obtaining informed consent

12. History or current evidence of any condition, therapy, or lab abnormality that might confound the results of the study, interfere with the patient‘s participation for the full duration of the study treatment, or is not in the best interest of the patient to participate.
13. Immunocompromised patients.
14. Patients with known active hepatic disease (i.e. , Hepatitis B or C).

5.1.3 Restrictions During Study

1. Patients of child bearing potential and their partners who are sexually active must agree to the use of 2 highly effective forms of contraception throughout their participation during the study treatment and for 6 months after last dose of study treatment(s):

a. Condom with spermicide and 1 of the following:
b. Oral contraceptive or hormonal therapy (e.g., hormone implants)
c. Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:
a. Total sexual abstinence. Abstinence must be for the total duration of the trial and the drug washout period.
b. Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
c. Tubal occlusion plus male condom with spermicide
d. Intrauterine Device (IUD) plus male condom+spermicide. Provided coils are copper-banded

Acceptable hormonal methods include:
a. Etonogestrel implants (e.g., Implanon, Norplan)+male condom with spermicide
b. Normal and low dose combined oral pills+male condom with spermicide
c. Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
d. Intravaginal device+male condom with spermicide (e.g., EE and etonogestrel)
e. Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

2. No other anticancer therapy is permitted during the course of the study treatment for any

patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to enrollment, as per exclusion criteria above). If the patient discontinues study treatment, this restriction no longer applies, however the patient will remain enrolled in the study for the purpose of collecting subsequent outcomes, including tolerance of

subsequent anticancer treatments. Palliative radiotherapy is allowed for preexisting small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

3. Prophylactic cytokine (Granulocyte Colony-Stimulating Factor [GCSF]) administration should not be given in the first cycle of the study, but may be administered in subsequent cycles.
4. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown and therefore they should not be administered to patients in the study.
5. Patients who are blood donors should not donate blood during the study and for 3 months after the last dose of study treatment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 3

Table 3 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Niraparib	200mg or 300mg*	QD	Oral	QD during each treatment cycle	Experimental
Bevacizumab	15mg/kg or	Q3W	IV infusion	Q3W; Day 1 of each 3 week cycle	Background therapy

Abbreviations: QD = once daily; Q3W = every 3 weeks

* The recommended starting dosage of niraparib is 200mg QD. For patients who weigh ≥77 kg and have baseline platelet count ≥150,000/μL, the recommended starting dosage is 300 mg QD

Trial treatment should begin on the day of allocation or as close as possible to the date on which treatment is allocated/assigned.

Niraparib and Bevacizumab have to be discontinued if the disease progression or an unacceptable adverse drug reaction occurs.

5.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

5.2.2 Niraparib Dosing Modifications

To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. The recommended dose modifications for adverse reactions are listed in Table 3, 4, and 5. Treatment must be interrupted for any non-hematologic National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 5.0) ≥ Grade 3 adverse event which the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved within 28 days, the patient may restart treatment with niraparib, but with a dose level reduction according to Table 4.
If the CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered, the patient must discontinue medication with niraparib.

Table 3 Recommended Dose Modifications for Adverse Reactions

Starting dose	200 mg/day	300 mg/day
First dose reduction	100 mg/day	200 mg/day
Second dose reduction	Discontinue medication	100 mg/day[a]

[a]If further dose reduction below 100 mg/day is required, discontinue ZEJULA.

Table 4 Dose Modifications for Non-Hematologic Adverse Reactions

Non-hematologic CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	● Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction. ● Resume ZEJULA at a reduced dose per Table 3
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered ZEJULA 100 mg/day	Discontinue medication.

CTCAE=Common Terminology Criteria for Adverse Events

Management of hematologic adverse reactions is described in Table 5.

Table 5 Dose Modifications for Hematologic Adverse Reactions

Monitor complete blood counts weekly for the first cycle, periodically according to the study flow after this time.	
Platelet count <100,000/μL	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.
Neutrophil <1,000/μL or Hemoglobin <8g/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	● 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.

[a] If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue niraparib.

For major surgery, up to 28 days of drug interruption is allowed.
Once the dose of study treatment has been reduced, any re-escalation must be discussed with the medical monitor.
All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the eCRF.

5.2.3 Bevacizumab Dose Modification

Bevacizumab, may be reduced, interrupted, or discontinued at the investigator's discretion per the approved product label and local regulations. If bevacizumab is interrupted or discontinued, niraparib may be continued.

5.3 Randomization or Treatment Allocation

Not available

5.4 Stratification

Not available

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participants's primary physician.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Parcticipants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial: (Refer 5.1.3)

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than niraparib
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor

5.6 Participant Withdrawal/Discontinuation Criteria

Patients may be discontinued from treatment or from the study for the following reasons:
Discontinuation from treatment:

• Any treatment-related CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or 4 events that have not reverted to CTCAE grade 1 or less within 4 weeks (28-days). At the Investigator‘s discretion, following dose interruption (no longer than 28 days), patients may be considered for dose reductions, providing they have not already undergone the maximum number of 2 dose reductions allowed. If upon re-challenging with study treatment at the lowest allowable dose, any CTCAE grade 3 or 4 adverse events recur, the patient must be discontinued.

- Disease progression according to RECIST 1.1 criteria
- Risk to patients as judged by the Investigator and/or Sponsor
- Severe non-compliance with the protocol as judged by the Investigator and/or Sponsor
- Patient request
- The patient becomes pregnant

Discontinuation from the study
: Patients who discontinue from treatment will continue to receive follow-up assessments as part of the study unless they are discontinued from the study by one of the following events:

- Withdrawal of consent by the patient, who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Death from any cause
- Patient lost to follow-up

Patients who withdraw from the main study will not be replaced.

5.7 Participant Replacement Strategy

Not available

5.8 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

In the event of TAKEDA decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles**										**End of Treatment**	**Post-Treatment**		
		1						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	D1	D8	D15	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits [i]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	0	±1	±1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon + 7	Every 12 weeks post discon (± 7)	Every 12 weeks (± 7)
Administrative Procedures															
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X														
Post-study anticancer therapy status												X	X	X	X
Survival Status		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments															
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X														
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG	X														
Bevacizumab		X			X	X	X	X	X	X	X				
Niraparib		X	X	X	X	X	X	X	X	X	X				
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															

Trial Period:	**Screening Phase**	**Treatment Cycles**										**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1			2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits [i]	Survival Follow-Up
		D1	D8	D15				5	6	7	8				
Scheduling Window (Days):	-28 to -1	0	±1	±1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon + 7	Every 12 weeks post discon (± 7)	Every 12 weeks (± 7)
Pregnancy Test – Urine or Serum β-HCG	X											X			
PT/INR and aPTT	X														
CBC with Differential[b]	X	X[a]	X	X	X	X	X	X	X	X	X	X			
Comprehensive Serum Chemistry Panel[c]	X	X[a]	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X	X[a]			X	X	X	X	X	X	X	X			
T3, FT4 and TSH[d]	X						X			X		X			
CA-125 [e]	X						X			X					
HIV/HBV/HCV[f]	X														
Efficacy Measurements															
Tumor Imaging[g]	X	X [j]												X	X
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood															
Archival Tissue Collection	X														
Correlative Studies Blood Collection[i] (Blood sample A)		X	X		X		X			X		X			
Correlative Studies Blood Collection[i] (Blood sample B)		X													
Tumor biopsy[h]	X											X			

a. If the screening test was performed within 7days prior to C1D1, additional test is not required.

b. Perform prior to each cycle as below test:

- WBC(total) / Hemoglobin / Platelets / ANC(Absolute Neutrophil Count)

c. Perform prior to each cycle as below test:

- Calcium / Phosphorus / Glucose / Uric acid / BUN / Creatinine / Cholesterol / Total protein / Albumin / Total bilirubin / Alkaline phosphate / AST(SGOT) / ALT(SGPT) / LDH / Magnesium / Sodium / Potassium / Chloride / CO2(or bicarbonate)

d. If TSH result is not within normal range, perform the T3/Free T4 test additionally.

e. . After the first day of cycle 1, proceed according to the cycle at intervals of 3 cycles. It may be performed more frequently if clinically indicated.

f. Perform the test as below:

- HIV / HBsAg / Anti-HCV

g. For participants who discontinued for reasons other than radiographic PD, imaging continues until radiographically documented PD by the investigator, initiation of a new anti-cancer therapy, withdrawal of consent, becoming lost to follow-up, pregnancy, or death, whichever occurs first. Follow-Up visits may be scheduled to coincide with Follow-Up imaging.

h. Tissue collection of the screening period and at the end of treatment can only be performed optionally for those who agree.

i. The collection of correlative blood sample can only only be performed optionally for those who agree.

j. Tumor imaging assessment should be performed every 9 weeks(± 7days) from cycle 1 day 1. It may be performed more frequently if clinically indicated.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to enrollment. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.
Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.
A single participant cannot be assigned more than 1 treatment/randomization number.

7.1.2 Clinical Procedures/Assessments

Blood tests and imaging tests performed in this study were planned to be performed under standard medical procedures. The tester or qualified person shall monitor adverse reactions and perform tumor imaging tests for diseases according to the clinical trial schedule.

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

When the Investigator identifies radiographic progression per RECIST 1.1, efforts should be made to verify radiologic PD. Treatment should continue until PD has been verified.

Note: For the purpose of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of allocation.

Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

Tumor Imaging During the Study

The study imaging assessment should be performed every 9 weeks (±7 days) from the date of allocation. more frequently if clinically indicated. After approximately 3 years (After Week 156), participants who remain on study And have no evidence of disease will have imaging performed every 24 weeks (168 days±14 days). Imaging should continue to be performed until disease progression is identified by the Investigator. The timing of tumor imaging should follow the calendar days and should not be rescheduled even if the start of the cycle of tumor imaging is delayed.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 3cycles, starting with the next scheduled imaging time point. Participants who receive additional imaging for

confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or every 12 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

Imaging Visit	Description
Baseline	Perform imaging within 28 days prior to allocation To confirm CR or PR from previous platinum-based chemotherapy, imaging must be performed.
Treatment period	Imaging performed every 9 weeks (± 7days) from the date of allocation.
Post-treatment Follow-up imaging	Participants who discontinue study treatment without documented disease progression should continue monitoring disease status by tumor imaging Q9W (63 days ± 7) through Week 54 and Q12W thereafter.
End of Treatment	Imaging performed at the time of treatment discontinuation (±4 weeks). If previous imaging was obtained within 4 weeks before the date of discontinuation, then imaging at treatment discontinuation is not mandatory.
Abbreviations: CR = complete response; PD = progressive disease; PR = partial response	

RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment).

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Participant in this study will be dependent upon participants supplying tumor tissue and blood for biomarker analysis. An archival tissue and/or pre, on, post-treatment core needle or excision biopsy is preferred. Submission of either FFPE tumor blocks or unstained slides for archival tissue and pre-chemotherapy sample is acceptable.

- Collection of archival samples (FFPE or fresh-frozen)
- Pre-chemotherapy radiological guided biopsy (3 cores) if lesions are deemed safe and accessible by the investigator
- Pre-treatment & Post-treatment radiological guided biopsy (3 cores) if lesions are deemed safe and accessible by the investigator
- Blood will be collected for ctDNA, PBMC, and plasma analysis.

Participants must sign the main study ICF prior to submitting existing tissue samples and/or undergoing a new biopsy.

Archival samples, pre-treatment/ on-treatment sample, and post-treatment sample will be submitted. Blood samples A will be collected in C1D1, C1D8, C2D1 and, every 3 cycles after C4D1 during treatment period. Blood sample B will be collected twice, before the C1D1 and after the end of the test.

Comprehensive genomic profiling & immune biomarker exploration (exome sequencing, RNA sequencing, and immunohistochemistry) will be performed for all samples to find the predictive biomarkers for combination therapy of niraparib and bevacizumab.

- Responder for combination therapy

BRCA reversion and HRD phenotype changes will be checked through serial samples. (somatic HR mutations, germline HR mutations, altered gene expression, functional HR deficiency, genomic scars, RAD51 foci formation).

BRCA reversion mutations will be checked through circulating tumor DNA serial samples

- Immune dynamic change

RNA sequencing will be performed to identify immune dynamic changes between at pre-treatment and at progression.

- Analysis of immune marker using FACS

FACS will be performed to examine the phenotypic characteristics of CD4 and CD8 T cells in terms of various immune check points (PD-1, CTLA4, TIM3, LAG3) and memory markers (CD45RO+CCR7+) in fresh tissue and PBMC.

tumor infiltrating immune cells including Treg cells and MDSCs will be evaluated on pre-treatment & at progression.

- PD-L1 testing and multiplex IHC

PD-L1 expression level will be checked through serial samples. TPS and CPS will be calculated.

Using established platform of Vectra, multispectral imaging will be performed to identify tumor microenvironment compresensively.

- Exploratory biomarker analysis

From C1D1 blood samples, ctDNA, PBMCs and plasma will be isolated and stored for exploratory biomarker analysis. Serial blood samples A will be collected in C1D1 and C1D8 and every 3 cycles after C4D1 during treatment period for ctDNA. Blood sample B will be collected twice, before the C1D1 and after the end of the test.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
WBC (total and differential)	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)[a]
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
Absolute Neutrophil Count	Aspartate aminotransferase (AST)	Specific gravity	aPTT
	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)[c]
	Carbon Dioxide [b] *(CO_2 or biocarbonate)*	results are noted	Free tyroxine (T4) [c]
	Uric Acid	Urine pregnancy test [a]	Thyroid stimulating hormone (TSH)
	Calcium		CA-125
	Cholesterol		HIV
	Chloride		HBsAg
	Glucose		Anti-HCV
	Phosphorus		
	Potassium		Blood for correlative studies
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

a. Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

b. If considered standard of care in your region.

c. If TSH result is not within normal range, perform the T3/Free T4 test additionally.

7.1.4 Other Procedures

7.1.4.7 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

7.1.4.8 Blinding/Unblinding

Not available

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.7 Screening

Screening Period

Within 28 days prior to allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.
Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28-day Screening Period, except for the following:
o Laboratory tests are to be performed within 10 days prior to the initiating study treatment. An exception is HIV and hepatitis testing which may be done up to 28 days prior to the first dose of study treatment if required by thelocal health authority.

o Clinical chemistry and hematological parameters are to be reassessed within 10 days of treatment
o Evaluation of ECOG is to be performed within 10 days prior to allocation.
o For WOCBP, a urine pregnancy test will be performed within 72 hours prior to initiating allocation. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
o Newly obtained tissue may be obtained at any time prior to the administration of investigational product.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial Screening Period are acceptable in lieu of a repeat

screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

7.1.5.8 Treatment Period

Visit requirements are outline in the study flow chart. Specific procedure-related details are provided in Section

7.1.5.9 Post-Treatment Visits

7.1.5.3.1 Post-Treatment Visits

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

7.1.5.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.2 Safety Reporting

Institution/Investigator is solely responsible for reporting all Adverse Events and Serious Adverse Events to regulatory authorities, investigators, IRBs or IECs and Takeda, as applicable, in accordance with national regulations in the countries where the study is conducted.

Regardless of expectedness or causality, all SAEs, Adverse Events of Special Interest (AESI), if applicable and pregnancy reports must also be reported in English by email to Takeda Pharmacovigilance or designee within 24 hrs of the Institution / Investigator awareness of the event.

If there is additional information on the reported adverse drug reactions, they should be reported until the adverse drug reaction is terminated (ie, the adverse drug reaction disappears or the follow-up investigation becomes impossible).

Takeda Safety Reporting Contact Information

E-mail: DSO-KR@takeda.com

Takeda requires that all information be communicated to Takeda's Pharmacovigilance Department as outlined in the study contract.

All reported adverse drug reactions and safety issues related to Takeda compound must be included in the final study report.

Describe procedures for reporting Adverse Events and Serious Adverse Events.

Definitions:

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure*.

* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

Serious AE (SAE) means any untoward medical occurrence that at any dose:

1) results in **death**,
2) is **life-threatening**,
   Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
3) requires inpatient **hospitalization or prolongation of present hospitalization**,
4) results in **persistent or significant disability/incapacity**,
5) leads to a **congenital anomaly/birth defect**,

6) Important Medical Event that satisfies any of the followings
   - may require intervention to prevent one of 1)-5) above or may expose the patient to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (TMSL) below.

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
COVID-19 related disease	Neuroleptic malignant syndrome / malignant hyperthermia
COVID-19 pneumonia	Spontaneous abortion / stillbirth and fetal death

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must report a completed Pregnancy Form in English by email to the Takeda Pharmacovigilance or designee immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee will request this information from the sponsor-investigator. Please refer to study contract for Takeda pharmacovigilance contact information.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately report a completed Pregnancy Form in English by email to the Takeda Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome. Please refer to study contract for Takeda pharmacovigilance contact information.

Procedures for Reporting Adverse Events of Special Interest (AESI)

An AESI (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the Investigator to Takeda Pharmaceuticals Korea may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for Investigators as to how and when they should be reported to Takeda Pharmaceuticals Korea. AESI for niraparib are the following:

-Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)

-Second Primary Malignancies (Other than MDS & AML)

-Embryo-fetal toxicity

-Severe Renal Impairment

-Severe Hepatic Impairment

8.0 STATISTICAL ANALYSIS PLAN

8.1 Sample Size Determination

The sample size was calculated based on a Simon's Two-stage optimal design with assumptions concerning the estimated PFS rate in ovarian cancer. Prior to interim analysis, conditions were given to register more than half of patients to register. After recruiting 22 patients, interim analysis to determine futility of the treatment will be conducted.

The rate of patients with progression-free state at 6 months is expected as 50% without maintenance (current SOC, results from GOG 213 & SOLO-2), and HR of adding maintenance therapy of niraparib retreatment with bevacizumab was assumed to 0.5, which was equivalent to 70.7% of PFS rate. When applying the same expected efficacy (HR=0.5) with PAOLA-1 study (PARP inhibitor+ anti-angiogenic therapy), the null hypothesis for this study will be 50% of 6 month PFS rate, and alternative hypothesis of interest will be 70% of 6 month PFS rate.

Using Simon’s two stage optimal design at a one-sided 5% level of significant and 80% power, totally 39 patients are required in this study. In 1st stage, 22 patients will be enrolled and followed up for 6 months, then if 10 or more PD are observed, the trial will be terminated. If not, the trial continues to the 2nd stage, a total of 39 patients will be studies. If the total number of PD is less than 15 or equal to, the null hypothesis is rejected. Considering 10% follow-up loss, the sample size will be 44 patients.

8.2 Statistical Analysis Plan

- A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

- Efficacy and safety analyses are based on the modified intent-to-treat (ITT) approach (patients should receive at least one treatment dose).
- The primary analysis of the primary endpoint of 6 months-PFS rate will be performed when all enrolled patients have completed 6 months of follow-up and/or investigator-assessed response assessments have been completed for all patients. All secondary endpoints will be evaluated at this time. Additional updated analyses of efficacy and safety may be conducted at later times if deemed appropriated.

- Safety analyses are based on the safety population (at least one dose of study drug). Adverse events are graded according to CTCAE version 5.0. Safety analyses will include summaries of the following:
    - AEs, including severity and possible relationship to study drug
    - SAEs, including possible relationship to study drug
    - AEs leading to dose adjustments
    - discontinuations from study treatment due to AEs or death
    - treatment emergent abnormal changes in laboratory values
    - treatment emergent abnormal changes in vital signs and ECGs.
- Missing data will not be replaced by other data, and if tumor imaging assessment was missed, disease progression or death, if new anticancer therapy has been initiated, the data will be censored at the last assessment prior to initiation of new anticancer treatment.
- Descriptive statistics will be used to summarize the characteristics of the study patients.
- From time-to-event variables, such as PFS, Duration of response and OS, the Kaplan-Meier method will be used to estimate the curves, median time and 95% CI.

Endpoint	Statistical Analysis Methods
6 months PFS rate	The 6-month PFS rate is defined as the proportion of patients who are alive and progression-free 6 months after the first dose of study therapy . For 6 months PFS rate, point estimate and the one-sided 95% CI will be provided.
PFS	PFS according to RECIST 1.1, is defined as the time from first administration of study intervention until date of the first documentation of PD or death due to any cause in the absence of documented PD, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death), for participants who start new anticancer treatment prior to an event, or for participants with an event after two or more missing tumor assessments. Participants who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the date of first administration of study intervention unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

	Kaplan-Meier estimates will be provided; Median PFS and the 95% confidence interval for the median will be calculated.
Overall survival	Overall survival is defined as the time from first administration of study intervention to the date of death due to any cause. Participants last known to be alive will be censored at date of last contact. Kaplan-Meier estimates will be provided; Median OS and the 95% confidence interval for the median will be calculated.

Other endpoints

- PFS2 is defined the time from initial treatment to the earlier data of assessment of progression on the next anticancer therapy following study treatment or death by an cause.
- Time to first subsequent therapy (TFST) is defined as the date of initial treatment in the current study to the start date of the first subsequent anticancer therapy.
- Time to second subsequent therapy (TSST) is defined as the date of initial treatment in the current study to the start date of the second subsequent anticancer therapy.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Niraparib will be provided by TAKEDA as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Zejula (Niraparib) 100mg	Capsule

1.1 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

1.2 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

1.3 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

1.4 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from TAKEDA or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

2.0 ADMINISTRATIVE AND REGULATORY DETAILS

Not available

3.0 REFERENCES

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Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. The Lancet Oncology 2014;15:1207-14.

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Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-2164.

Mirza, M.R, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol, 2019. 20(10): p. 1409-1419.

Ray-Coquard, I, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med, 2019. 381(25): p. 2416-2428.

APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8 during the protocol-defined time frame.

Table 8Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 180 days following the last dose of Niraparib and at least following the last dose of bevacizumab. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.