Protocol Amendment 01 (Version:2.0)

Study ID: 213358

Official Title of Study: A PHASE 2, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NIRAPARIB COMBINED WITH BEVACIZUMAB AS MAINTENANCE TREATMENT IN PATIENTS WITH ADVANCED OVARIAN CANCER, FALLOPIAN TUBE CANCER, OR PRIMARY PERITONEAL CANCER FOLLOWING FRONT-LINE PLATINUM-BASED CHEMOTHERAPY WITH BEVACIZUMAB

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NIRAPARIB; BEVACIZUMAB

3000-02-004

A PHASE 2, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NIRAPARIB COMBINED WITH BEVACIZUMAB AS MAINTENANCE TREATMENT IN PATIENTS WITH ADVANCED OVARIAN CANCER, FALLOPIAN TUBE CANCER, OR PRIMARY PERITONEAL CANCER FOLLOWING FRONT-LINE PLATINUM-BASED CHEMOTHERAPY WITH BEVACIZUMAB

Sponsor:	TESARO, Inc. 1000 Winter Street, Suite 3300 Waltham, MA 02451 PPD	TESARO UK, Limited 55 Baker Street London W1U7EU United Kingdom PPD
Medical Monitor:	PPD , MD PPD PPD	
Clinical Research Organization:	Not applicable	
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SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title (3000-02-004): A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of Niraparib Combined with Bevacizumab as Maintenance Treatment in Patients with Advanced Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer Following Front-Line Platinum-Based Chemotherapy with Bevacizumab

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

PPD

Divya Gupta, MD
Medical Director, TESARO

PPD

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for niraparib. I have read the 3000-02-004 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SYNOPSIS

Name of Sponsor/Company: TESARO

Name of Investigational Product: Niraparib and bevacizumab

Name of Active Ingredient: Niraparib and bevacizumab

Title of Study: A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of Niraparib Combined with Bevacizumab as Maintenance Treatment in Patients with Advanced Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer Following Front-Line Platinum-Based Chemotherapy with Bevacizumab

Study center(s): Approximately 35 sites

Principal Investigator: To be determined

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled: Q4 2017 Estimated date last patient completed: Q4 2022	Phase 2

Objectives:

Primary:

- To evaluate the efficacy of niraparib in combination with bevacizumab, as assessed by 18-month progression-free survival (PFS) landmark analysis, in patients with Stage IIIB to IV ovarian cancer who have complete response (CR), partial response (PR), or no evidence of disease (NED) following front-line, platinum-based chemotherapy with bevacizumab

Secondary:

- To evaluate additional measures of clinical benefit, including PFS, RECIST or CA-125 progression free survival, overall survival (OS), patient-reported outcome (PRO) measures, time to first subsequent therapy (TFST), and time to second subsequent therapy (TSST)
- To evaluate the safety and tolerability of niraparib and bevacizumab combination in the indicated target population

Exploratory

- To evaluate PFS rate at 6 months (PFS6) and 12 months (PFS12)
- Retrospective analysis to evaluate homologous recombination deficiency (HRD) per the Myriad myChoice® HRD test as a potential biomarker for response to the niraparib and bevacizumab combination

Methodology:

Overall Study Design

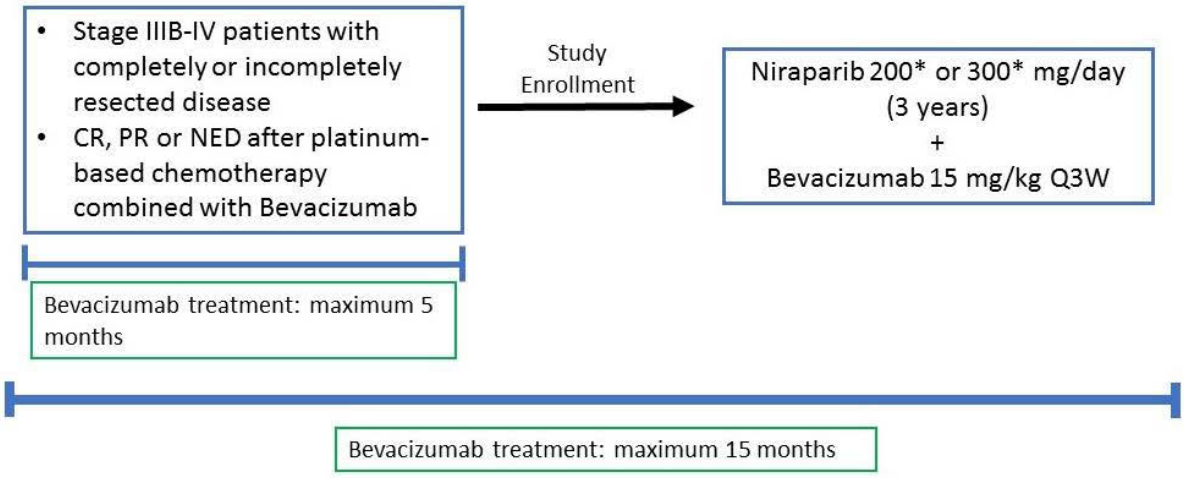
This is a multicenter, Phase 2, single-arm, open-label study to evaluate niraparib combined with bevacizumab as maintenance treatment in patients with advanced (Stage IIIB-IV) ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with completely or incompletely resected disease who are recovered from primary debulking surgery.

Approximately 90 patients will be enrolled.

Eligible patients who achieve CR, PR, or NED following treatment with platinum-based chemotherapy in addition to bevacizumab will be enrolled in the study and receive maintenance treatment with niraparib (for up to 3 years) combined with bevacizumab (for up to 10 months during the maintenance phase or up to a total of 15 months inclusive of the approximately 5 months of bevacizumab received with

chemotherapy) or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death, whichever comes first (see Study Design Schema). Patients who have not progressed after 3 years of niraparib maintenance treatment will be given the option to continue with niraparib beyond 3 years if they are tolerating and benefiting from treatment and after consultation with the Sponsor.

Study Design Schema



Abbreviations: CR = complete response; NED = no evidence of disease; PR = partial response.
*Patients ≥77 kg **and** with platelet count of ≥150,000/µL will receive 300 mg/day; patients <77 kg **and/or** with platelet count of <150,000 u/L will receive 200 mg/day

Study Conduct

Safety assessments conducted throughout the treatment period include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment discontinuations or dose reductions due to adverse events (AEs), changes in Eastern Cooperative Oncology Group (ECOG) performance status, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications.

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 tumor assessment via computed tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen/pelvis and clinically indicated areas is required at screening, then every 12 weeks (±7 days) from Cycle 1/Day 1 visit for the first 48 weeks, then every 24 weeks (±14 days) until disease progression, at which point a final follow-up set of imaging scans is required. Positron emission tomography (PET)/CT may be used according to RECIST v1.1 guidelines, but its use is not a study requirement.

Tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans should continue at the specified intervals

RECIST v1.1 is used to define progressive disease (PD) in this study. Tumor assessment by CT/MRI must unequivocally show PD according to RECIST v1.1 criteria. PD will not be diagnosed in case of CA-125 progression in the absence of radiologic evidence of progressive disease.

If a patient had a CT/MRI of the abdomen/pelvis and clinically indicated areas within the 28-day screening window before Cycle 1/Day 1 but prior to signing the main informed consent form (ICF), the patient is not required to complete an additional CT/MRI scan for study screening.

PROs (Functional Assessment of Cancer Therapy-Ovarian Symptom Index [FOSI]) will be collected every 6 weeks (±7 days) for 6 months, then every 12 weeks (±7 days) thereafter while the patient is receiving study treatment. Once a patient discontinues treatment, PRO evaluations will be performed 4 weeks (±7 days), 8 weeks (±7 days), 12 weeks (±7 days), and 24 weeks (±7 days) after treatment discontinuation, regardless of subsequent treatment.

All patients will undergo an End of Treatment Visit within 7 days of the decision to discontinue treatment for any reason. Post-treatment follow-up visits will be conducted every 12 weeks (±14 days) after the last dose of study treatment.

All AEs and SAEs, regardless of causality, will be collected and recorded for each patient from the day the ICF is signed until 90 days after the last dose of study treatment. Any pregnancies that occur are to be reported. All AEs and SAEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the change(s) observed, until the patient is lost to follow-up or withdraws consent, or until the patient has died.

The adverse events of special interest (AESIs) for this study are myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), pneumonitis, embryo-fetal toxicity, and secondary cancer (new malignancies other than MDS/AML). AESIs must be reported to the Sponsor as soon as the Investigator becomes aware of them or within 24 hours.

Number of patients (planned): Approximately 90 patients will be enrolled into the study

Diagnosis and main criteria for inclusion:

Criteria for inclusion

To be considered eligible to participate in this study, all of the following inclusion criteria must be met:

1. Patients must be female, be ≥ 18 years of age, be able to understand the study procedures, and agree to participate in the study by providing written informed consent.
2. Patients must have newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) Stage IIIB to IV epithelial ovarian, fallopian tube, or peritoneal cancer and have recovered from debulking surgery.
3. Patients must have high-grade serous or endometrioid or high-grade predominantly serous or endometrioid histology, regardless of HRD or germline breast cancer susceptibility gene (g*BRCA*) mutation status. Patients with non-mucinous epithelial ovarian cancer and g*BRCA* mutation are eligible.
4. Patients must have completed front-line, platinum-based chemotherapy with CR, PR, or NED and have first study treatment dose within 12 weeks of the first day of the last cycle of chemotherapy:
    a. A platinum-based regimen must have consisted of a minimum of 6 and a maximum of 9 treatment cycles. Patients who discontinued platinum-based therapy early as a result of non-hematologic toxicity specifically related to the platinum regimen (ie, neurotoxicity or hypersensitivity) are eligible if they have received a minimum of 4 cycles of the platinum regimen.
    b. Intravenous (IV), intraperitoneal, or neoadjuvant platinum-based chemotherapy is allowed; for weekly therapy, 3 weeks is considered 1 cycle. Interval debulking is allowed.
5. Patients must have received, prior to enrollment, a minimum of 3 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy. Patients who undergo

interval debulking surgery are eligible if they have received only 2 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy.

6. Patients must have had 1 attempt at optimal debulking surgery.
7. Patients must have either CA-125 in the normal range or CA-125 decrease by more than 90% during front-line therapy that is stable for at least 7 days (ie, no increase > 15% from nadir).
8. Patients must have adequate organ function, defined as (Note: complete blood count [CBC] test should be obtained without transfusion or receipt of stimulating factors within 2 weeks before obtaining screening blood sample):
    a. Absolute neutrophil count (ANC) ≥ 1,500/μL
    b. Platelet count ≥ 100,000/μL
    c. Hemoglobin ≥ 9 g/dL
    d. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation
    e. Total bilirubin ≤ 1.5 × ULN OR direct bilirubin ≤ 1 × ULN
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN unless liver metastases are present, in which case they must be ≤ 5 × ULN
9. Patients must have an ECOG score of 0 or 1.
10. Patients must have normal blood pressure or well-controlled hypertension.
11. Patient must agree to complete PROs (FOSI) throughout the study, including after study treatment discontinuation.
12. Patients must be able to take oral medication.
13. Patient must agree to undergo tumor HRD testing at screening. The tumor sample must be confirmed to be available during the screening period and submitted after the patient has been enrolled; patients do not have to wait for the HRD test result to be enrolled. If archival tumor tissue is not available for testing, the patient must agree to undergo a fresh biopsy.
14. Patients of childbearing potential must have a negative serum or urine pregnancy test (beta human chorionic gonadotropin) within 72 hours prior to receiving the first dose of study treatment.
15. Patients must be postmenopausal, free from menses for > 1 year, surgically sterilized, or willing to use adequate contraception to prevent pregnancy or must agree to abstain from activities that could result in pregnancy throughout the study, starting with enrollment through 180 days after the last dose of study treatment.

Criteria for exclusion

A patient will be considered ineligible for study participation if any of the following exclusion criteria are met:

1. Patients with ovarian tumors of non-epithelial origin (eg, germ cell tumor) or any low-grade tumors.
2. Patients with clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, myocardial infarction, cardiac arrhythmia or unstable angina < 6 months to enrollment, New York Heart Association [NYHA] Grade II or greater

congestive heart failure, serious cardiac arrhythmia requiring medication, Grade II or greater peripheral vascular disease, and history of cerebrovascular accident [CVA] within 6 months).

3. Patients with gastrointestinal disorders or abnormalities that would interfere with absorption of study treatment.
4. History of bowel obstruction, including sub-occlusive disease, related to the underlying disease or history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscesses. Evidence of rectosigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction.
5. Patient has proteinuria as demonstrated by urine protein:creatinine ratio ≥ 1.0 at screening or urine dipstick for proteinuria ≥ 2 (patients discovered to have ≥ 2 proteinuria on dipstick at baseline should undergo a 24-hour urine collection and must demonstrate < 2 g of protein in 24 hours to be eligible).
6. Patient has any known history or current diagnosis of MDS or AML.
7. Patient has received treatment previously with a poly(ADP-ribose) polymerase (PARP) inhibitor.
8. Other than ovarian cancer, the patient has been diagnosed or treated for invasive cancer less than 5 years prior to study enrollment. Patients with cervical carcinoma in situ, non-melanomatous skin cancer, and ductal carcinoma in situ definitively treated are allowed.
9. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection.
10. Patient has known contraindication to PARP inhibitors or vascular endothelial growth factor (VEGF) inhibitors.
11. Patient is at increased bleeding risk due to concurrent conditions (eg, major injuries or surgery within the past 28 days prior to start of study treatment, history of CVA, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months).
12. Patient is immunocompromised (patients with splenectomy are allowed).
13. Patient has known, active hepatic disease (ie, hepatitis B or C).
14. Patient has a QT interval prolongation > 480 ms at screening. If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (ie, the patient otherwise has no cardiac abnormalities), then the patient may be eligible to participate in the study following discussion with the Medical Monitor.
15. Patient is pregnant or is expecting to conceive children while receiving study drug and for up to 180 days after the last dose of study drug; additionally, female patients should not breastfeed during treatment with niraparib and for 30 days after receipt of the last dose due to the potential for serious adverse reactions from niraparib in breastfed infants.

Investigational product, dosage and mode of administration:

On Day 1 of each 21-day cycle, bevacizumab 15 mg/kg will be administered via IV infusion.[1] Bevacizumab will be administered for up to 10 months during the maintenance phase or up to a total of 15 months inclusive of the approximately 5 months of bevacizumab received with chemotherapy. Niraparib will be administered orally once a day, continuously throughout each 21-day cycle, for up to

3 years in the absence of PD, unacceptable toxicity, patient withdrawal, Investigator's decision, or death; however, patients who are tolerating and benefiting from treatment will have access to niraparib maintenance treatment as long as considered acceptable by their treating physician and the patient. On Day 1 of each cycle, niraparib will be administered upon completion of bevacizumab infusion.

The starting dose of niraparib will be based on the patient's baseline actual body weight or platelet count. Patients with a baseline actual body weight of ≥77 kg **and** screening platelet count of ≥150,000/μL will take three capsules of 100 mg strength (300 mg) at each dose administration. Patients with a baseline actual body weight of <77 kg **and/or** screening platelet count of <150,000/μL will take two capsules of 100 mg strength (200 mg) at each dose administration. Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation.

Patients will be instructed to take their niraparib dose once a day or as instructed by the Investigator. Patients must swallow and not chew all capsules. The consumption of water and food is permissible.

For patients whose starting dose is 2 capsules (200 mg/day), escalation to 3 capsules (300 mg/day) is permitted if no treatment interruptions or discontinuations were required during the first 2 cycles of therapy. This escalation will occur at the discretion of the Investigator, following discussion with the Medical Monitor.

Dose interruption (no longer than 28 days) or dose reduction will be allowed based on treatment side effects. For patients whose initial dose is 3 capsules daily (300 mg/day), dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule daily (100 mg/day) will be allowed. No further dose reduction will be allowed without discussion with the Medical Monitor.

For patients whose initial dose is 2 capsules (200 mg/day), dose reduction to 1 capsule once daily (100 mg/day) will be allowed. No further dose reduction will be allowed without discussion with the Medical Monitor.

Duration of treatment:

Planned study conduct duration:

The primary efficacy analysis will occur approximately 18 months after the last patient has initiated treatment with maintenance niraparib combined with bevacizumab.

Planned study treatment duration:

Patients may continue bevacizumab maintenance treatment for up to approximately 15 months (up to 10 months during the maintenance phase or up to a total of 15 months inclusive of approximately 5 months of bevacizumab received with chemotherapy) and niraparib maintenance treatment for up to 3 years in the absence of PD, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Patients who are tolerating and benefiting from treatment will have access to niraparib maintenance treatment as long as considered acceptable by their treating physician and the patient.

Reference therapy, dosage and mode of administration: Not applicable.

Criteria for evaluation:

Efficacy:

Primary endpoint

The primary efficacy endpoint is PFS rate at 18 months (PFS18), which is defined as the proportion of patients who have not progressed or died within 18 months after niraparib combined with bevacizumab treatment initiation. Progression will be assessed by RECIST v1.1 criteria per Investigator assessment.

Secondary endpoints

The following secondary endpoints will be evaluated:

- PFS, defined as the time from niraparib combined with bevacizumab treatment initiation to the earlier date of assessment of progression, as assessed by RECIST v1.1 criteria, based on Investigator assessment, or death by any cause in the absence of progression
- RECIST or CA-125 progression-free survival, defined as the time from initiation of treatment of niraparib in combination with bevacizumab to the earliest date of progression assessed by RECIST v1.1 or CA-125 progression, or death by any cause.
- OS as measured from the date of initiation of treatment of niraparib in combination with bevacizumab treatment to the date of death by any cause
- The observed change from baseline in the FOSI PRO assessment
- TFST, defined as the date of initiation of niraparib treatment in combination with bevacizumab treatment in the current study to the start date of the first subsequent anticancer therapy
- TSST, defined as the date of initiation of niraparib treatment in combination with bevacizumab in the current study to the start date of the second subsequent anticancer therapy
- Safety and tolerability of the combination

Exploratory endpoints

The following exploratory endpoints will be evaluated:

- PFS rate at 6 months (PFS6) and 12 months (PFS12)
- HRD status as a potential biomarker for response to niraparib-bevacizumab treatment

Statistical methods:

Sample size considerations

The sample size of the study is driven by the primary endpoint: PFS18. A sample size of 90 patients will provide an 11% precision on the 95% exact confidence interval (CI) of PFS18, assuming a true PFS18 rate of 48%, which corresponds to a median PFS of 17 months based on exponential PFS assumption. The primary endpoint analysis will occur after approximately 3 months of enrollment and an additional 18 months of follow-up.

Analysis populations

Three analysis populations will be defined as follows:

- Safety population: All patients who receive any amount of study treatment (ie, any amount of bevacizumab or niraparib during the study). All safety endpoints will be assessed in the safety population.
- Efficacy population: All patients who receive any amount of niraparib (at least 1 dose). Analyses of baseline characteristics and the primary analysis of efficacy endpoints will be performed on the efficacy population.
- Per-protocol population: All patients in the efficacy population who have no major protocol violations during the study and have at least 1 protocol-required postbaseline tumor assessment.

General methods

The primary endpoint for the study, PFS18, will be estimated using percentage with 95% exact CI. In addition, the probability of PFS at 18 months will be estimated using the Kaplan-Meier method.

All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using the Kaplan-Meier method. Two-sided 95% CIs will be provided where appropriate. No formal statistical testing will be performed. Further details will be provided in the study statistical analysis plan (SAP).

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	activity of daily living
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
BER	base excision repair
BRCA	breast cancer susceptibility gene
CA-125	cancer antigen 125
CBC	complete blood count
CI	confidence interval
CR	complete response
CT	computed tomography
CVA	cerebrovascular accident
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ESMO	European Society for Medical Oncology
EU	European Union
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy–Ovarian Symptoms Index
g*BRCA*	germline breast cancer susceptibility gene
g*BRCA*mut	germline *BRCA* mutation
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
HR	hazard ratio

Abbreviation or Specialist Term	Explanation
HRD	homologous recombination deficiency
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ICF	informed consent form
IV	intravenous
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NED	no evidence of disease
OAE	other adverse events
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFS6	PFS rate at 6 months
PFS12	PFS rate at 12 months
PFS18	PFS rate at 18 months
PR	partial response
PRO	patient-reported outcome
QD	once daily
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
s*BRCA*	somatic *BRCA*
TEAE	treatment-emergent adverse event
TFST	time to first subsequent therapy
TSST	time to second subsequent therapy

Abbreviation or Specialist Term	Explanation
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
WHO	World Health Organization

3. INTRODUCTION

Homologous recombination deficiency (HRD) and dependency on neo-angiogenesis are 2 major vulnerabilities of human cancers that have been successfully exploited therapeutically, as evidenced by recent approvals of poly(ADP-ribose) polymerase (PARP) inhibitors including niraparib (Zejula®) for ovarian cancer and angiogenesis inhibitors including bevacizumab (Avastin®; Genentech/Roche United States [US]) for several indications including ovarian cancer. Emerging pre-clinical and clinical data suggest that combination of these 2 classes of agents may increase therapeutic options for women with ovarian cancer.

3.1. Background of PARP and PARP Inhibition

PARP1 and PARP2 are key enzymes for repairing single-strand deoxyribonucleic acid (DNA) breaks. When they are inhibited, single-strand DNA breaks become double-strand DNA breaks after DNA replication, forcing cancer cells to rely on double-strand break repair mechanisms, in particular homologous recombination, for survival and proliferation.

PARP inhibitors selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline breast cancer susceptibility gene mutation (g*BRCA*mut) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on base excision repair (BER), a pathway blocked by PARP inhibitors, for maintenance of genomic integrity. In addition to breast cancer susceptibility gene (*BRCA*) mutations, DNA-repair defects can be caused by germline or somatic alterations to dozens of genes in the homologous recombination DNA repair pathway. In a recent analysis of ~500 high-grade serous ovarian cancer tumors, approximately 50% contained homologous recombination defects, which could sensitize tumors to PARP inhibitors.[2] This concept of inducing tumor cell death in tumors with inherent defects in DNA repair using PARP inhibitors is called synthetic lethality.[3]

3.2. Background of Niraparib

Niraparib is a PARP inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who exhibit a complete response (CR) or partial response (PR) to platinum-based chemotherapy.

Niraparib is an oral inhibitor of PARP-1 and PARP-2, which play a role in DNA repair. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage, apoptosis, and cell death. Increased niraparib-induced cytotoxicity was observed in tumor cell lines with or without deficiencies in *BRCA*1/2. Niraparib decreased tumor growth in mouse xenograft models of human cancer cell lines with deficiencies in *BRCA*1/2 and in human patient-derived xenograft tumor models with homologous recombination deficiency that had either mutated or wild type *BRCA*1/2.

Niraparib has been evaluated in a series of Phase 1 clinical studies in patients with solid tumors, as well as in a Phase 3 study of 546 patients with platinum-sensitive recurrent ovarian cancer who had received at least 2 previous chemotherapy regimens and received niraparib or placebo maintenance ("ENGOT-OV16/NOVA" study).

The ENGOT-OV16/NOVA study[4] is a double-blind, 2:1 (niraparib:placebo) randomized, placebo-controlled study of maintenance treatment with niraparib compared with placebo in patients with platinum- sensitive ovarian cancer who have received at least 2 platinum-based regimens, had a response to their last regimen, and have no measurable disease >2 cm and normal cancer antigen 125 (CA-125) (or >90% decrease) following their last treatment. There were 2 independent patient cohorts comprising patients who have deleterious g*BRCA*mut versus those who have a tumor with high-grade serous histology but without g*BRCA*mut (non-g*BRCA*mut). Patients in the non- g*BRCA*mut cohort are further characterized by tumor HRD status (positive or negative).

A total of 553 patients were randomized into this Phase 3 study at 107 centers worldwide. The study population comprises 203 patients randomized into the g*BRCA*mut cohort and 350 patients randomized into the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were defined as HRDpos and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined (HRDnd) for 54 patients.

Demographic and baseline characteristics were well-balanced.

Table 2 shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, g*BRCA*mut cohort, HRDpos cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRD negative (HRDneg) tumors was 6.9 months (95% CI: 5.6, 9.6) in the niraparib arm compared to 3.8 months (95% CI: 3.7, 5.6) in the placebo arm with an HR of 0.58 (95% CI: 0.361, 0.922) (p=0.0226).

Table 2: Progression-Free Survival in Ovarian Cancer Patients in NOVA

	gBRCAmut Cohort		**non-gBRCAmut Cohort** (regardless of HRD status)		**HRDpos (within non-gBRCAmut cohort)**	
	Niraparib (N=138)	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**	**Niraparib (N=106)**	**Placebo (N=56)**
PFS Median (95% CI)[a]	21.0 (12.9, NR)	5.5 (3.8, 7.2)	**9.3 (7.2, 11.2)**	**3.9 (3.7, 5.5)**	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value	<0.0001		<0.0001		<0.0001	
Hazard Ratio (Nir:Plac) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	
Progression-free survival is defined as the time in months from the date of randomization to progression or death.						

The primary data to support the safety of treatment with niraparib in this proposed indication are derived from the ENGOT-OV16/NOVA main study in which a total of 546 patients received study treatment. Safety presentations for the NOVA study are derived from the analyses included in the clinical study report and include comparisons of the safety profile of niraparib maintenance treatment versus placebo in women with platinum-sensitive recurrent ovarian cancer.

All patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the

placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Grade 3/4 TEAEs (74% vs 23%), serious adverse events (SAEs) (30% vs 15%), TEAEs leading to treatment interruption (69% vs 5%), TEAEs leading to dose reduction (67% vs 15%), and TEAEs leading to treatment discontinuation (15% vs 2%) were higher for niraparib. There were no on-treatment deaths reported. The incidence of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) in patients who received niraparib (5 of 367; 1.4%) was similar to the incidence in patients who received placebo (2 of 179; 1.1%). MDS/AML and secondary cancers (new malignancies other than MDS or AML) are potential risks of PARP inhibitors.

The selection of the 300 mg starting dose of niraparib for the phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in the ENGOT-OV16/NOVA study was based on data from the Phase 1 MAD study PN001 conducted by Merck & Co. There were no formal Phase 2 dose-ranging studies conducted. The Phase 1 study included both a dose escalation phase to determine the maximal tolerated dose and an expansion arm to further evaluate the selected dose. A total of 104 patients with advanced solid tumors were evaluated in this study, including 60 during dose escalation from 30 mg to 400 mg and 54 during expansion at the 300 mg dose level. The dose escalation stage determined that 400 mg exceeded the maximal tolerated dose (by traditional dose-limiting toxicity evaluations and by using the pooled adjacent violators algorithm). No dose-limiting toxicities were observed at 290 or 300 mg dose levels. In the Phase 3 study, daily niraparib improved progression-free survival (PFS) in a cohort of patients with g*BRCA* mutation as well as in a cohort of patients without g*BRCA* mutation. Within the g*BRCA*mut cohort, the median PFS was 21.0 months in patients on niraparib versus 5.5 months on placebo (hazard ratio [HR], 0.27; $p < 0.0001$). In recurrent ovarian cancer patients, efficacy was assessed in patients with HRD-positive tumors as identified by the Myriad's myChoice HRD test as well in the overall non-g*BRCA* mutation cohort regardless of HRD status. As observed in the g*BRCA*mut cohort, PFS was significantly longer with niraparib in the homologous recombination deficient-positive group of the non-g*BRCA*mut (without germline *BRCA* mutation) cohort (median, 12.9 months vs 3.8 months; HR, 0.38; $p < 0.0001$). Lastly, PFS was significantly improved in the overall non-g*BRCA*mut cohort (median, 9.3 months vs 3.9 months; HR, 0.45; $p < 0.0001$). Secondary endpoints, including chemotherapy-free interval, time to first subsequent therapy (TFST), and progression-free survival 2 (PFS2), confirmed the PFS benefit of niraparib treatment in both cohorts. This provides compelling evidence that niraparib does not diminish responsiveness to subsequent therapy and that the niraparib treatment effect persists. Subsequently in 2017, a recommendation to consider niraparib maintenance therapy in this setting in cases of CR and PR was added to the National Comprehensive Cancer Network (NCCN) guidelines.[5]

The most commonly observed non-hematologic treatment-emergent adverse events (TEAEs) of any National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade were nausea, fatigue, constipation, and vomiting; the majority of the non-hematologic TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (any grade) were anemia (48.5%), thrombocytopenia 66.2%), and neutropenia (31.4%).

TEAEs leading to treatment interruption, reduction or discontinuation were 68.9%, 66.5% and 14.7% respectively. Approximately 50% of patients required dose interruption during the first month of niraparib therapy, and 47% required dose reduction during the second month of therapy. Most patients achieved their individual maximal tolerated dose by the third month. The average dose of niraparib during the study was 206 mg. After Month 3 or 4, new incidents of thrombocytopenia were reported in < 1% of patients. Although Grade 3 or 4 hematologic laboratory events were common at the initiation of treatment, no severe clinical sequelae were observed, and relatively few patients discontinued due to these AEs (discontinuation rate was 3.3% for thrombocytopenia, 1.4% for anemia and 1.9% for neutropenia). Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these events beyond Cycle 3. Furthermore, PFS in patients who were dose reduced to either 200 mg or 100 mg was consistent with PFS for the patients who remained at 300 mg indicating that patients who required dose reduction do not appear to have decreased efficacy relative to those who remain at the 300 mg starting dose.

These data support that each patient has an optimal benefit/risk at their individualized dose. As lower doses are associated with substantial improvements in the incidence of TEAEs while not appearing to compromise efficacy, approaches to quickly transition patients to their individualized optimal dose, particularly patients at the highest risk of grade 3 or 4 thrombocytopenia in cycle 1were further evaluated. In addition, an exploratory analysis was conducted to determine if risk factors could be identified for a subgroup of patients which were associated with higher rates of hematologic toxicity. In the updated analysis, two factors were identified as being associated with thrombocytopenia, baseline platelet count and baseline body weight.

Baseline Platelet Count and Weight as Predictors of Thrombocytopenia.

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase 1 study, PN001. This analysis determined that only baseline platelets had an impact on platelet nadir; lower baseline platelets (<180,000/μL) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

The potential relationship between body weight and TEAEs was further explored in an analysis to evaluate the correlation of grade 3 or 4 thrombocytopenia and baseline body weight. The lowest platelet count in the first 30 days was plotted versus baseline body weight to determine if low body weight identified a subgroup of patients with higher levels of thrombocytopenia during

Cycle 1. In the first 30 days of treatment, a baseline body weight ≥77 kg is associated with a lower incidence of grade 3 or 4 thrombocytopenia (14%) relative to the group with body weight <58 kg (43%).

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥Grade 3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg **or** baseline platelet count <150,000/µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg **and** a platelet count >150,000/µL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000/µL, and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000/µL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of niraparib or placebo) in patients whose baseline weight is <77 kg or baseline platelet count is <150,000/µL.

Guidance on monitoring patients for new events of MDS and AML and the follow-up of patients with suspected MDS or AML is provided in Section 10.2.7. Additional niraparib clinical safety data reported to date, including Phase 1 and NOVA results, dose-limiting toxicities, and toxicity profile, are provided in detail in the Investigator's Brochure.

3.3. Background of Bevacizumab

Bevacizumab is an antiangiogenic recombinant humanized monoclonal immunoglobulin G1 antibody against the vascular endothelial growth factor (VEGF) protein. Bevacizumab (Avastin; Genentech/Roche US) has been approved in the US and European Union (EU) for the treatment of multiple tumor types in combination with certain other treatments. In the EU, bevacizumab is approved for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics [FIGO] Stages IIIB, IIIC, and IV) ovarian cancer. In the US, bevacizumab is approved for the treatment of patients with platinum-sensitive recurrent ovarian cancer, either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent.

Bevacizumab has been evaluated in multiple clinical studies, including in 1,873 patients with newly diagnosed, Stage III (incompletely resected) or Stage IV epithelial ovarian cancer who had undergone debulking surgery as part of a Phase 3 study (GOG218).[6] Patients receiving bevacizumab administered concurrently with chemotherapy and as a maintenance treatment showed statistically significant improvement in PFS compared to placebo (14.1 months vs 10.3 months; HR, 0.717; $p < 0.001$).

Bevacizumab was also evaluated in 1,528 patients with ovarian cancer, regardless of FIGO stage as part of a Phase 3 study (ICON7).[7] Patients receiving bevacizumab administered concurrently with chemotherapy and as a maintenance treatment showed statistically significant improvement in PFS compared to chemotherapy alone (19.0 months vs 17.3 months; HR, 0.81; $p = 0.004$), with maximum improvement compared to chemotherapy alone at 12 months (15.1%; 95% confidence interval [CI], 10.7-19.5). The improvement was even more pronounced in

patients at high risk of progression (ie, FIGO Stage IV or FIGO Stage III and >1.0 cm of residual disease after debulking surgery; 15.9 months vs 10.5 months; HR, 0.68; p = <0.001).

3.4. Disease Background and Current Treatment Options

Approximately 75% of ovarian cancer patients respond to front-line, platinum-based therapy and are considered platinum sensitive, standardly defined as a minimum duration of 6 months with no relapse or progression following treatment. Up to 70% of these patients, however, relapse within 1 to 3 years.[8,9]

Maintenance or consolidation treatments have been explored in patients with platinum-sensitive disease, with the goal of delaying disease progression and the subsequent intensive chemotherapy, which may present tolerability issues for many patients. Studies conducted in the maintenance setting have produced conflicting results. A meta-analysis of 8 randomized studies in which maintenance chemotherapy was compared with no further intervention, maintenance radiotherapy, or another type of maintenance treatment demonstrated no significant difference in PFS or 3-, 5-, or 10-year overall survival (OS).[10] Another meta-analysis of 20 consolidation and 9 maintenance treatment studies, however, demonstrated a significant improvement in PFS (HR, 0.82; 95% CI, 0.70-0.96; p < 0.02).[11] Recent clinical trials of anti-angiogenic agents (such as bevacizumab and pazopanib) administered in a maintenance setting have demonstrated a benefit in PFS[6,12,13] but resulted in an increase in toxicity.

Given the expectation of disease recurrence for patients who demonstrate a CR to front-line, platinum therapy, the NCCN guidelines recommend observation, clinical trial participation, or maintenance therapy with paclitaxel (Level 3 recommendation) or pazopanib (Level 2B recommendation); observation is the most common approach.[1] It is also recommended that patients initiated on bevacizumab in combination with front-line paclitaxel and carboplatin continue single-agent bevacizumab as maintenance therapy. For patients who demonstrate a PR to front-line therapy, NCCN guidelines recommend clinical trial participation, recurrence therapy, or best supportive care. Recommendations from the European Society for Medical Oncology (ESMO) include bevacizumab in front-line therapy followed by single agent bevacizumab maintenance for a total duration of up to 15 months.[1,14]

A Phase 3 clinical study of niraparib maintenance treatment in patients with advanced ovarian cancer following response to front-line, platinum-based therapy, excluding patients who receive bevacizumab in combination with their front-line chemotherapy, is ongoing (PRIMA). In the current study, maintenance with niraparib combined with bevacizumab following front-line, platinum-based therapy with bevacizumab will be explored.[1,14]

3.5. Background of Combination of Niraparib and Bevacizumab

The combination of a PARP inhibitor and an angiogenesis inhibitor has the potential for improved PFS benefits in patients with or without HRD.

As described earlier, tumor cells with a deficiency in homologous recombination are exquisitely sensitive to PARP inhibitors due to synthetic lethality. It has been observed that, for tumors without genetic or epigenetic defects in homologous recombination pathway genes, a functional state of HRD may be induced by hypoxia through transcriptional downregulation of homologous recombination-related genes, including *RAD51* and *BRCA1*. In addition, cyclic (acute) hypoxia

and reoxygenation can induce both single-strand and double-strand DNA breaks within tumor cells due to increased levels of reactive oxygen species. These 2 mechanisms working together lead to heightened sensitivity to PARP inhibitors when cells are under hypoxic stress exerted by angiogenesis inhibitors. It has been observed that PARP inhibitors selectively induce apoptosis in hypoxic tumor regions in vivo, supporting the idea of contextual synthetic lethality between hypoxia-induced functional HRD and PARP inhibition. In the clinical setting, preliminary evidence of clinical efficacy has been observed in patients with platinum-sensitive ovarian cancer treated with either niraparib combined with bevacizumab (ENGOT-OV24/AVANOVA trial) or olaparib combined with cediranib (Phase II), irrespective of their *BRCA* mutation or HRD status. These data provide a strong rationale for combining a PARP inhibitor with an angiogenesis inhibitor.

To validate the hypothesis that tumors without HRD can be effectively treated with the combination of niraparib and bevacizumab, the HRD status for pretreatment tumor tissue will be determined using the Myriad myChoice® HRD test.

The combination of niraparib and bevacizumab treatment is currently being explored in patients with recurrent platinum-sensitive ovarian cancer as part of an ongoing Phase 1/2 study (AVANOVA).[15] Phase 1 of the study (dose escalation) has determined the recommended Phase 2 dose in this population to be 300 mg niraparib orally once daily and 15 mg/kg bevacizumab via intravenous (IV) infusion every 3 weeks. Results to date, although limited, indicate clinical activity of the combination in this patient population.

Overall, the combination of niraparib and bevacizumab appears to be safe for administration, with a manageable safety profile. AEs observed to date are consistent with those of the individual components and are readily managed through routine laboratory testing (ie, CBC), clinical surveillance (ie, blood pressure monitoring), and adherence to the recommended dose modifications.

3.6. Rationale for Current Trial

Niraparib is approved in the US for the maintenance treatment of women with recurrent ovarian cancer who have a CR or PR to platinum-based chemotherapy following at least 2 previous chemotherapy regimens. In addition, a Phase 3 clinical study to evaluate the safety and efficacy of niraparib maintenance treatment in patients with advanced ovarian cancer following response to front-line, platinum-based therapy, excluding patients who receive bevacizumab in combination with their front-line chemotherapy, is ongoing ("PRIMA" study).

Recent data suggest that the combination of a PARP inhibitor, like niraparib, with a VEGF inhibitor, like bevacizumab, in maintenance treatment has the potential for improved PFS benefits after front-line chemotherapy in platinum-responsive (CR or PR) ovarian cancer patients. This hypothesis is supported by the mechanism of action of both treatments, nonclinical studies, and an ongoing Phase 1/2 study in this patient population. To date, the combination has proven to be safe for administration for extended periods in patients with advanced ovarian cancer.[15]

Based upon the above preclinical and clinical data, the current study is being conducted to explore the safety and efficacy of maintenance with PARP inhibitor combined with anti-angiogenic agent following front-line, platinum-based therapy combined with bevacizumab.

4. TRIAL OBJECTIVES AND PURPOSE

4.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of niraparib in combination with bevacizumab, as assessed by 18-month PFS landmark analysis, in patients with Stage IIIB to IV ovarian cancer who have CR, PR, or no evidence of disease (NED) following front-line, platinum-based chemotherapy with bevacizumab.

4.2. Secondary Objectives

Secondary objectives include the following:

1. To evaluate additional measures of clinical benefit, including PFS, RECIST or CA-125 progression-free survival, OS, patient-reported outcome (PRO) measures, TFST, and time to second subsequent therapy (TSST)
2. To evaluate the safety and tolerability of niraparib and bevacizumab combination in the indicated target population

4.3. Exploratory Objectives

Exploratory objectives include the following:

1. To evaluate PFS rate at 6 months (PFS6) and 12 months (PFS12)
2. Retrospective analysis to evaluate HRD per the Myriad myChoice® HRD test as a potential biomarker for response to the niraparib and bevacizumab combination

5. INVESTIGATIONAL PLAN

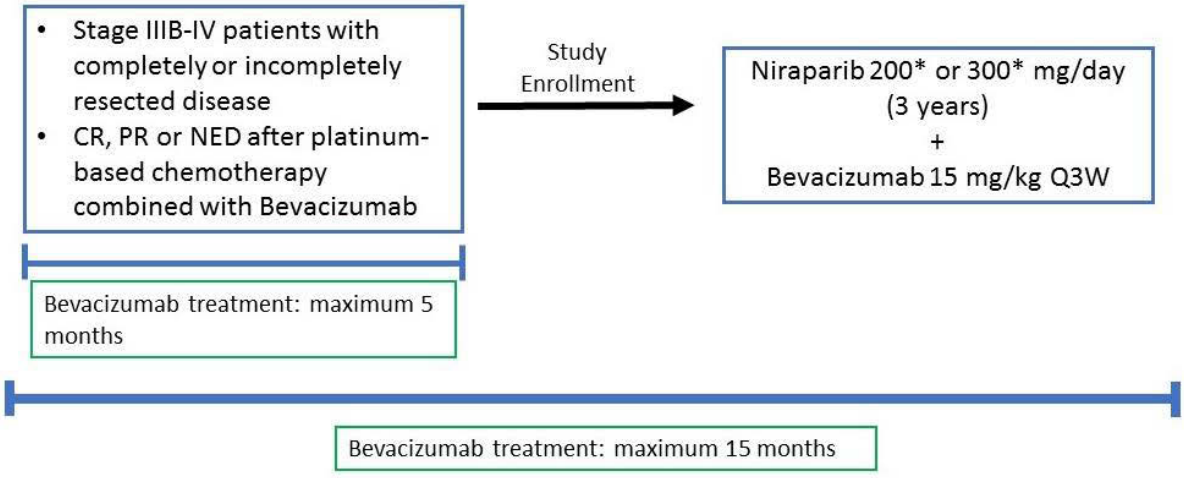
5.1. Overall Study Design

This is a multicenter, Phase 2, single-arm, open-label study to evaluate niraparib combined with bevacizumab as maintenance treatment in patients with advanced (Stage IIIB-IV) ovarian cancer with completely or incompletely resected disease who are recovered from primary debulking surgery.

Approximately 90 eligible patients who achieve CR, PR, or NED following treatment with platinum-based chemotherapy in addition to bevacizumab will receive maintenance treatment with niraparib (for up to 3 years) combined with bevacizumab (administered for up to 10 months during the maintenance phase or up to a total of 15 months inclusive of approximately 5 months of bevacizumab received with chemotherapy) or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death, whichever comes first (see Figure 1). Patients who have not progressed after 3 years of niraparib maintenance treatment will be given the option to continue with niraparib beyond 3 years if they are tolerating and benefiting from treatment and after consultation with the Sponsor.

Study assessments and timing are outlined in Figure 1.

Figure 1: Study Schema



Abbreviations: CR = complete response; NED = no evidence of disease; PR = partial response.
*Patients ≥77 kg **and** with platelet count of ≥150,000/µL will receive 300 mg/day; patients <77 kg **and/or** with platelet count of <150,000/µL will receive 200 mg/day

5.2. Number of Subjects

Approximately 90 patients will be enrolled into the study.

5.3. Treatment Assignment

All patients in this single-arm study will receive maintenance treatment with niraparib in combination with bevacizumab.

5.4. Dose Adjustment Criteria

5.4.1. Niraparib

To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation, the recommended dose modifications for adverse reactions should be followed as listed in Table 3, Table 4, and Table 5.[16] Niraparib should be discontinued for selected adverse events that persist beyond 28 days as noted in the tables.

For patients whose initial dose is 3 capsules daily, dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule once daily (100 mg/day) will be allowed. No further dose reduction will be allowed.

For patients whose initial dose is 2 capsules, dose reduction to 1 capsule once daily (100 mg/day) will be allowed. No further dose reduction will be allowed without discussion with the Medical Monitor.

Table 3: Recommended Dose Modifications for Adverse Reactions

Dose level	Initial Dose: 3 capsules per day	Initial Dose: 2 capsules per day
Starting dose	300 mg/day (three 100-mg capsules)	200 mg/day (two 100-mg capsules)
First dose reduction	200 mg/day (two 100-mg capsules)	100 mg/day (one 100-mg capsules)
Second dose reduction[a]	100 mg/day (one 100-mg capsules)	N/A

[a] If further dose reduction is required due to adverse event management, discussion with the Medical Monitor is required.

Table 4: Dose Modifications for Non-hematologic Adverse Reactions

Non-hematologic NCI-CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	• Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 3.
NCI-CTCAE ≥ Grade 3 treatment-related adverse reaction event lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue medication.

Abbreviations: NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events.

Table 5: Dose Modifications for Hematologic Adverse Reactions

Monitor complete blood counts weekly for the first 2 cycles, and on Day 1 of every cycle thereafter.	
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. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the Medical Monitor is required to resume niraparib. • Resume niraparib at same or reduced dose per Table 3:. • If nadir platelet count was < 75,000/µL, resume at a reduced dose after recovery.
	Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the Medical Monitor is required to resume niraparib. • 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 QD.[a]
Neutrophil < 1,000/µL or Hemoglobin < 8 g/dL	• Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥ 1,500/µL or hemoglobin returns to ≥ 9 g/dL. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 3. • Discontinue niraparib if neutrophil or hemoglobin level 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 QD.[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.

Abbreviations: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; QD = once daily.

[a] If MDS/AML is confirmed, discontinue niraparib.

5.4.2. Bevacizumab

The investigator is advised to consult the current bevacizumab label. Dose reductions of bevacizumab are not permitted in this study.[1,17]

Interrupt bevacizumab treatment for the following adverse events: proteinuria, medically significant hypertension that cannot be adequately controlled with antihypertensive therapy, hypertension in the presence of posterior reversible encephalopathy syndrome, development of hypertensive crisis or hypertensive encephalopathy, or nephrotic syndrome. In case of uncontrolled hypertension, niraparib should also be held in addition to bevacizumab.

Resume bevacizumab treatment only when 1) hypertension is controlled by hypertensive regimen, or 2) urine protein is < 2 g per 24 hours urine collection.[17] Niraparib should be resumed with bevacizumab when hypertension is controlled by hypertensive regimen. If hypersensitivity or infusion reactions occur during bevacizumab infusion, the infusion should be discontinued. Except in cases where permanent discontinuation of bevacizumab is indicated, resumption of the standard dose of bevacizumab upon resolution of other adverse reactions is at the discretion of the investigator.
Bevacizumab treatment should be withheld 4 weeks prior to elective surgery. In patients who experience wound healing complications during the study, treatment with bevacizumab should be withheld until the wound is fully healed.

5.5. Criteria for Study Termination

The Sponsor may terminate this study at any time. The Sponsor will notify the Investigators when the study is to be placed on hold, completed, or terminated.

Table 6: Schedule of Events

Visit/Procedure	**Screening**	**Cycle 1**[a]	**Cycle 2**[a]	**Subsequent cycles**[a]	**EOT**[b]	**Post-treatment assessments**
Day	**-28 to -1**	**1**	**1**	**C(n)/D1**	**Within 7 days of the decision to discontinue treatment**	**Every 12 weeks**
Visit Window		**±3 days**	**±3 days**	**±3 days**		**±14 days (unless otherwise specified)**
Informed consent	X					
Demographics and height	X					
Medical, surgical, cancer (including genotyping), and medication history	X					
Medical history/concomitant medications		X	X	X	X	
Sample collection (tumor) for HRD testing[c]	X					
12-lead ECG	X					
Serum or urine pregnancy test[d]	X[d]	X	X	X	X	
Physical examination	X	X	X	X	X	
Vital signs and weight	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	
CBC[e]	X	Days 1, 8, and 15 of Cycle 1[f] and Cycle 2		X	X	
Serum chemistry and coagulation	X	X[f]	X	X	X	
Urinalysis	X					
Urine sample for protein[g]	X	X[g]	X[g]	X[g]		

Visit/Procedure	**Screening**	**Cycle 1**[a]	**Cycle 2**[a]	**Subsequent cycles**[a]	**EOT**[b]	**Post-treatment assessments**
Day	**-28 to -1**	**1**	**1**	**C(n)/D1**	**Within 7 days of the decision to discontinue treatment**	**Every 12 weeks**
Visit Window		**±3 days**	**±3 days**	**±3 days**		**±14 days (unless otherwise specified)**
Serum CA-125	X	X	X	X	X	X
RECIST v1.1 assessment[h]	X			X[h]	X	X
Chest CT or MRI[i]	X					
PRO	X	Q6W (±7 days) for 6 months, then Q12W (±7 days)			4, 8, 12, and 24 weeks (±7 days) after last dose	
Niraparib dispensed or collected		X	X	X	X	
Bevacizumab infusion		X	X	X		
Adverse event monitoring[j]	X	X	X	X	X	X
Anticancer therapies assessment						X
Survival assessment (telephone assessment allowed)[k]						X
Bone marrow aspirate and biopsy		For any suspected case of MDS/AML or secondary cancer (new malignancy other than MDS/AML) reported while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist.				

Abbreviations: AE = adverse event; AML = acute myelogenous leukemia; C = cycle; CA-125 = cancer antigen 125; CBC = complete blood count; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FOSI = Functional Assessment of Cancer Therapy–Ovarian Symptom Index; HRD = homologous recombination deficiency; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging; PE = physical examination; QxW = every x weeks; RECIST = Response Evaluation Criteria in Solid Tumors

[a] Treatment cycles are 21 days (±3 days) long.

[b] EOT is defined as the discontinuation of treatment for any reason.

[c] The tumor sample must be confirmed to be available during the screening period and submitted after the patient has been enrolled; patients do not have need to wait for the HRD test result to be enrolled. If archival tumor tissue is not available for testing, the patient must agree to undergo a fresh biopsy.
[d] For patients of childbearing potential only. If completed within 72 hours of the first dose, pregnancy testing does not need to be repeated.
[e] If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.
[f] Screening assessments completed within 7 days of the first dose do not need to be repeated, unless otherwise specified.
[g] Urine dipstick for protein determination should be performed prior to each bevacizumab administration. Patients discovered to have ≥ 2 proteinuria on dipstick should not be administered bevacizumab, should undergo a 24-hour urine collection, and must demonstrate < 2 g of protein in 24 hours to be eligible for bevacizumab treatment to resume.
[h] RECIST v1.1 tumor assessment via CT or MRI scan of the abdomen/pelvis and clinically indicated areas required at screening, every 12 weeks (±7 days) from Cycle 1/Day 1 for the first 48 weeks, then every 24 weeks (±7 days) until disease progression, at which point a final follow-up set of imaging is required.
[i] Chest CT or MRI if not done as part of RECIST tumor assessment. If the chest CT or MRI is clear at screening, repeat chest imaging is not required in the absence of lesions to be followed or in the absence of clinical indication requiring follow-up; otherwise, repeat chest imaging should be completed at the same time as RECIST imaging.
[j] All AEs and SAEs, regardless of causality, will be collected and recorded for each patient from the day the ICF is signed until 90 days (±14 days) after the last dose of study treatment or until alternate anticancer therapy has been initiated, whichever occurs first.
[k] Patients will be followed until study closeout for survival status and study-drug related SAEs. Patients will be followed for AESI as outlined in Section 10.2.7

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Inclusion Criteria

To be considered eligible to participate in this study, all of the following inclusion criteria must be met:

1. Patients must be female, be ≥ 18 years of age, be able to understand the study procedures, and agree to participate in the study by providing written informed consent.
2. Patients must have newly diagnosed FIGO Stage IIIB to IV epithelial ovarian, fallopian tube, or peritoneal cancer and have recovered from debulking surgery.
3. Patients must have high-grade serous or endometrioid or high-grade predominantly serous or endometrioid histology, regardless of HRD or g*BRCA* mutation status. Patients with non-mucinous epithelial ovarian cancer and g*BRCA* mutation are eligible.
4. Patients must have completed front-line, platinum-based chemotherapy with CR, PR, or NED and have first study treatment dose within 12 weeks of the first day of the last cycle of chemotherapy:
    a. A platinum-based regimen must have consisted of a minimum of 6 and a maximum of 9 treatment cycles. Patients who discontinued platinum-based therapy early as a result of non-hematologic toxicity specifically related to the platinum regimen (ie, neurotoxicity or hypersensitivity) are eligible if they have received a minimum of 4 cycles of the platinum regimen.
    b. IV, intraperitoneal, or neoadjuvant platinum-based chemotherapy is allowed; for weekly therapy, 3 weeks is considered 1 cycle. Interval debulking is allowed.
5. Patients must have received, prior to enrollment, a minimum of 3 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy. Patients who undergo interval debulking surgery are eligible if they have received only 2 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy.
6. Patients must have had 1 attempt at optimal debulking surgery.
7. Patients must have either CA-125 in the normal range or CA-125 decrease by more than 90% during front-line therapy that is stable for at least 7 days (ie, no increase > 15% from nadir).
8. Patients must have adequate organ function, defined as (Note: CBC test should be obtained without transfusion or receipt of stimulating factors within 2 weeks before obtaining screening blood sample):
    a. Absolute neutrophil count (ANC) ≥ 1,500/μL
    b. Platelet count ≥ 100,000/μL
    c. Hemoglobin ≥ 9 g/dL
    d. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation
    e. Total bilirubin ≤ 1.5 × ULN OR direct bilirubin ≤ 1 × ULN

f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN unless liver metastases are present, in which case they must be ≤ 5 × ULN

9. Patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.
10. Patients must have normal blood pressure or well-controlled hypertension.
11. Patient must agree to complete PROs (FOSI) throughout the study, including after study treatment discontinuation.
12. Patients must be able to take oral medication.
13. Patient must agree to undergo tumor HRD testing at screening. The tumor sample must be confirmed to be available during the screening period and submitted after the patient has been enrolled; patients do not have to wait for the HRD test result to be enrolled. If archival tumor tissue is not available for testing, the patient must agree to undergo a fresh biopsy.
14. Patients of childbearing potential must have a negative serum or urine pregnancy test (beta human chorionic gonadotropin) within 72 hours prior to receiving the first dose of study treatment.
15. Patients must be postmenopausal, free from menses for > 1 year, surgically sterilized, or willing to use adequate contraception to prevent pregnancy (see Appendix 1)or must agree to abstain from activities that could result in pregnancy throughout the study, starting with enrollment through180 days after the last dose of study treatment.

6.2. Subject Exclusion Criteria

A patient will be considered ineligible for study participation if any of the following exclusion criteria are met:

1. Patients with ovarian tumors of non-epithelial origin (eg, germ cell tumor) or any low-grade tumors.
2. Patients with clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, myocardial infarction, cardiac arrhythmia or unstable angina < 6 months to enrollment, New York Heart Association [NYHA] Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, Grade II or greater peripheral vascular disease, and history of cerebrovascular accident [CVA] within 6 months).
3. Patients with gastrointestinal disorders or abnormalities that would interfere with absorption of study treatment.
4. History of bowel obstruction, including sub-occlusive disease, related to the underlying disease or history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscesses. Evidence of rectosigmoid involvement by pelvic examination or bowel involvement on computed tomography (CT) scan or clinical symptoms of bowel obstruction.
5. Patient has proteinuria as demonstrated by urine protein:creatinine ratio ≥ 1.0 at screening or urine dipstick for proteinuria ≥ 2 (patients discovered to have ≥ 2 proteinuria

on dipstick at baseline should undergo a 24-hour urine collection and must demonstrate < 2 g of protein in 24 hours to be eligible).

6. Patient has any known history or current diagnosis of MDS or AML.
7. Patient has received treatment previously with a PARP inhibitor.
8. Other than ovarian cancer, the patient has been diagnosed or treated for invasive cancer less than 5 years prior to study enrollment. Patients with cervical carcinoma in situ, non-melanomatous skin cancer, and ductal carcinoma in situ definitively treated are allowed.
9. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection.
10. Patient has known contraindication to PARP inhibitors or VEGF inhibitors.
11. Patient is at increased bleeding risk due to concurrent conditions (eg, major injuries or surgery within the past 28 days prior to start of study treatment, history of CVA, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months).
12. Patient is immunocompromised (patients with splenectomy are allowed).
13. Patient has known, active hepatic disease (ie, hepatitis B or C).
14. Patient has a QT interval prolongation > 480 ms at screening. If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (ie, the patient otherwise has no cardiac abnormalities), then the patient may be eligible to participate in the study following discussion with the Medical Monitor.
15. Patient is pregnant or expecting to conceive children while receiving study drug and for 180 days after the last dose of study drug; additionally, female patients should not breastfeed during treatment with niraparib and for 30 days after receipt of the last dose due to the potential for serious adverse reactions from niraparib in breastfed infants.

6.3. Subject Withdrawal Criteria

6.3.1. Discontinuation from Treatment

Patients may be discontinued from either study treatment at any time. Patients who discontinue from study treatment or from the study will not be replaced.

Specific reasons for discontinuing either treatment include the following, in addition to those indicated in Section 5.4:

- AE
  - Any treatment-related NCI-CTCAE v4.03 Grade 3 or 4 events (see separate guidelines for platelet count below) that have not reverted to NCI-CTCAE v4.03 Grade 1 or better within 28 days. Patients determined to be deriving clinical benefit may continue study treatment following discussion with the medical monitor.

  - At the Investigator's discretion, following dose interruption (no longer than 28 days), patients may be considered for niraparib dose reductions, provided they have not already undergone the maximum number of 2 dose reductions allowed. If upon re-challenge with study treatment at the lowest allowable dose any NCI-CTCAE v4.03 Grade 3 or 4 AEs recur, the patient must be discontinued from niraparib treatment.

- In the case of thrombocytopenia, if the platelet count has not returned to ≥ 100,000/μL within 28 days of dose interruption, then the patient should be discontinued. Patients determined to be deriving clinical benefit may continue study treatment following discussion with the medical monitor.
- Disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria per Investigator assessment
- Risk to patients as judged by the Investigator, Sponsor, or both
- Severe noncompliance with protocol as judged by the Investigator, Sponsor, or both
- Patient becomes pregnant
- Withdrawal of consent
- Loss to follow-up
- Death

In addition, specific reasons for permanently discontinuing bevacizumab treatment include the following:

- Gastrointestinal perforation
- Tracheosophageal fistula or any NCI-CTCAE v4.03 Grade 4 fistula
- NCI-CTCAE v4.03 Grade 3 or 4 bleeding
- Arterial thromboembolic reactions
- NCI-CTCAE v4.03 Grade 4 thromboembolic reactions, including pulmonary embolism
- Medically significant hypertension that cannot be adequately controlled with antihypertensive therapy, hypertension in the presence of posterior reversible encephalopathy syndrome, or development of hypertensive crisis or hypertensive encephalopathy
- Nephrotic syndrome

6.3.2. Discontinuation from the Study

Specific reasons for discontinuing from the study include the following:

- Withdrawal of consent by the patient, who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Loss to follow-up

- Death from any cause
- Sponsor decision to terminate study

If a patient is thought to be lost to follow-up, discontinues study treatment, or discontinues the study, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are thought to be lost to follow-up, at least 3 documented attempts, including 1 attempt via certified mail, should be made to contact the patient before the patient is deemed lost to follow-up.

7. TREATMENT OF SUBJECTS

7.1. Description of Study Drug

Table 7: Investigational Products

	Investigational product	
Product name	Niraparib	Bevacizumab (Avastin)
Dosage form	Capsule	Infusion
Unit dose	100 mg per capsule	15 mg/kg infusion
Route of administration	Oral	Intravenous
Physical description	Capsules in high-density polyethylene bottles	Clear to slightly opalescent, colorless to pale brown, sterile solution
Manufacturer	QSP (Charles River Laboratories Contract Manufacturing)	Genentech, Inc.

7.2. Concomitant Medications

Any medication the patient takes other than the study treatment, including herbal and other non-traditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the electronic case report form (eCRF). The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

Niraparib has potential to weakly induce cytochrome P450 (CYP) 1A2. Therefore, patients should be advised to use caution with drugs that are substrates of CYP1A2 with narrow therapeutic range. The substrates of CYP1A2 with narrow therapeutic range include theophylline and tizanidine. The niraparib safety profile includes risk for thrombocytopenia, and bevacizumab may increase the potential for bleeding. Therefore, patients should be advised to use caution with anticoagulants (eg, warfarin) and antiplatelet drugs (eg, aspirin).

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; therefore, live virus and bacterial vaccines should not be administered to patients in the study.

No other anticancer therapy is permitted during the course of the study treatment for any patient. Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing > 20% of the bone marrow within 1 week of the first dose of study treatment) is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics, as long as no evidence of disease progression is present.

Prophylactic cytokines (granulocyte colony-stimulating factor) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to local guidelines.

7.3. Treatment Compliance

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 6.1 and Section 6.2, respectively.

Niraparib and bevacizumab will be administered by site personnel at study sites as detailed in Section 8.5.

Study drug accountability will be monitored as detailed in Section 8.6.

7.4. Randomization and Blinding

Not applicable; this is a single-arm, open-label study.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Study Drug

8.1.1. Niraparib

Niraparib ([3S]-3-[4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP1 and PARP2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate. Niraparib will be supplied as 100-mg capsules.

8.1.2. Bevacizumab

Bevacizumab (Avastin) is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for IV infusion.[17] The excipients for bevacizumab are trehalose dihydrate, sodium phosphate, polysorbate 20, and water for injections. Bevacizumab is obtained from commercial sources according to local practice standards and it is provided as a commercially available dosage.

8.2. Study Drug Packaging and Labeling

The label text of the study treatments will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and not patient-specific.

8.3. Study Drug Storage

All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed or administered to the patients, the study treatment will be stored in a securely locked area that is accessible only to authorized personnel.

8.4. Study Drug Preparation

Please refer to the Bevacizumab USPI for instructions and precautions regarding preparation.

8.5. Administration

8.5.1. Niraparib

Niraparib will be administered orally once a day, continuously throughout each 21-day cycle, for up to 3 years in the absence of progressive disease (PD), unacceptable toxicity, patient withdrawal, Investigator's decision, or death; however, patients who are tolerating and benefiting from treatment will have access to niraparib maintenance treatment as long as considered acceptable by their treating physician and by the patient. On Day 1 of each cycle, niraparib will be administered upon completion of bevacizumab infusion.

The starting dose of niraparib will be based on the patient's baseline actual body weight or platelet count. Patients with a baseline actual body weight of ≥77 kg **and** baseline platelet count of ≥150,000/μL will take three capsules of 100 mg strength (300 mg/day) at each dose administration. Patients with a baseline actual body weight of <77 kg **and/or** baseline platelet

count of <150,000/µL will take two capsules of 100 mg strength (200 mg) at each dose administration. Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation.

For patients whose starting dose is 2 capsules (200 mg/day), escalation to 3 capsules (300 mg/day) is permitted if no treatment interruptions or discontinuations were required during the first 2 cycles of therapy. This escalation will occur at the discretion of the Investigator, following discussion with the Medical Monitor.

Table 8: Recommended Initial Starting Dose

Baseline Criteria	Starting Dose
≥77 kg and ≥150,000/µL	300 mg (3 X 100 mg capsules) daily
<77 kg and/or <150,000/µL	200 mg (2 X 100 mg capsules) daily

Patients will be instructed to take their niraparib dose once daily or as instructed by the Investigator. Patients must swallow and not chew all capsules. The consumption of water and food is permissible. If a patient vomits or misses a dose of niraparib, a replacement dose should not be taken.

Details on the administration of niraparib can be found in the Pharmacy Manual.

8.5.2. Bevacizumab

Maintenance bevacizumab 15 mg/kg will be administered at the study site via a 30-minute IV infusion on Day 1 of every 21-day cycle in the absence of PD, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.[1] Bevacizumab will be administered for up to 10 months during the maintenance phase or up to a total of 15 months inclusive of approximately 5 months of bevacizumab received with chemotherapy.

Details on the administration of bevacizumab can be found in the bevacizumab USPI.

8.6. Study Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study.

Details of maintaining drug accountability, including information on the accountability log, will be provided in the Pharmacy Manual.

All dispensation and accountability records will be available for Sponsor review. The Study Monitor will assume the responsibility to reconcile the study treatment accountability log. The Pharmacist will dispense study treatment for each patient according to the protocol and Pharmacy Manual, if applicable.

8.7. Study Drug Handling and Disposal

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of study drug according to local regulations. If a site does not

have the capability for onsite destruction, the Sponsor will provide a return for destruction service through a third party. Both the unused and expired study treatment must be destroyed, upon authorization of the Sponsor, according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.

The medication provided for this study is to be used only as indicated in this protocol and only for the patients entered in this study.

9. ASSESSMENT OF EFFICACY

9.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS rate at 18 months (PFS18), which is defined as the proportion of patients who have not progressed or died within 18 months after niraparib combined with bevacizumab treatment initiation. Progression will be assessed by RECIST v1.1 criteria per Investigator assessment. PFS18 will be estimated using percentage with 95% exact CI. In addition, the probability of PFS at 18 months will be estimated using the Kaplan-Meier method.

The date of PD will be determined by Investigator assessment. This review will be based on imaging assessment according to RECIST v1.1 criteria (Appendix 2). Positron emission tomography (PET)/CT may be used according to RECIST v1.1 guidelines, but its use is not a study requirement.

RECIST v1.1 is used to define PD in this study. Tumor assessment by CT/magnetic resonance imaging (MRI) must unequivocally show PD according to RECIST v1.1 criteria (Appendix 2). If a patient had a CT/MRI of the abdomen/pelvis and clinically indicated areas within the 28-day screening window before Cycle 1/Day 1 but prior to signing the main informed consent form (ICF), the patient is not required to complete an additional CT/MRI scan for study screening.

The Investigator will describe how PD criteria is met. When required to determine CA-125 progression, CA-125 levels should be evaluated ± 2 weeks from the primary PD assessments and must be confirmed by a second determination ≥ 7 days later. In case assessments of CA-125 levels that occur > 2 weeks from the primary PD assessments, the date of the primary assessment of PD will be used to define the date of PD.

GCIG criteria for CA-125 progression are as follows:

Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 ≥ 2 × ULN on 2 occasions at least 1 week apart, **OR**

1. Patients with elevated CA-125 pretreatment that never normalizes must show evidence of CA-125 ≥ 2 × the nadir value on 2 occasions at least 1 week apart, **OR**
2. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 ≥ 2 × ULN on 2 occasions at least 1 week apart.

PD will not be diagnosed in case of CA-125 progression in the absence of radiologic evidence of progressive disease.

If CT/MRI shows existing (baseline) lesions that only equivocally suggest PD and additional diagnostic tests are required to determine unequivocal PD, the official date of PD will be the date PD was unequivocally determined. Alternatively, with new lesions (except ascites and effusions) that are initially equivocal and are later unequivocally determined, the date of progression will be the date the lesion was initially identified.

Tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans should continue at the specified intervals.

9.2. Secondary Efficacy Endpoints

9.2.1. Progression-free Survival

For each patient in the study, PFS will be assessed. PFS is defined as the time from niraparib combined with bevacizumab treatment initiation to the earlier date of assessment of progression, as assessed by RECIST v1.1 criteria, based on Investigator assessment, or death by any cause in the absence of progression.

9.2.2. Overall Survival

OS is defined as the date of initiation of niraparib treatment in combination with bevacizumab to the date of death by any cause. Following the End of Treatment Visit, survival status will be collected for all patients using acceptable means, including telephone contact. New malignancy information will also be collected as part of this assessment.

9.2.3. RECIST or CA-125 Progression-free Survival

RECIST or CA-125 progression-free survival is defined as the time from initiation of niraparib treatment in combination with bevacizumab to the earliest date of progression assessed by RECIST v1.1. or CA-125 progression or death by any cause. CA-125 progression will be defined as described in Section 9.1. (Note: CA-125 progression without radiologic evidence of progressive disease will not be considered disease progression.)

CA-125 levels must be normal at screening or have a > 90% decrease compared to baseline prior to their last platinum-based chemotherapy course that is stable for at least 7 days (i.e., no increase > 15% from nadir). Abnormal CA-125 levels on study do not represent disease progression; however, they may prompt imaging if clinically indicated.

9.2.4. Patient Reported Outcome - Functional Assessment of Cancer Therapy–Ovarian Symptom Index

Observed changes from baseline in the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI) PRO will be assessed (see Appendix 4).

The FOSI is a validated 8-item measure of symptom response to treatment for ovarian cancer.[18] Patients respond to their symptom experience over the past 7 days using a 5-point Likert scale scored from CCI [redacted] to CCI [redacted]. The average score is calculated as an average of the 8 items. The total symptom index is calculated as the total of the 8 symptoms.

PROs will be collected every 6 weeks (± 7 days) for 6 months, then every 12 weeks (± 7 days) thereafter while the patient is receiving study treatment. Once a patient discontinues treatment, PRO evaluations will be performed 4 weeks (± 7 days), 8 weeks (± 7 days), 12 weeks (± 7 days), and 24 weeks (± 7 days) after treatment discontinuation, regardless of subsequent treatment.

PROs may be completed remotely. It is estimated that PRO evaluations will take less than 20 minutes at each timepoint. Since these are questionnaires, their completion will not interfere with or prevent future treatment or clinical studies. PRO evaluations should be administered prior to conducting any other procedures at each visit.

9.2.5. Time to First Subsequent Therapy

TFST is defined as the date of initiation of niraparib treatment in combination with bevacizumab treatment in the current study to the start date of the first subsequent anticancer therapy.

9.2.6. Time to Second Subsequent Therapy

TSST is defined as the date of initiation of treatment of niraparib in combination with bevacizumab treatment in the current study to the start date of the second subsequent anticancer therapy.

9.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are PFS rate at 6 months (PFS6) and 12 months (PFS12), which are defined as the proportion of patients who have not progressed or died within 6 months and 12 months after initiation of treatment of niraparib in combination with bevacizumab treatment, respectively. Progression will be assessed by RECIST v1.1 criteria based on Investigator assessment. Additional landmark PFS analyses may be performed as deemed appropriate.

9.4. Biomarker Analysis

HRD will be evaluated retrospectively as a potential biomarker for response to niraparib combined with bevacizumab maintenance treatment using archival tumor sample. For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation.

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

Safety will be evaluated based on the incidence of TEAEs, serious adverse events (SAEs), treatment discontinuations or dose reductions due to AEs, changes in ECOG performance status, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications. All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system.

10.1.1. Demographic/Medical History

Demographic and baseline characteristics consist of those variables that are assessed at screening/baseline. Patient demographics consist of age at screening, race, ethnicity, and sex.

10.1.1.1. Disease History

For disease history, the following will be documented:

- Date of diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis
- Genotyping, such as g*BRCA* or somatic *BRCA* (s*BRCA*) status, if known
- Information on first anticancer treatment:
  - Adjuvant or neoadjuvant and adjuvant chemotherapy
  - Date of start and end of platinum-based treatment and date of start and end of bevacizumab treatment
  - Number of cycles (21 days = 1 cycle) of platinum-based chemotherapy and number of cycles of bevacizumab
  - Agents used in treatment
- Best response (CR, PR, or NED) following first-line anticancer treatment
- Toxicities (including hematologic events) due to first-line anticancer treatment

10.1.1.2. Medical and Surgical History

Major medical and surgical history (including medication history and history of thrombocytopenia, neutropenia, leukopenia, or anemia) will be collected. Details of any prior invasive malignancy will be collected. Medical and surgical history will be obtained by interviewing the patient or by reviewing the patient's medical records.

10.1.1.3. Previous and Concomitant Medications

Previous and concomitant medications will be documented as described in Section 7.2. Medications will be coded using World Health Organization (WHO) Anatomical Therapeutic Chemical classification.

10.1.2. Vital Signs

Vital signs include blood pressure, pulse rate, and temperature and will be measured in accordance with the schedule of events (Table 6).

10.1.3. Weight and Height

Weight and height will be measured in accordance with the schedule of events (Table 6). Height will be measured at screening only.

10.1.4. Physical Examination

Physical examinations will be performed in accordance with the schedule of events (Table 6).

Any physical examination or vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the finding should be recorded and reported according to the SAE reporting process (see Section 10.2.5).

10.1.5. Laboratory Assessments

The following laboratory variables will be determined in accordance with the schedule of events (Table 6). These tests will be performed by the local laboratory at the clinical site.

Any laboratory values assessed as clinically significant should be recorded as an AE. If SAE criteria are met or if the laboratory abnormality is an adverse event of special interest (AESI; see Section 10.2.7), the event should be recorded and reported according to the SAE reporting process (see Section 10.2.5).

Hematologic testing may occur more frequently than is specified in Section 10.1.5.1, if additional testing is medically indicated per Investigator judgment or if the event meets the criteria for niraparib dose modification (see Section 5.4.1). Additional tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study site must keep a copy of test results with the patient's study file, and the results must be entered into the eCRF.

Any suspected case of MDS/AML or secondary cancer (new malignancy other than MDS/AML) reported while a patient is receiving treatment or followed for post-treatment assessments must be referred to a local hematologist to perform bone marrow aspirate and biopsy. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to WHO[19], and other sample testing reports related to MDS/AML. Report data will be entered in the appropriate eCRF pages, and the site must keep a copy of all reports with the patient's study file.

10.1.5.1. Hematology

The following hematologic parameters will be measured:

- **CBC:**
  - Hemoglobin
  - Platelet count
  - Mean corpuscular volume
  - White blood cell count
  - Differential white blood cell count
- **Coagulation factors:**
  - International normalized ratio
  - Activated partial thromboplastin time

10.1.5.2. Blood Chemistry

The following blood chemistry parameters will be measured:

- **Serum chemistry:**
  - Sodium
  - Potassium
  - Total bilirubin
  - Calcium
  - Magnesium
  - AST
  - Chloride
  - Glucose
  - ALT
  - Total protein
  - Creatinine
  - Albumin
  - Urea or blood urea nitrogen

10.1.5.3. Urinalysis

Urinalysis will be performed at screening, as follows:

- Specific gravity
- Protein

- Leukocyte esterase
- Glucose
- Nitrite
- Ketones
- Blood
- Urobilinogen
- Bilirubin

In addition, urine dipstick for protein determination will be performed at screening and prior to each bevacizumab administration. Patients discovered to have ≥ 2 proteinuria on dipstick should not be administered bevacizumab, should undergo a 24-hour urine collection, and must demonstrate < 2 g of protein in 24 hours to be eligible for bevacizumab treatment to resume.

10.1.5.4. Drug Screen

Not applicable.

10.1.5.5. Pregnancy Screen

A negative serum or urine pregnancy test is required within 72 hours prior to Day 1 of Cycle 1 for females of childbearing potential. Urine pregnancy testing will be performed on Day 1 of each subsequent cycle and at the End of Treatment Visit. Any pregnancies that occur within 180 days post-treatment are to be reported as described in Section 10.2.8.

10.1.6. ECOG Performance Status

Performance status will be assessed using the ECOG scale (see Appendix 3) in accordance with the schedule of events (Table 6). The same observer should assess performance status each time.

10.1.7. Electrocardiogram

Standard 12-lead electrocardiograms will be performed at screening.

10.2. Adverse and Serious Adverse Events

10.2.1. Definitions

10.2.1.1. Adverse Event

Any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including clinically significant laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the

signing of the informed consent, including baseline or washout periods, even if no study treatment has been administered. (See Section 10.2.3 for information about AE collecting and reporting.)

10.2.1.2. Serious Adverse Event

Any untoward medical occurrence, that, at any dose:

- Results in death;
- Is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization* or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Is an important medical event**

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be captured in medical history section in the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered serious adverse events: an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug. (See Section 10.2.5 for information about SAE reporting.)

10.2.1.3. Treatment-Emergent Adverse Event (TEAE)

Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

10.2.1.4. Adverse Events of Special Interest (AESI)

Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.

10.2.1.5. Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Abuse:** the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.

- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose occurs, the Investigator and the Sponsor should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be documented on the applicable sections within the eCRF. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as described in Section 10.2.9.
- **Accidental /Occupational exposure:** the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

10.2.2. Assessment of Adverse Events

10.2.2.1. Severity Assessment

All AEs will be assessed by the Investigator for severity* according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03: 14 June 2010; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each adverse event. The CTCAE v4.03 is available on the NCI/NIH website.

Please note that there is a distinction between serious and severe AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.2.1.2. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

10.2.2.2. Relationship to Study Intervention

The Investigator must provide a causality assessment regarding the relationship of the event with the study drug and/or study procedure for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- Related: A causal relationship between the medicinal product (and/or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be

explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.

- Not Related: A causal relationship between the medicinal product (and/or study procedures) and AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

10.2.2.3. Expectedness

The Sponsor will be responsible for determining whether an adverse event is 'expected' or 'unexpected'. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information provided in the Reference Safety Information of the effective niraparib Investigator Brochure (IB).

10.2.3. Collection and Recording Adverse Events

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as, "How have you been feeling since your last study visit?" The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All SAEs will be collected from the signing of the ICF for this study up to 90 days (±14 days) after the last dose of study treatment and recorded in the eCRF. SAEs will also be reported on an SAE form as described in Section 10.2.5 of this protocol. SAEs considered by the Investigator to be related to study medication are reported until study closeout.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, or reported by patient), will be collected and recorded in the eCRF for each patient from the signing of the ICF for this study up to 90 days (±14 days) after the last dose of study treatment.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as Medical History in the eCRF and on the SAE Report Form.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be reported within the eCRF. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 10.2.5.

10.2.4. Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

If an Investigator becomes aware of an SAE after the specified follow up period and considers the SAE related to the study drug, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in Section 10.2.3.

10.2.5. Reporting

The Investigator must report all SAEs, and all follow up information to the Sponsor on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information. The Investigator must provide a causality assessment and must sign and date all SAE Report Forms.

It is the responsibility of the Investigator to review source documentation and describe pertinent information on the SAE Report Form. If supporting documentation is requested (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any patient's personal identifiers (including Medical Record number) are removed, and submit the documents with the SAE Form to the Sponsor. The Sponsor (or designee) will return a confirmation of receipt for all email reports (if received from other than a "no reply" domain) within 1 business day.

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information. The Investigator must promptly respond to queries from the Sponsor.

10.2.6. Submission and Distribution of Serious Adverse Event Reports

Per regulatory requirements, if an event is assessed by the Sponsor as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor to submit the SUSAR Regulatory Authorities according to applicable regulations.

In addition, the SUSAR will be distributed to the Investigators/sites, utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) per the governing institutional requirements and in compliance with local laws and guidelines.

10.2.7. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for niraparib are the following:

- Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- Secondary cancers (new malignancies [other than MDS or AML])
- Pneumonitis

- Embryo-fetal toxicity

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor until death or loss to follow-up.
- Pneumonitis should be reported to the Sponsor through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first).
- Embryo-fetal toxicity should be reported as outlined in Section 10.2.8.

10.2.8. Pregnancy

The Investigator must report all pregnancies and the outcomes to the Sponsor. The Sponsor has the responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Each pregnancy must be reported by the Investigator to the Sponsor on an Initial Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE in the eCRF unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. The Investigator must follow-up all pregnancies, document the course and the outcome, and report this information to the Sponsor on a Pregnancy Outcome Report Form within 24 hours of becoming aware - even if the patient was withdrawn from the study or the study has finished.

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE in the eCRF. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

10.2.9. Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on a Special Situation Form to the Sponsor regardless of whether an AE or SAE has occurred. The form should be submitted as soon as possible, and if there is no AE or SAE, it should be indicated that 'no AE has occurred'. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an SAE, an SAE report form must be submitted to the Sponsor within 24 hours of awareness.

11. STATISTICS

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

All analyses will include summary statistics, including the number and percentage for categorical variables and the number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using the Kaplan-Meier method. Two-sided 95% CIs will be provided where appropriate. Time-to-event data may be censored according to criteria provided in the SAP. Further details will be provided in the SAP.

No formal statistical testing will be performed.

11.1. Sample Size Determination

The sample size of the study is driven by the primary endpoint: PFS18. A sample size of 90 patients will provide an 11% precision on the 95% exact CI of PFS18, assuming a true PFS18 rate of 48%, which corresponds to a median PFS of 17 months based on exponential PFS assumption. The primary endpoint analysis will occur after approximately 3 months of enrollment and an additional 18 months of follow-up.

11.2. Analysis Populations

Three analysis populations will be defined as follows:

- Safety population: All patients who receive any amount of study treatment (ie, any amount of bevacizumab or niraparib during the study). All safety endpoints will be assessed in the safety population.
- Efficacy population: All patients who receive any amount of niraparib (at least 1 dose). Analyses of baseline characteristics and the primary analysis of efficacy endpoints will be performed on the efficacy population.
- Per-protocol population: All patients in the efficacy population who have no major protocol violations during the study and have at least 1 protocol-required postbaseline tumor assessment.

11.3. Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographics, baseline characteristics, and medical history information will be summarized for the Safety population using descriptive statistics. No formal statistical comparisons will be performed.

Demographics, baseline characteristics, concomitant medications, and medical history data for each patient will be provided in data listings.

11.4. Efficacy Analyses

All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using the Kaplan-Meier method. Two-sided 95% CIs will be provided where appropriate. Time-to-event data may be censored according to criteria provided in the SAP. Further details will be provided in the SAP.

The primary endpoint for the study, PFS18, will be estimated using percentage with 95% exact CI. In addition, the probability of PFS at 18 months will be estimated using the Kaplan-Meier method.

Time-to-events endpoints (ie, PFS, RECIST or CA-125 progression-free survival, OS, TFST, and TSST) will be summarized descriptively using the Kaplan-Meier method. A sensitivity analysis will be performed on PFS18 by including CA-125 progression, in addition to RECIST progression and death, to define progression events.

The FOSI will be used in this study. Changes from baseline in overall score, subscores, and individual items will be analyzed descriptively. A repeated-measures model adjusting for covariates and subject evaluating change in symptoms and QoL will be conducted. Time to symptom worsening on the FOSI will be analyzed using time-to-event methodology.

No formal statistical testing will be performed.

In addition, biomarkers will be evaluated retrospectively. Further details will be provided in the SAP.

11.5. Safety Analyses

The safety and tolerability of niraparib in combination with bevacizumab will be analyzed based on the incidence of TEAEs, SAEs, changes in ECOG performance status, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications. The incidence of TEAEs and use of concomitant medications will be summarized. Clinical laboratory parameters and vital signs will be summarized by study visits. Descriptive summary statistics for observed values as well as changes from baseline will be presented.

All AEs will be coded using the current version of the MedDRA coding system and displayed in tables and data listings using system organ class and preferred term. AESIs will be summarized for each AESI category and preferred term.

The number and percentage of patients with any TEAE, with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any SAE will be summarized. In these tabulations, each patient will contribute only once (ie, the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

The occurrence of and reasons for any requirement for dose interruption or modification will be tabulated and distinguished as to presumptive causality from niraparib or bevacizumab, if known.

All AEs occurring on study will be listed in patient data listings. By-patient listings will also be provided for the following: patient deaths, SAEs, and AEs leading to treatment discontinuation.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs, and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

12.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

12.3. Institutional Review Board (IRB)/Institutional Ethics Committee (IEC)

The Principal Investigator must obtain IRB or IEC approval, as appropriate, for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCPs and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 12.2 for more details regarding the audit process.

14. ETHICS

14.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (please see Appendix 5) and are consistent with ICH/GCP guidelines, applicable regulatory requirements, and the Sponsor's policy on Bioethics.

14.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

16. PUBLICATION POLICY

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

17. LIST OF REFERENCES

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18. APPENDICES

APPENDIX 1. CONTRACEPTION GUIDELINES

Patients of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 180 days after last dose of study treatment(s):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral route
  - intravaginal route
  - transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence, if the preferred and usual lifestyle of the subject

APPENDIX 2. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS V.1.1

Response Criteria by RECIST v.1.1[20]

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 9: For Patients with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 10: For Patients with Non-measurable Disease (ie, Non-target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of SD: SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

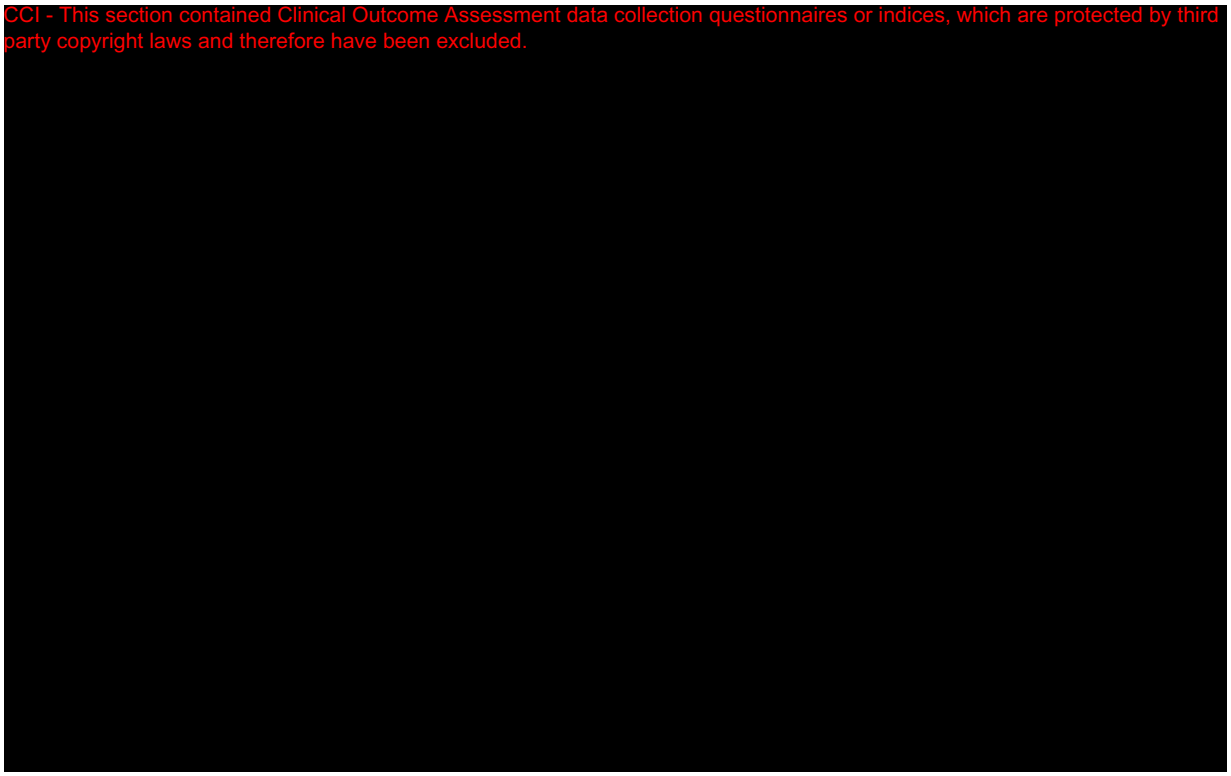
APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Description	Grade
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

Source: [21]

APPENDIX 4. SAMPLE FUNCTIONAL ASSESSMENT OF CANCER THERAPY – OVARIAN SYMPTOM INDEX (FOSI)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**



APPENDIX 5. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
- 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
- 59th WMA General Assembly, Seoul, Republic of Korea, October 2008
- 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development, and effects of diseases and improve preventive, diagnostic and

therapeutic interventions (methods, procedures, and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries, as well as applicable international norms and standards. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training, and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic, or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens, and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in

comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed, and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify, or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices, or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects, and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor, and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is

to be performed, as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study, and the discomfort it may entail, post-study provisions, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects, as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential

subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances, the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage, and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations, the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention

identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations, and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Source: [22]