A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy

Sponsor:	TESARO 1000 Winter Street Suite 3300 Waltham, MA 02451 PPD	TESARO Bio Netherlands B.V Joop Geesinkweg 901 1114AB Amsterdam-Duivendrecht The Netherlands PPD
Medical Monitor:	PPD, MD Senior Medical Director PPD	
Clinical Research Organizations:	PAREXEL International PSI CRO	
Sponsor Protocol No.:	PR-30-5017-C	
IND No.:	100,996	
EudraCT No.:	2015-000952-11	
NCT No.	026550156	
Study Drug Name:	Niraparib	
Development Phase:	3	
Date of Original Protocol:	26 October 2015	
Date of Amendment 1	22 November 2016	
Date of Amendment 2	16 November 2017	
Date of Amendment 3	12 February 2018	
Date of Amendment 4	27 August 2019	
Version of Protocol:	5.0	

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy

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

PPD , MD
Senior Medical Director

8/27/2019
Date

INVESTIGATOR SIGNATURE PAGE

Declaration of the Principal Investigator

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (2013), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Principal Investigator

_____ _____

Name: **Date**
Title:
Institution:

SYNOPSIS

Name of Sponsor/Company: TESARO	
Name of Investigational Product: Niraparib	
Name of Active Ingredient: Niraparib	
Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy	
Study Center(s): Up to approximately 250 international sites	
Studied Period (years): Estimated date first patient enrolled: Q1 2016 Estimated date last patient completed: Q4 2021	**Phase of Development:** 3

Objectives:

Primary Objective:

The primary objective of this study is to evaluate the efficacy of niraparib versus placebo as maintenance treatment, as measured by progression-free survival (PFS), in patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) with a complete response (CR) or partial response (PR) following front-line platinum-based chemotherapy treatment.

Secondary Objectives:

1. To evaluate additional measures of clinical benefit for niraparib versus placebo as maintenance treatment, such as overall survival (OS), patient-reported outcomes (PROs), time to first subsequent therapy (TFST), and time to progression on the next anticancer therapy (PFS2).
2. To evaluate the safety and tolerability of niraparib versus placebo

Exploratory Objectives:

1. To assess population pharmacokinetics (PK) and estimate PK parameters for niraparib and its major metabolite
2. To evaluate potential biomarkers related to ovarian cancer and poly(ADP-ribose) polymerase (PARP) inhibition (e.g. DNA repair pathways)
3. To explore the relationship between homologous recombination-deficient (HRD) status and platinum sensitivity in ovarian cancer patients who have initial response to front-line platinum therapy

Methodology:

Niraparib is a potent, orally active PARP 1/2 inhibitor being developed as an agent for tumors with defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway.

This study is a double-blind, randomized, placebo-controlled (2:1 niraparib:placebo) study in patients with Stage III or IV ovarian cancer. Patients must have completed front-line platinum-based regimen with a physician-assessed response of CR or PR. Additionally, patients must have a normal or >90% decrease in cancer antigen 125 (CA-125) following front-line platinum treatment. The study will assess the efficacy of niraparib as maintenance treatment, as measured by PFS.

Stratification factors will include administration of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), and HRD status (HRDpositive [HRDpos], includes g*BRCA*mut and s*BRCA*mut patients; or HRDnegative/not determined [HRDneg/HRDnd] evaluated by a central test).

Oral niraparib capsules or placebo (appearance-matched capsules) will be administered once daily (QD, continuously in 28-day cycles) in a double-blind fashion. The starting dose of study treatment will be based upon the patient's baseline body weight or baseline platelet count. Patients with a baseline body weight ≥ 77 kg **and** baseline platelet count ≥150,000 µL will be administered niraparib 300 mg (3 X 100 mg capsules) or placebo (3 capsules) daily. Patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL will be administered niraparib 200 mg (2 X 100 mg capsules) or placebo (2 capsules) daily. Additional dose modifications of study treatment will not be based upon changes in the patient's body weight during study participation. For patients whose starting dose is 2 capsules once daily, escalation to 3 capsules once daily is permitted if no treatment interruption or discontinuation was required during the first 2 cycles of therapy. Patients will be instructed to take their dose once a day or as instructed by the Investigator. Patients must swallow and not chew all capsules. The consumption of water and food with study treatment is permissible. The first dose will be administered at the site.

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. The timing of efficacy or safety evaluations will not be affected by dose interruptions or reductions.

Blood samples for PK will be collected on Cycle 1/Day 1 and Cycle 2/Day 1 predose (within 30 minutes prior to dosing) and 2 hours (± 15 minutes) postdose. Additional samples for PK on Cycle 4/Day1 and Cycle 8/Day 1 will be collected at predose (within 30 minutes before scheduled dose) only. If study drug is held one day prior to and on C2D1, PK sample collection on that day is not required. If study drug is held on C4D1 or C8D1, PK sample collection on those days is not required.

Clinic visits (other than Cycle 1) will occur every cycle (28 days ± 3 days). Response Evaluation Criteria in Solid Tumors (RECIST) (v.1.1) 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 until progression is confirmed by blinded independent central review (BICR). For patients who stayed on study treatment for over 2 years (approx. 26 cycles) the CT/MRI will be required every 24 weeks (6 cycles). Positron emission tomography (PET)/CT may be used according to RECIST guidelines, but its use is not a study requirement. Cycle timing will not be delayed for treatment interruptions, and 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. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals until progression is confirmed or the start of subsequent anticancer treatment.

Predose blood samples from Cycle 1/Day 1 will be collected for exploratory biomarker analyses. For patients who discontinue study treatment due to progressive disease, a blood sample will be requested. Additionally, the provision of a tumor sample for exploratory biomarker analyses will be optional. All patients will continue to be followed for tumor response and tolerability with subsequent anticancer treatment, PFS2, and OS.

Patient-reported outcomes (PROs) (Functional Assessment of Cancer Therapy – Ovarian Symptom Index [FOSI], European Quality of Life scale, 5-Dimensions [EQ-5D-5L], European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 [EORTC-QLQ-C30], EORTC-QLQ ovarian module [EORTC-QLQ-OV28]) will be collected while on study. The PROs may be completed in person or remotely (i.e., by standard mail). It is estimated that PRO evaluations will take less than 20 minutes at each time point.

HRD prescreening Informed Consent: Reporting of safety events is to be begin at time of HRD pre-screening ICF signature date only if related to the procedure of a fresh biopsy. If archival tissue is submitted when patient consents to HRD pre-screening ICF, then reporting of safety events is to begin at time of Main study ICF signature date. Main study Informed Consent: All adverse events (AEs) will be collected and recorded in the electronic case report form (eCRF) for each patient from the day of signed main informed consent until 30 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen. If, at any time after the study is completed, an Investigator becomes aware of a serious adverse event (SAE) that is considered related to the investigational product, or an adverse event of special interest (AESI) regardless of causality, the Investigator should report the SAE/AESI to the Sponsor's Pharmacovigilance Department within 24 hours of becoming aware of the SAE. The AESIs for this study are myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), secondary cancers (new malignancies other than MDS/AML), pneumonitis, and embryo-fetal toxicity. MDS/AML and secondary cancers (new malignancies other than MDS or AML) must be reported until death or loss to follow-up. Pneumonitis must be reported for up to 90 days after the last dose of study treatment and pregnancy must be reported for up to 180 days after the last dose of study treatment.

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, abnormal laboratory values have returned to baseline or

normalized, there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient has died.

Number of Patients (Planned): Approximately 620 patients are planned to enroll in this study.

To be considered eligible to participate in the study, the patient must meet the all inclusion criteria as outlined in Section 4.1.

Main Criteria for Inclusion:

- Patients must be female ≥18 years of age, able to understand the study procedures and agree to participate in the study by providing written informed consent.
- Histological and staging criteria:
  - Patients must have histologically diagnosed high-grade serous or endometrioid, or high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that is Stage III or IV according to FIGO criteria.

    Note: Patients who have received neoadjuvant chemotherapy may be included in the study if post-chemotherapy tumor grade is not evaluable.
- Surgical criteria:
  - Patients with inoperable Stage III and IV disease are eligible;
  - All Stage IV patients with operable disease are eligible;
  - Patients with Stage III or IV disease treated with neoadjuvant chemotherapy and interval debulking surgery are eligible;
  - Patients with Stage III disease who have visible residual disease after primary debulking surgery are eligible;
- Chemotherapy criteria:
  - Patients who have received intraperitoneal chemotherapy are eligible;
  - All patients must have had ≥6 and ≤9 cycles of platinum-based therapy;
  - Patients must have had ≥2 post-operative cycles of platinum-based therapy following interval debulking surgery;
  - Patients must have physician assessed CR or PR after ≥ 3 cycles of therapy;
  - 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 (i.e., no increase >15% from nadir).
- Patients must be randomized within 12 weeks of the first day of the last cycle of chemotherapy.
- All patients must agree to undergo a central tumor HRD testing:

- The central HRD test result must be available for randomization as it is a stratification factor. Patients with documented breast cancer susceptibility gene g*BRCA*1 or g*BRCA*2 mutation or somatic *BRCA1/2* mutation may be randomized without HRD test status results.
- The tumor sample may be submitted for HRD testing prior to the screening period if it appears the patient is likely to meet other eligibility requirements. Patients are not required to have repeat HRD testing if HRD result is "not determined" (eg, due to insufficient tumor specimen).
- Patients with known HRD test results from a commercially available source are allowed to participate in the study; however, they must still agree to submit a tumor sample for central HRD testing. The results of the central HRD testing must be available prior to randomization and must be used for stratification. Additional testing related to HRD may be performed post randomization. Sites may be requested to provide additional tissue from the sample used during screening if there is an inadequate quantity of tissue remaining subsequent to the screening analysis.

To be considered eligible to participate in the study, the patient must not meet any of the following exclusion criteria as outlined in Section 4.2.

Main Criteria for Exclusion:

- Patient has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer;
- Patients with Stage III disease who have had complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery;
- Patient has undergone more than 2 debulking surgeries for the study disease;
- Patient is to receive bevacizumab as maintenance treatment. Patients who have received bevacizumab with their first-line platinum based therapy but are unable to receive bevacizumab as maintenance therapy due to adverse events or any other reason are not excluded from study as long as the last dose of bevacizumab was received $\geq$ 28 days prior to signing the main informed consent form;
- Patient has a condition (such as transfusion dependent anemia or thrombocytopenia), or laboratory abnormality that might confound the study results or interfere with the patient's participation for the full duration of the study treatment, including:
  - Patient received a transfusion (platelets or red blood cells) within 2 weeks of the first dose of study treatment;
  - Patient received colony-stimulating factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 2 weeks prior to the first dose of study treatment;

- Patient is pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and for up to 180 days after the last dose of study treatment;
- Patient has a known hypersensitivity to the components of niraparib or its excipients;
- Patient has had investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study;
- Patient has had any known ≥Grade 3 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted >4 weeks.
- Patient has been diagnosed and/or treated for any invasive cancer (other than study disease) less than 5 years prior to study enrollment. Note: Patients with definitively treated uterine cervical or urinary tract carcinoma in situ, non-melanomatous skin cancer or ductal carcinoma in situ (DCIS) of the breast are not excluded

Investigational Product, Dosage, and Mode of Administration:

Niraparib will be administered using 100 mg capsules. Placebo will be administered using capsules matched in appearance. The starting dose of study treatment will be based upon the patient's baseline body weight or baseline platelet count. Patients with a baseline body weight ≥ 77 kg **and** baseline platelet count ≥150,000 µL will be administered niraparib 300 mg (3 X 100 mg capsules) or placebo (3 capsules) daily. Patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL will be administered niraparib 200 mg (2 X 100 mg capsules) or placebo (2 capsules) daily. Additional dose modifications of study treatment will not be based upon changes in the patient's body weight during study participation. For those patients whose starting dose is 2 capsules once daily, escalation to 3 capsules once daily is permitted if no treatment interruption or discontinuation occurred during the first 2 cycles of therapy. For any dose modification, the number of capsules administered will be modified accordingly.

All study treatment capsules will be administered orally QD continuously (in 28-day cycles) in a double-blind fashion. Patients will be instructed to take their dose once a day or as instructed by the Investigator. Patients must swallow and not chew all capsules. The consumption of water and food with study treatment is permissible. The first dose will be administered at the site.

Study treatment will be packed in high-density polyethylene bottles with child-resistant closures.

Duration of Treatment: Approximately 3 years. (Note, patient may continue to receive treatment >3 years, if deriving clinical benefit as assessed by the Investigator.)

Planned Study Conduct Duration: Approximately 5 years

Criteria for Evaluation:

Efficacy:

Efficacy will be evaluated using the primary endpoint, PFS, defined as the time from treatment randomization to the earlier date of assessment of progression or death by any cause in the absence of progression.

OS is a key secondary endpoint and defined as the time from the date of randomization to the date of death by any cause.

Efficacy will also be evaluated using the following secondary endpoints such as changes from baseline in patient reported outcomes, time to first subsequent therapy (TFST), and PFS2.

Pharmacokinetics:

Blood samples for PK will be collected on Cycle 1/Day 1 and Cycle 2/Day 1 predose (within 30 minutes prior to dosing) and 2 hours (± 15 minutes) postdose. Additional samples for PK on Cycle 4/Day1 and Cycle 8/Day 1 will be collected at predose (trough; within 30 minutes before scheduled dose) only. If study drug is held one day prior to and on C2D1, PK sample collection on that day is not required. If study drug is held on C4D1 or C8D1, PK sample collection on those days is not required.

A population PK modeling approach will be used to describe plasma concentrations of niraparib and its metabolite in patients. In the analysis, covariates will be evaluated to determine if they contribute to differences in the PK estimates among individuals.

In addition, the PK/PDy relationship between concentrations of niraparib and its metabolite and efficacy and safety measures will be investigated. The exposure to niraparib and its metabolite will be correlated with safety (selected AEs) and efficacy variables.

Safety:

Safety will be evaluated based on incidence of treatment-emergent AEs (TEAEs), changes in clinical laboratory results (hematology, chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications. All AEs will be coded using the current version of the MedDRA coding system.

Statistical Methods: The primary endpoint is PFS, defined as the time from the date of treatment randomization to the date of first documentation of progression (by blinded central review) or death due to any cause in the absence of documented progression, whichever occurs first. A hierarchical testing for the PFS endpoint will be used to control the overall Type I error rate. First, PFS analysis will be conducted in the HRDpos patients (including g*BRCA*mut and s*BRCA*mut patients) at the 1-sided alpha level of 0.025. If the result is positive, PFS analysis will be conducted in the overall intent-to-treat (ITT) population with the 1-sided alpha level of 0.025; otherwise, PFS analysis becomes exploratory in the overall ITT population. PFS data may be censored according to criteria provided in the statistical analysis plan (SAP). The analysis of OS is also included in the hierarchical testing to ensure a strong control of the overall Type I error. OS will be only tested if statistical significance is

both shown for PFS in HRDpos and ITT populations. OS will be analyzed sequentially using the full alpha first in the ITT population and then in HRDpos population.

Sample Size Considerations:

In the studies of the maintenance therapy following first line chemotherapy for advanced ovarian cancer, the median PFS has been shown to be up to approximately 14 months in the broad population of patients.[1-3] In addition, several studies showed that patients with gBRCA mutation had a longer median PFS (approximately 30 months) than those without the mutation[4,5]. Therefore the median PFS for all placebo patients is assumed as 14 months and the median PFS for placebo patients with BRCAmut is assumed as 30 months. As the data are limited for the prognostic role of HRD in BRCAwt patients in the first line maintenance, median PFS for BRCAwt/HRDpos and HRDneg placebo patients is assumed to be the same.

The median PFS for HRDpos placebo patients is calculated as follows: Assuming an exponential distribution, the PFS for all placebo patients has a mixture of exponential distributions (35% with BRCAmut and 65% with BRCAwt) with the median PFS of 14 months. Since the median PFS for BRCAmut placebo patients is assumed to be 30 months, data simulation yields a median PFS of 10 months for BRCAwt placebo patients and 21 months for HRDpos placebo patients.

Assuming a median PFS of 21 months for HRDpos placebo group, to detect an expected benefit corresponding to hazard ratio of 0.5 with 90% power and a 2:1 randomization ratio, 99 PFS events are required. Current projections suggest that approximately 50% of all patients randomized will be HRDpos. Therefore enrollment of approximately 620 patients (310 with HRDpos) will be needed to compete the study in about 44 months. This assumes that 15% of patients will not provide a PFS event for the primary endpoint (lost-to-follow-up, discordance between investigator and central reviewer, etc.).

The key secondary endpoint is the PFS for all randomized patients regardless of their HRD status. The final analyses for the primary and key secondary endpoints will be performed in a sequential manner when approximately 99 HRDpos PFS events are reached. The analysis of the key secondary endpoint will include all PFS events at the time of the final analysis. Assuming a median PFS of 14 months for all placebo patients, a total of approximately 270 PFS events are expected for the final analysis. This will provide at least 90% power to detect a true HR of 0.65 in all patients.

Patients will be randomized according to the following stratification factors: administration of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), HRD status (pos [includes gBRCAmut and sBRCAmut patients] or neg/nd).

If a statistically significant PFS treatment difference is observed in the ITT population, the sequential testing will continue for OS endpoint first in the ITT population and then in HRDpos population. The analysis of OS will include an interim analysis of OS at the time of the final analysis of PFS and a final analysis of OS when approximately 440 deaths have occurred in the ITT population (60% data maturity). A Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundaries will be used to determine the significance levels for interim and final analyses based on the observed fraction of OS events. The final

analysis of OS is expected to occur approximately 70 months after first patient randomized. To detect a statistically significant OS treatment difference at 1-sided 0.025 Type I error, the analysis of OS with 440 events will have at least 80% power if the true HR is 0.75 or less in the ITT population. Although this study is not powered for OS analysis in HRDpos population, about one third of deaths in the ITT population are estimated to be HRDpos patients at the time of final analysis of OS, thus the analysis of OS with 150 HRDpos events will have at least 70% power if the true HR is 0.65 or less in HRDpos population.

Efficacy:

The PFS analysis will be performed using a 1-sided stratified log-rank test. A stratified Cox proportional hazards model will be used to estimate the treatment efficacy by hazard ratio (HR) and its 95% confidence interval (CI). PFS will also be descriptively summarized using Kaplan-Meier methodology.

Subgroups will also be explored for the primary efficacy endpoint based on age, race, geographic region, HRD status, neoadjuvant chemotherapy (yes or no), and best response to first platinum regimen (CR or PR). Subgroups involving *BRCA* mutation markers may also be explored for the primary efficacy endpoint. Details of these subgroup analyses (including exploring subgroups for any other study endpoints) will be detailed in the SAP.

Safety:

Safety parameters will be summarized descriptively, for the overall population and by subgroup. No inferential statistical analyses are planned.

Biomarkers:

Biomarker analyses will be specified in the SAP.

Pharmacokinetics/pharmacodynamics:

Plasma samples for population PK assessment will be analyzed for concentrations of niraparib and its primary metabolite and time of measurement. A population PK modeling approach will be used to describe plasma concentrations of niraparib and its metabolite in patients. In the analysis, a number of covariates will be evaluated to determine if they contribute to differences in the PK estimates among individuals. In addition, the PK/PDy relationship between concentrations of niraparib and its metabolite and efficacy and safety measures will be investigated. The exposure to niraparib and its metabolite will be correlated with safety (selected AEs) and efficacy variables.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	activities of daily living
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
alt-NHEJ	alternative non-homologous end-joining
AST	aspartate aminotransferase
AUC	area under the curve
BER	base excision repair
BICR	blinded independent central review
BP	blood pressure
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
CA-125	cancer antigen 125
CBC	complete blood count
CI	confidence interval
CIOMS	Council for International Organization of Medical Sciences
CN	copy number
CNS	central nervous system
CP	conditional power
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CYP	cytochrome P450
DCIS	ductal carcinoma in situ
DCR	disease control rate
DoR	duration of response
DNA	deoxyribonucleic acid
ECG	electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ- C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30
EORTC-QLQ-OV28	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Ovarian Cancer Module- OV28
EOC	epithelial ovarian cancer
EOT	end of treatment
EQ-5D-5L	European Quality of Life Scale, 5-Dimensions
ESMO	European Society for Medical Oncology
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FOSI	Functional Assessment of Cancer Therapy –Ovarian Symptom Index
gBRCAmut	germline BRCA mutation
gBRCAnd	germline BRCA (mutation) not determined
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
g-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
hCG	human chorionic gonadotropin
HR	hazard ratio
HRD	homologous recombination deficiency
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IND	investigational new drug
IP	intra-peritoneal
IRB	institutional review board
ITT	intent to treat
IV	intravenous
LOH	loss of heterozygosity

Abbreviation	Definition
LST	large-scale state transitions
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
MRI	magnetic resonance imaging
nd	Not determined
ND	no disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NHEJ	nonhomologous end-jointing
non-gBRCAmut	non-gBRCA mutant
ORR	overall response rate
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PD	progressive disease
PDy	pharmacodynamics
PDS	primary debulking surgery
PET	positron emission tomography
PFS	progression-free survival
PFS2	time to second objective disease progression
P-gp	P-glycoprotein
PK	pharmacokinetic
PP	per protocol
PR	partial response
PRO	patient-reported outcome
QD	once daily
QLQ	Quality of Life Questionnaire
QoL	quality of life
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
sBRCAmut	somatic BRCA mutation
SD	stable disease
StDev	standard deviation
TAI	telomeric allelic imbalance in tumor
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cells
WHO	World Health Organization
wt	wild type

1. INTRODUCTION

1.1. Background

Niraparib is a potent, orally active poly(ADP-ribose) polymerase (PARP) 1/2 inhibitor being developed as an agent for tumors with defects in the homologous recombination deoxyribonucleic acid (DNA) repair pathway.

1.1.1. Disease Background

The term epithelial ovarian carcinoma (EOC) has been used to refer to a large group of malignant neoplasms that typically present as ovarian tumors and involve the fallopian tube and peritoneum. Evidence suggests that these epithelial neoplasms can be divided into two groups in terms of probable site of origin: either ovarian or tubal primary peritoneal carcinoma. Tubal primary peritoneal carcinoma, also known as peritoneal serous carcinoma, is histologically indistinguishable from serous ovarian cancer; clinically, the peritoneal cancer is distinguished from ovarian cancer by its extensive extra-ovarian involvement.[6] Due to their shared clinical behavior and treatment options, since 2014 the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) has combined ovarian, fallopian tube, and peritoneal cancers into a single staging classification.[7]

At diagnosis, most women with epithelial ovarian cancer present with advanced disease (Stages III and IV), which contributes to its high mortality rates (approximately 15,500 deaths in the United States and 42,704 deaths in Europe in 2012).[8,9] A pivotal study compared standard 24 hour intravenous (IV) infusion of paclitaxel on Day 1 followed on Day 2 by either IV cisplatin infusion or intraperitoneal (IP) infusion of cisplatin. Patients with Stage III tumors with "low volume" residual disease (i.e., no gross residual disease >1.0 cm after surgery; also described as "R1 resection") on both regimens received IP infusion of paclitaxel on Day 8. In comparison to IV cisplatin, the use of IP cisplatin resulted in statistically and clinically significant improvements in progression-free survival (median progression-free survival (PFS): 23.8 months vs 18.3 months) and overall survival (OS, median survival: 65.6 months vs 49.7 months).[10] Approximately 40% of the study patients had no visible residual disease following surgery (described as "R0 resection"). Among patients with ovarian cancer and with R0 resection, the use of intraperitoneal (IP) cisplatin resulted in non-significant trends in improved PFS (median PFS: 37.5 months versus 35.2) and OS (median survival: not achieved in IP cisplatin patients versus 78.2 months in IV cisplatin patients. Despite the improved outcomes with the combination of IV and IP chemotherapy in patients with Stage III disease, its use is not widespread due to concerns over toxicity (e.g., only 42% of patients completed the prescribed 6 cycles of therapy), lack of familiarity with IP administration of chemotherapy, and peritoneal catheter complications.

After the diagnosis, patients with Stage III or IV disease generally undergo "primary" debulking surgery (meaning upfront or immediate surgery followed by chemotherapy) or "interval" or "delayed" debulking surgery (i.e., surgery that is bracketed by chemotherapy). A study conducted by European Organisation for Research and Treatment of Cancer (EORTC) investigators compared primary debulking surgery (PDS) followed by at least 6 cycles of platinum-based chemotherapy to 3 cycles of neoadjuvant chemotherapy (NACT), plus interval debulking surgery and 3 cycles of chemotherapy post-operatively in patients with Stage IIIC or

IV ovarian cancer.[11] NACT patients had non-inferior outcomes to PDS patients based upon the primary study endpoint of overall survival (OS) (median survival: 30 months versus 29 months) and progression-free survival (PFS) (median PFS of 12 months in both arms). In addition, the use of NACT was associated with lower rates of post-operative morbidity (e.g., hemorrhage, infection, venous complications) and mortality (0.7 versus 2.5%). This study also demonstrated that the most favorable outcomes were observed in patients with R0 resection (median survival: 39 months for NACT patients and 45 months for PDS patients.[11] Based upon these results, the use of NACT is increasingly administered in patients with large volume Stage IIIC/IV disease.

Approximately 75% of patients respond to front-line 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. Attempts to improve the standard platinum-based chemotherapy by adding a third cytotoxic drug have failed to affect either PFS or OS and resulted in increased toxicity.[12, 13]

Maintenance or consolidation treatments have also 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 trials 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 OS.[14] Another meta-analysis of 20 consolidation and 9 maintenance treatment trials, however, demonstrated a significant improvement in PFS (hazard ratio [HR] of 0.82; 95% confidence interval (CI): 0.70 to 0.96 [$p<0.02$]).[15] Recent clinical trials of anti-angiogenic agents (such as bevacizumab and pazopanib) administered in a maintenance setting have demonstrated a benefit in PFS[1, 16, 17] but also resulted in an increase in toxicity.

Given the expectation of disease recurrence for patients who demonstrate a complete response (CR) to front-line platinum therapy, the National Comprehensive Cancer Network (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. 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 partial response (PR) to first-line therapy, NCCN guidelines recommend clinical trial participation, recurrence therapy, or best supportive care.

In a pivotal maintenance study of 2 doses of paclitaxel in patients with complete response to front-line platinum therapy, researchers demonstrated that extended paclitaxel therapy (12 cycles) significantly improved PFS compared to abbreviated paclitaxel therapy (3 cycles)[18]. There was also a significant increase in neurotoxicity, without an improvement in OS with prolonged therapy. Compared to placebo, pazopanib maintenance significantly improved PFS in ovarian cancer patients with CR, PR or stable disease (SD) following first-line platinum therapy.[1] However, therapy was also associated with significantly more grade 3-4 hypertension, neutropenia, hepatotoxicity, diarrhea, fatigue, thrombocytopenia, and palmar-plantar erythrodysesthia.

The ICON-7 Investigators have demonstrated that in patients with ovarian cancer and with stage IV or incompletely debulked stage III disease that compared to paclitaxel-carboplatin alone, the addition of bevacizumab to that combination followed by its prolonged single agent use significantly extended the primary endpoint of PFS (median PFS: 14.1 months versus 10.3 months, respectively; hazard ratio=0.717, p<0.0001). While there was no difference in overall survival for the entire ICON 7 study population, there was also improvement in of OS in a pre-planned exploratory analysis in poor prognosis patients (all patients with stage IV disease, and patients with inoperable or sub-optimally debulked stage III disease.[16] The ICON 7 investigators also studied bevacizumab in combination with 6 cycles of first-line platinum therapy only or in combination with first-line platinum therapy but followed by prolonged single agent use in patients with stage IIB-IV ovarian cancer.[19] The use of bevacizumab significantly improved PFS but not overall survival (OS) in the overall population. In a pre-planned exploratory analysis of "poor prognosis" patients (stage IV, or stage III with > 1cm residual tumor), both PFS and OS were significantly improved with the addition of bevacizumab platinum-taxane therapy followed by prolonged single agent bevacizumab.[20]

Bevacizumab has been approved by the FDA and EMA in combination with and following platinum-taxane therapy in patients with advanced ovarian cancer, as well as in patients with platinum sensitive and platinum resistant ovarian cancers. Although the European Society for Medical Oncology (ESMO) endorses its use in the maintenance setting, the authors also acknowledge that bevacizumab is not consistently used in this patient population in Europe or US as several questions remain regarding the appropriate treatment setting, dose, and duration of bevacizumab treatment as well as the benefit/risk balance of the treatment[21].

1.1.2. Compound Background

Poly(ADP-ribose) polymerases (PARP-1 and -2) are zinc-finger deoxyribonucleic acid (DNA)-binding enzymes that play a crucial role in DNA repair. Upon formation of DNA breaks, PARP binds at the end of broken DNA strands, a process that activates its enzymatic activity. Activated PARP catalyzes addition of long polymers of adenosine diphosphate (ADP)-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins. This results in chromatin relaxation, fast recruitment of DNA repair proteins, and efficient repair of DNA breaks. In this manner, PARP plays a key role in sensing DNA damage and converting it into intracellular signals that activate the base excision repair (BER) and single-strand break repair pathways.

Normal cells repair up to 10,000 DNA defects daily, and single-strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the homologous recombination or BER pathways, are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. They enter the S (DNA replication) phase of the cell cycle with unrepaired single- and double-strand breaks. Pre-existing single strand breaks are converted to double-strand breaks as the replication machinery passes. Accumulated double-strand breaks present during S phase are repaired by homologous recombination. Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells unable to perform DNA repair via homologous recombination (e.g., due to inactivation of genes required for homologous recombination, such as breast cancer susceptibility gene 1 [*BRCA*1] or *BRCA*2) are at risk for

accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S phase and are more likely to use the error-prone nonhomologous end-joining (NHEJ) or alternative (alt)-NHEJ pathways to repair double-strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to mutations that promote the development of cancer. Over time, the buildup of excessive DNA errors in combination with the inability to complete S phase (because of stalled replication forks) contributes to cell death.

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline *BRCA* mutation (g*BRCA*mut) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on NHEJ, alternative (alt)-NHEJ, and BER for maintenance of genomic integrity. PARP inhibitors block alt-NHEJ and BER, forcing tumors with *BRCA* deficiencies to use the error-prone NHEJ to fix double strand breaks. Non-BRCA deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors. The rationale for anticancer activity in a subset of non-g*BRCA*mut tumors is that they share distinctive DNA repair defects with g*BRCA*mut carriers, a phenomenon broadly described as "*BRCA*ness."[22] DNA repair defects can be caused by germline or somatic alterations to the homologous recombination DNA repair pathway. In a recent analysis of approximately 500 high-grade serous ovarian adenocarcinoma tumors, approximately 50% contained homologous recombination defects[23]. A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib.

Nonclinical data on niraparib in ovarian cancer are discussed in detail in the Investigator's Brochure and described briefly in Section 1.1.2.1.

1.1.2.1. Nonclinical Experience

Nonclinical data on niraparib are discussed in detail in the Investigator's Brochure. In summary, preclinical models have shown niraparib inhibits normal DNA repair mechanisms and induces synthetic lethality when administered to cells with homologous recombination defects. In a *BRCA*1-mutant xenograft study, niraparib dosed orally caused tumor regression, which was mirrored by >90% reduction in tumor weight compared with the control; in a *BRCA*2-mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib displayed strong antitumor activity in in vivo studies with BRCA1-mutant breast cancer (MDA-MB-436), BRCA2-mutant pancreatic cancer (CAPAN-1), ATM-mutant mantle cell lymphoma (GRANTA-519), serous ovarian cancer (OVCAR3), and colorectal cancer (HT29 and DLD 1) xenograft models and with patient-derived Ewing sarcoma mice models. Utilizing patient-derived ovarian xenografts, niraparib previously demonstrated response in both *BRCA* mutation and *BRCA* wild-type (wt) tumors[24].

1.1.2.2. Clinical Experience

The ENGOT-OV16/NOVA study[25] 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 1 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 1: 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 (Niraparib: Placebo) (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.[26]

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 10^9/L) 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.

1.2. Rationale for Current Trial

Defects in the homologous recombination pathway might result in specific structural changes in DNA. Previously, chromosomal copy number (CN) changes have been reported to be associated with *BRCA*1 and *BRCA*2 mutations.[27,28] Recent evidence, however, indicates that evaluation of the patterns of LOH and HRD may be more robust than CN changes alone. LOH results in the irreversible loss of one of the parental alleles. In contrast, CN gains are not necessarily permanent. Therefore, if HRD leaves a footprint of genomic alterations, LOH and CN variants may provide a more stable record of those changes compared with CN variants alone. In a recent study, the patterns of genome-wide LOH were analyzed in 3 different epithelial ovarian cancer data sets extensively characterized for *BRCA*1 and *BRCA*2 defects by evaluating HRD status.[29]

The HRD analysis is a DNA-based assay that is capable of detecting HRD independent of its etiology based on genome-wide single nucleotide polymorphism data. An HRD-(LOH) score was developed, which is strongly associated with functional defects in *BRCA*1 and *BRCA*2. This score also strongly correlated with promoter methylation of RAD51C, a gene implicated in the homologous recombination pathway. Additional DNA-based algorithms of HRD have been developed based on whole genome tumor telomeric allelic imbalance, HRD-(TAI)[30], and large-scale state transitions, HRD-(LST)[31]. In a recent study, all 3 HRD algorithms were independently associated with *BRCA*1/2 deficiency and response to cisplatin treatment in triple-negative breast cancer[32]. The arithmetic mean of the 3 HRD algorithms was significantly associated with *BRCA*1/2 status in a breast all-comers cohort and with cisplatin response in a second independent triple-negative breast cancer cohort. The final clinical HRD score results from the sum of HRD-LOH, HRD-TAI, and HRD-LST scores and is a single value along a continuous scale from 0 to 100. Analysis of more than 1,000 breast and ovarian cancer tumor samples has identified 2 distinct HRD populations, HRDneg and HRDpos with 95% of all g*BRCA*mut tumors with concomitant LOH at the *BRCA* gene in the sample classified as HRDpos.

In a Phase 1 study with niraparib (PN001), 104 patients with advanced solid tumors who had received a median of 5 prior therapies were enrolled, of which 49 were ovarian cancer patients (13 platinum-sensitive, 35 platinum-resistant, and 1 platinum-refractory). Of the 49 patients, 22 had confirmed *BRCA*1 or *BRCA*2 mutation, of whom 20 were radiologically assessable.

RECIST and CA-125 Gynecologic Cancer Intergroup criteria confirmed PR in 8 out of 20 patients (40%) at doses ranging from 80 to 400 mg per day. Median response duration was 387 days (range: 159 to 518 days). RECIST and CA-125 criteria confirmed PR in 3 out of 9 patients (33%) with platinum-resistant *BRCA*mut ovarian cancer. Additionally, a 50% response rate (5 out of 10 evaluable patients) was observed at daily doses ranging from 290 to 300 mg among patients with *BRCA*mut ovarian cancer who had received more than 3 lines of prior chemotherapy. Despite the initially high response rates observed in newly diagnosed ovarian cancer patients, a majority of patients will experience disease recurrence. The absence of an approved treatment or standard of care in the maintenance setting represents an unmet need. The NOVA data demonstrate that the PARP inhibitor niraparib offers substantial disease control in patients with platinum-sensitive recurrent ovarian cancer regardless of germline *BRCA* mutational status. Among patients without g*BRCA*mut, the PFS treatment effect was robust among patients whose tumors were HRD positive (PFS hazard ratio=0.38) and among all patients regardless of HRD status (PFS hazard ratio=0.45). Thus, the current study population includes all ovarian cancer patients with complete or partial response following front-line platinum-based therapy. As patients responding to front-line platinum therapy cannot be assumed to have truly platinum-sensitive ovarian cancer without at least a 6 month observation period, tumor HRD status will be assessed in all eligible patients as a potential surrogate of platinum sensitivity. Hierarchical testing for the primary PFS analysis will be used. First, PFS analysis will be conducted in patients with HRDpos tumors (including patients with g*BRCA*mut and s*BRCA*mut). If that test is positive, a second PFS analyses will be conducted in the study population as a whole.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of niraparib versus placebo as maintenance treatment, as measured by PFS, in patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) with a CR or PR following front-line platinum-based chemotherapy treatment.

2.2. Secondary Objectives

1. To evaluate additional measures of clinical benefit for niraparib versus placebo as maintenance treatment, such as OS, patient-reported outcomes (PROs), time to first subsequent therapy (TFST), and time to progression on the next anticancer therapy (PFS2)
2. To evaluate the safety and tolerability of niraparib versus placebo.

2.3. Exploratory Objectives

1. To assess population pharmacokinetics (PK) and estimate PK parameters for niraparib and its major metabolite
2. To evaluate potential biomarkers related to ovarian cancer and PARP inhibition (e.g. DNA repair pathways
3. To explore the relationship between HRD status and platinum sensitivity in ovarian cancer patients who have initial response to front-line platinum therapy.

3. INVESTIGATIONAL PLAN

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP).

3.1. Overall Study Design and Plan

This study is a double-blind, randomized (2:1 niraparib:placebo), placebo-controlled study in patients with advanced ovarian cancer. Stage III patients with R0 (i.e., no residual disease) are not eligible for this study due to the superior outcomes observed following appropriate post-operative therapy. For screening purposes, response assessment may be performed after the patient has completed at least 3 cycles of platinum therapy. Patients must have received at least 6 and no more than 9 cycles of front-line or neo-adjuvant/adjuvant platinum-based regimen with a physician-assessed response of CR or PR. Residual disease following chemotherapy must be 2 cm or less. Additionally, patients must have a normal or >90% decrease in CA-125 upon treatment completion. The study will assess whether maintenance treatment with niraparib will extend PFS in this population.

Stratification factors will include administration of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), and HRD status (HRDpos, includes g*BRCA*mut and s*BRCA*mut patients; or HRDneg/nd).

For all potentially eligible patients, a tumor sample will be sent for centralized HRD testing. To facilitate the screening and enrollment processes, the samples may be sent in advance of the protocol-defined screening period. For patients without a known g*BRCA* or s*BRCA* mutation, HRD test results are required prior to randomization. For patients with a documented deleterious g*BRCA* or s*BRCA* mutation by local results, randomization may occur before the HRD results are available; for stratification purposes, these patients will be considered as having HRDpos tumors. Given the study's multiple international sites, the Sponsor will accept *BRCA* results obtained according to local practice guidelines. To minimize bias, patients, investigators and the site investigative staff will be blinded to HRD status and treatment assignment.

Additional testing related to HRD may be performed on the sample used for screening and randomization post randomization. If there is inadequate tissue remaining subsequent to the screening analysis, sites may be requested to provide additional tissue from the block used for screening purposes.

Oral niraparib capsules or placebo (appearance-matched capsules) will be administered (QD, continuously in 28-day cycles) in a double-blind fashion. The starting dose of study treatment will be based upon the patient's baseline body weight or baseline platelet count (see Table 2). Patients with a baseline body weight ≥ 77 kg **and** baseline platelet count ≥150,000 µL will be administered niraparib 300 mg (3 X 100 mg capsules) or placebo (3 capsules) daily. Patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL will be administered niraparib 200 mg (2 X 100 mg capsules) or placebo (2 capsules) daily. Additional dose modifications of study treatment will not be based upon changes in the patient's body weight during study participation. For patients whose starting dose is 2 capsules once daily, escalation to 3 capsules once daily is permitted in patients who did not require treatment interruption or discontinuation during the first 2 cycles of therapy. Patients will be instructed to take their dose once daily or as instructed by the Investigator. Patients must swallow and not chew all capsules.

The consumption of water and food with study treatment is permissible. The first dose will be administered at the site.

Dose interruption (no longer than 28 days) or dose reduction will be allowed based on treatment side effects. For patients whose starting dose is 3 capsules daily, dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule daily (100 mg/day) will be allowed. No further dose reductions 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. The timing of efficacy or safety evaluations will not be modified due to dose interruptions or reductions.

Blood samples for PK will be collected on Cycle 1/Day 1 and Cycle 2/Day 1 predose (within 30 minutes prior to dosing) and 2 hours (± 15 minutes) postdose. Additional samples for PK on Cycle 4/Day1 and Cycle 8/Day 1 will be collected at predose (trough; within 30 minutes before scheduled dose) only. If study drug is held one day prior to and on C2D1, PK sample collection on that day is not required. If study drug is held on C4D1 or C8D1, PK sample collection on those days is not required.

Clinic visits (other than Cycle 1) will be every cycle (28 days ± 3 days). RECIST (v.1.1) tumor assessment via computed tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen/pelvis and other areas as clinically indicated is required at screening, then every 12 weeks (± 7 days) from Cycle 1/Day 1 visit until progression is confirmed by BICR. For patients who stayed on study treatment for over 2 years (approx. 26 cycles) the CT/MRI will be required every 24 weeks (6 cycles). Positron emission tomography (PET)/CT may be used according to RECIST guidelines, but its use is not a study requirement. Cycle timing will not be delayed for treatment interruptions, and 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. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals until progression is confirmed or the start of subsequent anticancer treatment.

For patients who discontinue study treatment due to progressive disease, provision of a tumor sample for exploratory biomarker analyses will be optional. All patients will continue to be followed for overall survival (OS) and other secondary objectives as outlined in Section 2.2.

PROs (Functional Assessment of Cancer Therapy – Ovarian Symptom Index [FOSI], European Quality of Life scale, 5-Dimensions [EQ-5D-5L], European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30), EORTC-QLQ ovarian module (EORTC-QLQ-OV28) will be collected during the study.

All AEs will be collected and recorded in the electronic case report form (eCRF) for each patient from the day of signed informed consent until 30 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen. All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, abnormal laboratory values have returned to baseline or normalized, there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient has died.

The Adverse Events of Special Interest (AESIs) for this study are MDS, AML, secondary cancers (new malignancies other than MDS/AML), pneumonitis, and embryo-fetal toxicity. AESIs must be reported to the Sponsor as soon as the Investigator becomes aware of them.

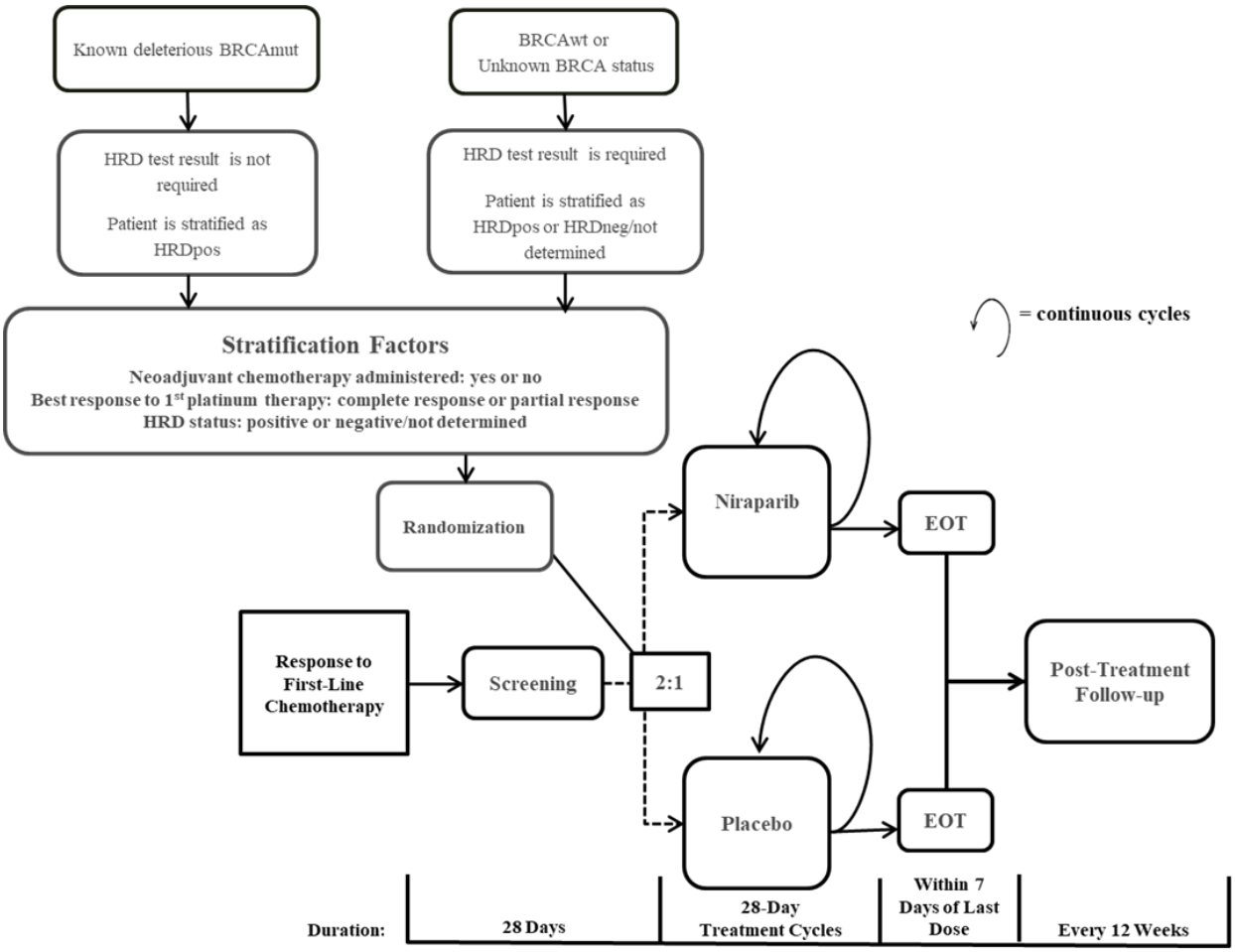
If, at any time after the study is completed, an Investigator becomes aware of an SAE that is considered related to the investigational product, or an AESI regardless of causality, the Investigator should report the SAE/AESI to the Sponsor's Pharmacovigilance Department within 24 hours of becoming aware of the SAE. MDS/AML and secondary cancers (new malignancies other than MDS or AML) must be reported until death or loss to follow-up. Pneumonitis must be reported for up to 90 days after the last dose of study treatment and pregnancy must be reported for up to 180 days after the last dose of study treatment.

An independent data monitoring committee (IDMC) will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study. The composition of the IDMC will consist of 3 independent individuals, including 1 biostatistician and 2 physicians. The IDMC is tasked with making a recommendation to the Sponsor to continue or stop the trial based on their assessment of efficacy and safety information. The membership, the key responsibilities of the IDMC, and the corresponding procedures will be defined in an IDMC charter.

No crossover to niraparib is permitted for patients randomized to placebo.

Approximately 620 patients are planned to enroll in this study at approximately 250 sites.

Figure 1: Study Design



Abbreviations: EOT = end-of-treatment; PFS = progression-free survival
Note: The starting dose of study treatment will be based upon the patient's baseline body weight or baseline platelet count. Patients with a baseline body weight ≥ 77 kg **and** baseline platelet count ≥150,000 µL will receive 300 mg; patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL will receive 200 mg.
Note: Treatment is continuous (in 28-day cycles) until patient discontinues treatment. Post-treatment follow-up is continuous (every 12 weeks) until patient discontinues study.

4. STUDY POPULATION

4.1. 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 ≥18 years of age, able to understand the study procedures and agree to participate in the study by providing written informed consent
2. Histological and staging criteria:
   a. Patients must have histologically diagnosed high-grade serous or endometrioid, or high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that is Stage III or IV according to FIGO criteria.

      Note: Patients who have received neoadjuvant chemotherapy may be included in the study if post-chemotherapy tumor grade is not evaluable.
3. Surgical criteria:
   a. Patients with inoperable Stage III and IV disease are eligible;
   b. All Stage IV patients with operable disease are eligible;
   c. Patients with stage III or IV disease treated with neoadjuvant chemotherapy and interval debulking surgery are eligible;
   d. Patients with stage III disease who have visible residual disease after primary debulking surgery are eligible.
4. Chemotherapy criteria:
   a. Patients who have received intraperitoneal chemotherapy are eligible;
   b. All patients must have had ≥6 and ≤9 cycles of platinum-based therapy;
      Patients must have had ≥2 post-operative cycles of platinum-based therapy following interval debulking surgery;
   d. Patients must have physician assessed CR or PR after ≥ 3 cycles of therapy;
   e. Patients must have either CA-125 in the normal range or CA-125 decrease by more than 90% during their front-line therapy that is stable for at least 7 days (i.e., no increase >15% from nadir).
5. Patients must be randomized within 12 weeks of the first day of the last cycle of chemotherapy.
6. All patients must agree to undergo central tumor HRD testing.
   a. The central HRD test result must be available for randomization as it is a stratification factor. Patients with documented g*BRCA*1 or g*BRCA*2 mutation or s*BRCA1/2* mutation may be randomized without HRD test results
   b. The tumor sample may be submitted for HRD testing prior to the screening period if it appears the patient is likely to meet other eligibility requirements. Patients are not required to have repeat HRD testing if HRD result is "not determined" (e.g., due to insufficient tumor specimen)
   c. Patients with known HRD test results from a commercially available source are allowed to participate in the study; however, they must still agree to submit a tumor

sample for central HRD testing. The results of the central HRD testing must be available prior to randomization and must be used for stratification. Additional testing related to HRD may be performed on the sample used for screening and randomization post randomization. If there is inadequate tissue remaining subsequent to the screening analysis, sites may be requested to provide additional tissue from the block used for screening purposes.

7. Patients of childbearing potential must have a negative serum or urine pregnancy test (beta human chorionic gonadotropin [hCG]) within 7 days prior to receiving the first dose of study treatment
8. Patients must be postmenopausal, free from menses for >1 year, surgically sterilized, or willing to use adequate contraception to prevent pregnancy (see Appendix A) 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
9. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix G)
10. Patients must have adequate organ function, defined as follows (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 ≥ 1,500/µL
    b. Platelets ≥ 100,000/µL
    c. Hemoglobin ≥ 10 g/dL
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault equation
    e. Total bilirubin ≤ 1.5 x ULN
    f. Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN
11. All patients must agree to complete PROs during study and then at 4 weeks, 8 weeks, 12 weeks, and 24 weeks after EOT, regardless of subsequent treatment
12. Patients must have formalin-fixed, paraffin-embedded tumor samples available from the primary cancer or agree to undergo fresh biopsy prior to study treatment initiation
13. Patients must be able to take oral medications

4.2. Exclusion Criteria

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

1. Patient has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer
2. Patients with Stage III disease who have had complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery;
3. Patient has undergone more than two debulking surgeries;

4. Patient is pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and for up to 180 days after the last dose of study treatment;
5. Patient has a known hypersensitivity to the components of niraparib or its excipients;
6. Patient is simultaneously enrolled in any clinical trial of niraparib or any other investigational therapy;
7. Patient has received prior treatment with a known PARP inhibitor or has participated in a study where any treatment arm included administration of a known PARP inhibitor;
8. Patient is to receive bevacizumab as maintenance treatment. Patients who have received bevacizumab with their first-line platinum based therapy but are unable to receive bevacizumab as maintenance therapy due to adverse events or for any other reason are not excluded from study as long as the last dose of bevacizumab was received ≥ 28 days prior to signing the main informed consent form;
9. Patient has had investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study;
10. Patient has had any known ≥Grade 3 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted >4 weeks
11. Patient has any known history or current diagnosis of MDS or AML;
12. Patient has undergone major surgery (per Investigator judgment) within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery;
13. Patient has had drainage of ascites within 4 weeks prior to enrollment;
14. Patient has undergone palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment;
15. Patient has a condition (such as transfusion dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results or interfere with the patient's participation for the full duration of the study treatment, including:
    a. Patient received a transfusion (platelets or red blood cells) within 2 weeks of the first dose of study treatment;
    b. Patient received colony-stimulating factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 2 weeks prior to the first dose of study treatment.
16. Patient is planning to donate blood during the study or for 90 days after the last dose of study treatment.
17. Patient has been diagnosed and/or treated for invasive cancer less than 5 years prior to study enrollment. Note: Patients with definitively treated uterine cervical or urinary tract carcinoma in situ, non-melanomatous skin cancer or ductal carcinoma in situ (DCIS) of the breast are not excluded
18. Patient has known brain or leptomeningeal metastases that are untreated or uncontrolled (i.e., new or worsening symptom or signs, or unstable steroid requirements);

- Note: A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and demonstrate evidence of clinically stable disease for 28 days.

19. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection;
    - Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
20. Patient is immunocompromised (patients with splenectomy are allowed).
21. Patient has known, active hepatic disease (i.e., hepatitis B or C).
22. Patient has a corrected QT interval (QTc) prolongation > 480 milliseconds at screening;
    - If a patient has a prolonged QTc interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (i.e., the patient otherwise has no cardiac abnormalities), then the patient may be eligible to participate in the study following discussion with the Medical Monitor.

4.3. Patient Discontinuation and Replacement

4.3.1. Discontinuation from Treatment

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

Specific reasons for discontinuing treatment include the following:

- AE
  - Any treatment-related National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; v.4.03) Grade 3 or 4 events (see separate guidelines for platelets below) that have not reverted to CTCAE Grade 1 or better within 28 days
  - At the Investigator's discretion, following dose interruption (no longer than 28 days), patients may be considered for dose reductions, providing they have not already undergone the maximum number of dose reductions allowed. If upon re-challenge with study treatment at the lowest allowable dose any CTCAE Grade 3 or 4 AEs recur, the patient must be discontinued
- 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
- Disease progression according to RECIST 1.1 criteria or clinical criteria by Investigator
- 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
- Completed therapy (3 years of niraparib/placebo)

Patients who are benefitting from treatment will have access to their assigned treatment as long as considered acceptable by their treating physician or until they are discontinued for one of the above reasons.

Patients who discontinue from treatment will continue to receive follow-up assessments as part of the study unless they are discontinued from study.

Duration of treatment will be approximately 3 years.

4.3.2. Discontinuation from Study

Specific reasons for discontinuing from the study are given below:

- Withdrawal of consent by the patient, who is at any time free to discontinue participation in the study, without prejudice to further treatment. Data for overall survival will be collected from public records, as allowed per country specific regulations.
- 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 via certified mail, should be made to contact the patient before the patient is deemed lost to follow-up.

If a patient withdraws consent, the Investigator must not access the patient's medical record or other confidential records requiring the consent for purposes of the study unless the patient expressly agreed to continued collection of their disease history information until the end of the study. Study data related to the patient collected prior to the patient's withdrawal from the study or loss to follow-up is permitted to be retained. The inclusion of information on survival status obtained from Investigator review of public records for those patients withdrawn or lost to follow-up is also permitted, dependent upon local regulations.

Remaining tumor tissue samples and tumor derived samples such as DNA and RNA may be stored for potential future biomarker testing.

Patients who withdraw after randomization will not be replaced. Patients who withdraw prior to randomization may be replaced at the discretion of the Sponsor.

4.4. Patient Identification and Randomization

4.4.1. Patient Identification

All patients who enter into the screening period of the study (defined as the point at which the patient signs the main study informed consent form [ICF]) or agree to pre-screening HRD testing (defined as the point at which the patient signs the HRD testing ICF) will receive a unique patient identification number. This number will be used to identify the patient throughout the study and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the entire study; it must not be changed at the time of randomization.

4.4.2. Randomization Scheme

Patients who meet the inclusion and exclusion criteria are eligible for randomization on Cycle 1/Day 1. Eligible patients will be randomized to treatment with niraparib or placebo in a 2:1 (niraparib:placebo) ratio. Randomization will be completed in a double-blind manner using an interactive web response system. Randomization may not be completed prior to receiving on-study HRD test results (unless g*BRCA*mut or s*BRCA*mut status is known, then can proceed to randomize). HRDpos tumor is defined by the presence of a tumor *BRCA* mutation or an HRD score ≥42. HRDneg tumor has none of these characteristics (neither *BRCA*mut nor other genomic instability nor large chromosomal rearrangement contributing to homologous recombination deficiency, score <42). Patients with HRDnd tumors (i.e., inadequate tissue) will be stratified together with HRDneg.

The investigative staff will enter the clinical stratification factors of chemotherapy regimen (neoadjuvant or not), and best response to front-line platinum therapy into electronic data capture system. An unblinded TESARO employee without affiliation to the study scientific team will enter the final stratification of HRD status into the electronic data capture system to initiate the randomization process.

It is recommended that patients receive the first dose on the day of randomization. If this is not possible, the site has 7 days to dose the patient. The laboratory tests must be repeated if performed more than 7 days before first dose.

4.5. Blinding and Breaking the Blind

The patient, Investigator, study staff, and the Sponsor study team and its representatives will be blinded to the patient's tumor HRD status and identity of the assigned treatment from the time of randomization until final study database lock. If an individual's role on the trial requires information about HRD status or treatment assignment (e.g., an individual is involved in emergency unblinding or entry of HRD status for stratification), procedures will be used to ensure all other personnel remain blinded. Study treatment assignment and tumor BRCA status will be available to the investigator upon request for post-study treatment planning.

The identity of the treatments will be concealed by the use of study treatments that are all identical in appearance, packaging, labeling, and schedule of administration. Patients and investigators will not be unblinded to HRD status or study treatment except in cases associated with important medical reasons as determined by the investigator and for specific non-urgent

medical events. The process for unblinding the identity of the assigned treatment is outlined in the Pharmacy Manual. Refer to the current version of the Pharmacy Manual for the treatment unblinding process.

Patients who require unblinding will be discontinued from study treatment but will remain on study until death, withdrawal of consent or loss to follow-up.

5. STUDY MEDICATION

5.1. Identity

Niraparib is an orally available, potent, highly selective PARP-1 and -2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate.

5.2. Administration

Niraparib will be administered as 100 mg capsules. Placebo will be administered using capsules matched in appearance. The starting dose of study treatment will be based upon the patient's baseline body weight or baseline platelet count (see Table 2). Patients with a baseline body weight ≥ 77 kg **and** baseline platelet count ≥150,000 µL will be administered niraparib 300 mg (3 X 100 mg capsules) or placebo (3 capsules) daily. Patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL will be administered niraparib 200 mg (2 X 100 mg capsules) or placebo (2 capsules) daily. Additional dose modifications of study treatment will not be based upon changes in the patient's body weight during study participation. For patients whose initial starting dose is 2 capsules (200 mg/day), escalation to 3 capsules once daily is permitted if no treatment interruption or discontinuation was required during the first 2 cycles of therapy. For any dose modification, the number of capsules administered will be modified accordingly.

Table 2: Recommended Initial Starting Dose

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

All study treatment capsules will be administered orally QD continuously (in 28-day cycles) in a double-blind fashion. Patients will be instructed to take study treatment once daily or as instructed by the Investigator. Patients must swallow and not chew all capsules. The consumption of water and food with study treatment is permissible. The first dose will be administered at the site.

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

5.3. Dose Modification

At the investigator's discretion, dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient.

Treatment must be interrupted for any nonhematologic CTCAE (v.4.03) Grade 3 or 4 AE that the Investigator considers to be related to administration of study treatment. If Grade 3 or 4 non-hematologic toxicity is appropriately resolved to baseline or Grade 1 or less within 28 days of interruption, the patient may restart treatment with niraparib but with a dose level reduction according to Table 3 if prophylaxis is not considered feasible. If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made.

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.

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.

If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 during the maximum 4-week (28-day) dose interruption period, and/or the patient has already undergone the maximum dose reductions, the patient must permanently discontinue study treatment.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts and are outlined in Table 4.

If the hematologic toxicity has not recovered to the specified levels in Table 4 within 4 weeks (28 days) of the dose interruption period, and/or the patient has already undergone the maximum dose reductions, the patient must permanently discontinue study treatment.

Table 3: Recommended Dose Modifications for Adverse Reactions

Dose level	Initial Dose: 3 capsules per day	Initial Dose: 2 capsules per day
Starting dose	3 capsules once daily (300 mg/day)	2 capsules once daily (200 mg/day)
First dose reduction	2 capsules once daily (200 mg/day)	1 capsule once daily (100 mg/day)
Second dose reduction	1 capsule once daily (100 mg/day)	NA

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

Table 4: Dose Modifications for Hematologic Adverse Reactions

Monitor CBC until the AE resolves. To ensure safety of the new dose, CBC weekly blood draws will be required for an additional 4 weeks after the AE resolves. Continue monitoring on Day 1 of every cycle thereafter. If MDS/AML or secondary cancers (new malignancies other than MDS/AML) is confirmed, discontinue niraparib.	
Platelet count < 100,000/μL	First occurrence: Withhold study treatment 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, study treatment should be discontinued. Otherwise, discussion with the Medical Monitor is required to resume niraparib. Resume study treatment at same or reduced dose per Table 3. If platelet count was <75,000/μL, resume at a reduced dose after recovery.

	Second occurrence: Withhold study treatment 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, study treatment should be discontinued. Otherwise, discussion with the Medical Monitor is required to resume niraparib. Resume niraparib at a reduced dose per Table 3. Discontinue study treatment 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 maximum dose reductions per Table 3.
Neutrophil < 1,000/µL or Hemoglobin < 8 g/dL	Withhold study treatment 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, study treatment should be discontinued. Otherwise, discussion with the Medical Monitor is required to resume niraparib. Resume niraparib at a reduced dose per Table 3. Discontinue study treatment 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 maximum dose reductions per Table 3.
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 study treatment at a reduced dose per Table 3.

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

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. To ensure safety of the new dose, weekly blood draws for CBC also will 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.

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

If a diagnosis of MDS/AML, is confirmed by a hematologist, or secondary cancer (new malignancies other than MDS/AML) is diagnosed while on study the patient must permanently discontinue study treatment.

For major surgery while on treatment, up to 28 days of study treatment interruption is allowed.

Once the dose of study treatment has been reduced, any re-escalation must be discussed with the medical monitor.

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

5.4. Packaging, Labeling, and Storage

Study treatment capsules will be packed in high-density polyethylene bottles with child-resistant closures. The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be labeled in a blinded fashion.

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

5.5. Drug Accountability/Reconciliation

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatment throughout the clinical study. Study drug accountability should be maintained by each site based on capsules dispensed versus returned to the clinic at each visit and the number days since last visit.

Accountability records should include receipt date, lot numbers, expiry dates, patient number, use by subject, dispensing dates, quantities (lowest unit) and stock balance. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as "returned" and kept separate from the products not yet dispensed. All dispensing 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.

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. All dispensing and accountability records will be available for Sponsor review. 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 on- site destruction, Sponsor will provide a return for destruction service to a third party.

Both the unused and expired study medication 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 trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.6. Concomitant Medications and Study Restrictions

Any medication that 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 may increase the potential for bleeding. Therefore, patients should be advised to use caution with anticoagulants (e.g., warfarin) and antiplatelet drugs (e.g., 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. Patient has to discontinue from study treatment if she develops a new malignancy and requires anticancer therapy for that neoplasm. Following treatment discontinuation, survival status will be collected for all patients using acceptable means including telephone contact.

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.

6. ENDPOINTS AND METHODS OF ASSESSMENT

6.1. Efficacy Endpoints

6.1.1. Primary Endpoint

The primary endpoint is PFS, defined as the time from treatment randomization to the earlier date of assessment of progression or death by any cause in the absence of progression.

6.1.1.1. Radiologic Determination of Disease Progression

RECIST v1.1. criteria are presented in Appendix B. The following special considerations are excerpted from Section 4.3.4 and 4.3.5 of the RECIST v1.1 publication.[33]

Equivocal Progression

In the case of equivocal (i.e. unclear) radiologic findings suggesting of disease progression (e.g., new but small lesion or increased ascites), the investigator should continue treatment until the next scheduled assessment or sooner as clinically indicated; if the follow-up assessment confirms PD, the reported PD date should be the earlier of the two assessments.

Unequivocal progression of non-target lesions (patients with measurable disease)

When a patient has measurable disease, to call unequivocal progression in baseline non-target lesions, there must be an overall level of substantial worsening in non-target lesions such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased enough to warrant discontinuation of study treatment and initiation of new anti-cancer therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR in target disease will therefore be rare using RECIST v1.1 criteria.

Unequivocal progression of non-target lesions (patients with non-measurable disease)

When the patient has non-measurable disease, to call unequivocal progression in baseline non-target lesions, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or an increase large enough to warrant discontinuation of study treatment and initiation of new anti-cancer therapy.

For patients with no baseline disease (CR, ND), the rules for new lesions that are non-measurable apply as described above.

6.1.1.2. Clinical Determination of Disease Progression

Clinical disease progression may be determined if 1 of the following 2 criteria are met:

- CA-125 progression according to Gynecologic Cancer Intergroup (GCIG)-criteria (below) AND additional diagnostic tests (eg, histology/cytology, ultrasound techniques, endoscopy, PET) may identify new lesions or determine existing lesions qualify for unequivocal PD;
- CA-125 progression according to GCIG criteria (below) AND definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes, such as: [1] intractable cancer-related pain; [2] malignant bowel obstruction/worsening dysfunction; or [3] unequivocal symptomatic worsening of ascites or pleural effusion.

GCIG criteria for CA-125 progression are as follows:

1. Patients with elevated CA-125 pretreatment and normalization of CA-125 during treatment with blinded study drug must show evidence of CA-125 $\geq$ 2 x ULN on 2 occasions at least 1 week apart, OR
2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 $\geq$ 2 x the nadir value on 2 occasions at least 1 week apart, OR
3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 $\geq$ 2 x ULN on 2 occasions at least 1 week apart.

CA125 elevation without accompanying radiological changes or clinical symptoms/signs consistent with PD will not be considered disease progression.

6.1.1.3. Determination of the Date of Progressive Disease

Determination of the date of progressive disease (PD) will be made by central blinded review.

If CT/MRI shows equivocal new lesion or equivocal increase in baseline non-target lesion (e.g., ascites), the investigator should continue treatment until the next scheduled assessment or sooner as clinically indicated; if the follow-up assessment confirms PD, the recorded PD date should be the earlier of the two assessments. If CT/MRI shows baseline target lesions which equivocally suggest PD and additional diagnostic tests are required to determine unequivocal PD, the official date of PD will be the date on which the equivocal lesion was initially identified.

The investigator will record in the eCRF the type of PD (i.e. radiological or clinical). The date of PD is defined as the earliest time point when one of the PD criteria is first met. When required to determine progression, CA-125 levels should be evaluated $\pm$ 2 weeks from the primary PD assessments (i.e., diagnostic test or clinical parameters) and must be confirmed by a second determination $\geq$ 7 days later. If assessments of CA-125 levels occur greater than 2 weeks from the primary PD assessments, the date of the primary assessment of PD will be used to define the date of PD.

For centrally confirmed radiologic progression, the central review date of PD will be used for the PFS analysis. For centrally confirmed clinical progression, the Investigator's date for PD will be used for the PFS analysis. In either case, the earlier of the of the 2 PD dates will be used for the PFS analysis.

6.1.1.4. Central Review Process

The following is an overview of the central review process:

1. When the Investigator finds that the patient has progressed, he/she submits the scans with suspected progression for central imaging review and the Sponsor Data Management team provides supportive clinical data for central review.
2. Central Radiologic assessment per RECIST v.1.1 criteria will be conducted by 2 independent radiologists (along with arbiter, as necessary).
3. A central blinded clinician will review clinical information for determination of PD, if Radiologic assessment does not confirm the investigator's assessment of PD.
4. BICR notifies site of central radiological determination of disease status.
5. In the case where the Investigator determines radiological PD, but central review does not concur with that assessment, the patient may continue study treatment as long as it is considered safe and the patient continues to meet other treatment criteria. In any case, the patient should continue to undergo scheduled imaging until radiologic or clinical PD is confirmed by BICR.

6.1.1.5. Central Blinded Clinician Review

The central blinded clinician will review clinical and radiographic data supporting clinical progression and will determine if the patient had protocol-defined clinical progression, and at which time points. The central blinded clinician will not provide an opinion on the presence or timing of radiographic progression. The central blinded clinician may not modify lesion selection performed by the independent radiologists. They may not select target lesions from clinical sources, even if no radiographic target lesions are present as determined by the independent radiologists. If lesions assessed by physical examination are documented by the investigator sites and the assessments provided to the central blinded clinician, they will be assessed qualitatively and incorporated into the central blinded clinician's assessment. The central blinded clinician cannot specify the date of progression; he/she can only verify whether or not PD occurred at specified dates (±7 days).

6.1.2. Secondary Endpoints

The secondary endpoints are the following:

- OS
- Observed changes from baseline in the following PROs:
  - FOSI
  - EQ-5D-5L
  - EORTC-QLQ-C30
  - EORTC-QLQ-OV28
- Time to first subsequent therapy (TFST)
- PFS2

6.1.2.1. Overall Survival

OS is defined as the time of randomization to the date of death by any cause. Following the treatment discontinuation 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.

6.1.2.2. Patient-Reported Outcomes

PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28) will be collected every 8 weeks (± 7 days) for 56 weeks beginning on C1D1, then every 12 weeks (± 7 days) thereafter while the patient is receiving study treatment. Once a patient discontinues treatment, PRO evaluations will be performed at the time of treatment discontinuation and then at 4 weeks, 8 weeks,12 weeks, and 24 weeks (± 1 week for each timepoint) after EOT, regardless of the status of subsequent treatment

PROs may only be completed by the study patient in their native language. PROs may be completed remotely. It is estimated that PRO evaluations will take less than 20 minutes at each time point. 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 assessment.

Functional Assessment of Cancer Therapy–Ovarian Symptom Index

The FOSI (Appendix C) is a validated, 8-item measure of symptom response to treatment for ovarian cancer[34]. Patients respond to their symptom experience over the past 7 days using a 5 point Likert scale scored from CCI to CCI 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.

European Quality of Life scale, 5-Dimensions

The EQ-5D-5L (Appendix D) is a well-validated general preference-based, health-related quality of life (QoL) instrument in oncology as well as other conditions and is intended to compliment other QoL instruments[35]. It was developed to assess health outcomes from a wide variety of interventions on a common scale for purposes of evaluation, allocation, and monitoring. The EQ-5D-5L encompasses 5 domains asking patients to rate their perceived health state today on the following dimensions: CCI and CCI The EQ-5D-5L domains are scored on a Likert-type scale with scores ranging from 1 to 3, with C associated with CCI associated with CCI and C associated with CCI In addition, a visual analog scale (VAS) is included in the EQ-5D-5L. The VAS measures current health status on a scale from 0 to 100, where C is CCI and CCI is CCI

EORTC-QLQ-C30 and EORTC-QLQ-OV28

The EORTC-QLQ-C30 (Appendix E) is a validated, 30-item, health-related QoL instrument developed to assess health outcomes from a wide variety of interventions on a common scale. The instrument comprises 3 domains. The first domain asks patients to rate their need for

assistance with or difficulty completing certain activities (such as [redacted]) and daily self-care tasks on a Likert-type scale, where [redacted] corresponds to [redacted] (i.e., [redacted] or [redacted] and [redacted] corresponds to [redacted] (i.e., [redacted] or [redacted] The second domain, using the same Likert scale, asks the patient to rate—specific to the previous week—their limitations on [redacted] and [redacted]; [redacted] and its interference with activity; [redacted] The third domain asks patients to rate their overall health and overall QoL on a 7-point Likert scale, where [redacted] corresponds to [redacted] and [redacted] corresponds to [redacted]

The EORTC-QLQ-C30 is often used as a companion to other disease-specific instruments such as the ovarian-specific EORTC-QLQ-OV28 (Appendix F), which assesses ovarian cancer patients' [redacted][36].

6.1.2.3. PFS2 (Progression-Free Survival-2)

PFS2 is defined as the time from treatment randomization to the earlier date of assessment of progression on the next anticancer therapy following study treatment or death by any cause. Using source documentation (including clinic notes), the following information will be collected for the next anticancer therapy following study treatment:

- Name of drug (and/or class)
- Start date
- Dose-limiting toxicities
- Best response (CR, PR, SD, PD)
- Progression date

6.1.3. TFST (Time to First Subsequent Treatment).

TFST is defined as the time from the date of randomization to date of the first subsequent anti-cancer therapy or death

6.2. Pharmacokinetic Assessments

Blood samples for PK will be collected on Cycle 1/Day 1 and Cycle 2/Day 1 predose (within 30 minutes prior to dosing) and 2 hours (± 15 minutes) postdose. Additional samples for PK on Cycle 4/Day 1 and Cycle 8/Day 1 will be collected at predose (trough; within 30 minutes before scheduled dose) only (Table 6). The collection will occur also at the end of treatment if the patient discontinued before Cycle 8. If study drug is held one day prior to and on C2D1, PK sample collection on that day is not required. If study drug is held on C4D1 or C8D1, PK sample collection on those days is not required.

Complete instructions for collection, processing, shipping, and handling are detailed in the Laboratory Manual.

A population PK modeling approach will be used to describe plasma concentrations of niraparib and its metabolite in patients. In the analysis, covariates will be evaluated to determine if they contribute to differences in the PK estimates among individuals.

In addition, the PK/pharmacodynamic (PDy) relationship between concentrations of niraparib and its metabolite and efficacy and safety measures will be investigated. The exposure to niraparib and its metabolite will be correlated with safety (selected AEs) and efficacy variables.

6.3. Safety Endpoints

Safety parameters evaluated during the conduct of the study include the following: TEAEs, clinical laboratory results (hematology, chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications. 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.

6.3.1. Definitions

Adverse event: An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical 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 abnormal 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, including baseline or washout periods, even if no study treatment has been administered.

Treatment-emergent adverse event: A TEAE is defined as any new AE that begins, or any preexisting condition that worsens in severity, after at least 1 dose of study treatment has been administered.

Serious adverse event: An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - Note: This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Any AE that prolongs hospitalization will be considered an SAE.
  - Exception: Planned hospitalization (e.g., for observation, protocol compliance, elective procedures, social reasons) will not be considered an SAE; however, the reason for the planned hospitalization should be captured in medical history.
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect
- Is an important medical event(s)
  - An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

6.3.2. Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories.

6.3.2.1. Intensity

Investigators should assess the severity of AEs according to CTCAE. In general, CTCAE (v. 4.03) severity grades are:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to [eg] preparing meals, shopping for groceries or clothes, using the telephone, managing money)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

A distinction should be made between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above in Section 6.3.1. 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. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

6.3.2.2. Causality

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Related: A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other

drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible

- Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals
- Unlikely related: A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide likely explanations
- Unrelated: A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other drugs or chemicals)

6.3.3. Collecting and Recording Adverse Events

HRD prescreening Informed Consent: Reporting of safety events is to be begin at time of HRD pre-screening ICF signature date only if related to the procedure of a fresh biopsy. If archival tissue is submitted when patient consents to HRD pre-screening ICF, then reporting of safety events is to begin at time of Main study ICF signature date. Main study Informed Consent: All AEs will be collected and recorded in the eCRF for each patient from the day of signed main informed consent until 30 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen (see Table 6 for schedule of events and Section 6.3.5 for additional requirements for SAEs). All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, abnormal laboratory values have returned to baseline or normal levels, there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient has died.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, reported by patient) must be documented in the eCRF.

AEs may be volunteered spontaneously by the study patient or discovered by the study staff during physical examinations or by asking an open-ended non-leading question such as: "How have you been feeling since you were last asked?" 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.

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom.

Concomitant illnesses that existed before entry into the study will not be considered an AE unless the illness worsens during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page as well as on the SAE Report Form medical history section.

6.3.4. Reporting Disease Progression

The event of Disease Progression is an efficacy criterion and is therefore not considered an AE. If AEs/SAEs occur in relation to disease progression, the AEs/SAEs must be reported per AE/ SAE reporting requirements described in Section 6.3.3 and Section 6.3.5.

6.3.5. Time Period for Collecting and Reporting Serious Adverse Events

The Investigator must report all SAEs within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE. The Investigator must provide a causality assessment and must sign and date all SAEs Report Forms.

It is the responsibility of the Investigator to review source documentation and describe pertinent information on the SAE Report Form.

HRD prescreening Informed Consent: Reporting of SAEs is to be begin at time of HRD pre-screening ICF signature date only if related to the procedure of a fresh biopsy. If archival tissue is submitted when patient consents to HRD pre-screening ICF, then reporting of SAEs is to begin at time of Main study ICF signature date. Main study Informed Consent: All SAEs will be collected and recorded in the electronic case report form (eCRF) for each patient from the day of signed main informed consent until 30 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen. If, at any time after the study is completed, an Investigator becomes aware of an SAE that is considered related to the investigational product, or an AESI regardless of causality, the Investigator should report the SAE/AESI to the Sponsor's Pharmacovigilance Department within 24 hours of becoming aware of the SAE according to timelines for reporting SAEs described in this section.

MDS/AML and secondary cancers (new malignancies other than MDS or AML) must be reported until death or loss to follow-up. Pneumonitis must be reported for up to 90 days after the last dose of study treatment and pregnancy must be reported for up to 180 days after the last dose of study treatment.

For all SAEs, an SAE Report Form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE Report must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, and protocol number. In addition, if the follow-up information involves any updates, changes, or the addition or removal of SAE terms, the follow-up SAE report should reiterate all SAEs reported and the associated information (e.g., onset date, causality) regardless of whether the SAE had updates or not. Aside from the aforementioned, only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information with the exception of the SAE term(s) does not have to be entered on the follow-up SAE Report Form.

The minimum information required for an initial SAE report is as follows:

- Name of person sending the report (i.e., name, address of Investigator)
- Patient identification (screening/randomization number, initials [if permitted by local data privacy regulations], but NOT patient identifiers that should be redacted as described above, such as patient name)
- Protocol number
- Description of SAE
- Causality assessment

Initial and follow-up SAE reports and any additional supporting documentation (e.g., hospital reports, consultant reports, death certificates, autopsy reports) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the investigator/site awareness. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. The Investigator must sign and date all SAE forms. Also, any additional SAE documentation must be a clear photocopy with patient identifiers removed. Patient identifiers include any of the following for the individual or the individual's relative, employers, or household members:

- Names
- Date of birth per country specific data privacy laws
- Initials per country specific data privacy laws
- Address
- Telephone numbers
- Social security numbers/country specific personal identification number
- Medical record numbers/country specific hospital identification number

The Investigator should fax or email the completed SAE Report Form to the Sponsor (or designee).

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

SAE REPORTING CONTACT INFORMATION

Email: PPD

Fax: PPD

6.3.5.1. Submission and Distribution of Serious Adverse Events

Per regulatory requirements, if an SAE is required to be submitted to a Regulatory Authority a copy of the report (Council for International Organization of Medical Sciences [CIOMS] or MedWatch 3500A) will be distributed to the investigator/site. The investigator/site will submit a

copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC), per local regulations.

6.3.6. Pregnancy

Pregnancies occurring in patients enrolled in a study must be reported and followed to outcome.

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Therapeutic abortions should be reported as a treatment procedure and the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE in the eCRF.

Spontaneous abortions should always be reported as SAEs. Pregnancy is not considered an SAE unless there is an associated serious outcome. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

The Investigator should complete the Initial Pregnancy Notification Report Form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification Report Form and SAE Report Form should be completed.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, and 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 in accordance with the procedure for reporting SAEs.

The Investigator should follow-up with the subject or subject female partner until delivery or termination of pregnancy even if the patient was withdrawn from the clinical study or if the clinical study has finished. At that time, the Pregnancy Outcome Report Form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after the outcome of the pregnancy is known to the investigator in accordance with the procedure for reporting SAEs (see Section 6.3.5).

6.3.7. Overdose

An overdose is 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 6.3.5.

6.3.8. Adverse Events of Special Interest

Selected non-serious AEs and SAEs are also known as Adverse Events of Special Interest (AESI), must be recorded as such on the eCRF and reported within 24 hours to the Sponsor as noted for SAEs in Section 6.3.5. The AESI for niraparib are the following:

- MDS
- AML
- Secondary cancers (new malignancies other than MDS/AML)
- Pneumonitis
- Embryo-fetal toxicity

These AESIs must be reported as follows:

- MDS, AML, and secondary cancers (new malignancies other than MDS/AML) should be reported to the Sponsor at any time the Investigator becomes aware of them.
- Pneumonitis should be reported to the Sponsor through 90 days after the last dose of study drug (or until the start of the alternative anticancer therapy, whichever occurs first).
- Embryo-fetal toxicity should be reported as outlined in Section 6.3.5

6.3.9. Clinical Laboratory Assessments

Serum samples for measuring CA-125, serum or urine samples for determining pregnancy status, and serum samples for measuring the variables in Table 5 will be collected according to the schedule given in Table 6.

Any laboratory values assessed as clinically significant should be recorded as an AE. If SAE criteria are met, the SAE should be recorded and reported according to the SAE reporting process (see Section 6.3.5).

Table 5: Clinical Laboratory Variables

Complete Blood Count	Serum Chemistry	
Hemoglobin	Sodium	ALP
Platelets	Potassium	AST
MCV	Calcium	ALT
WBC	Magnesium	Urea or BUN
Differential white cell count to include at least absolute neutrophil count (ANC)	Chloride	Total protein
Not applicable	Glucose	Albumin
Not applicable	Creatinine	Total bilirubin
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; MCV = mean corpuscular volume; WBC = white blood cells		

Hematological testing may occur more frequently than is specified in Table 6 when additional testing is medically indicated per principal investigator judgment. Additional tests may be performed at a laboratory facility other than the study site, but 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 electronic data capture system (EDC).

For any suspected case of MDS/AML or secondary cancer (new malignancies other than MDS/AML) reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. 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 World Health Organization (WHO) criteria and other sample testing reports related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the patient's study file.

6.3.10. Physical Examination and Vital Signs

Physical examinations, including height (screening only), weight, and vital signs (blood pressure [BP], pulse, and temperature), will be performed in accordance with the schedule of events (Table 6).

Any physical examination, vital signs, and laboratory tests assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the SAE reporting process (see Section 6.3.5).

6.3.11. Eastern Cooperative Oncology Group Performance Status

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

6.3.12. Additional Safety Assessments

Standard 12-lead ECGs will be performed at screening.

6.4. Demographics and Baseline Characteristics

Demographics and baseline characteristics consist of those variables that are assessed at screening/baseline.

6.4.1. Patient Eligibility

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 4.1 and Section 4.2, respectively.

6.4.2. Patient Demography

Patient demography consists of

- Age at screening
- Race (in accordance with local regulations)
- Ethnicity (in accordance with local regulations)
- Sex

6.4.3. Disease History

For disease history, the following will be documented:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- gBRCA or sBRCA status if known
- Date of start of first treatment
- Agents in first treatment
- Date of last dose of first treatment and total number of cycles
- Best response and toxicities (including hematologic events) for first treatment
- ECOG performance status
- Sites of metastatic disease

6.4.4. Medical History

Major medical and surgical history (including medication history), including history of prior thrombocytopenia, neutropenia, leukopenia, or anemia within 1 year prior to signing the main ICF, 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 his/her medical records. g*BRCA* or s*BRCA* status will be collected if known (g*BRCA1/BRCA2* mutation, or g*BRCA*wt; s*BRCA1/BRCA2* mutation, or s*BRCA*wt).

6.4.5. Previous and Concomitant Medications

Any medication the patient takes other than the study treatment, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the 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 prior to signing the main ICF. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking or have taken since the previous visit.

Previous and concomitant medication will be documented. Medications will be coded using WHO Anatomical Therapeutic Chemical classification.

6.5. Blood and Tissue Samples

Tumor samples, including archival biopsy, fresh biopsy, or both, will be collected for all patients during screening for the evaluation of tumor markers of niraparib sensitivity or resistance, such as those related to DNA repair deficiency, including centralized HRD testing. HRD results will be sent for stratification. Patients with known g*BRCA*mut or s*BRCA*mut may be randomized as HRDpos prior to HRD test result reporting. For patients without known g*BRCA*mut or s*BRCA*mut status, centralized HRD results must be available prior to randomization. Patients with known HRD test results from any commercially available source are allowed to participate in the study; however, they must still agree to submit a tumor sample for central HRD testing. The results of the central HRD testing must be available prior to randomization and must be used for stratification.

Additional testing related to HRD may be performed on the sample used for screening and randomization post randomization. If there is inadequate tissue remaining subsequent to the screening analysis, sites may be requested to provide additional tissue from the block used for screening purposes.

If a patient experiences disease progression during the study, an optional tumor sample may be collected at EOT for exploratory evaluations of biomarkers. These samples may be stored and used at a later time for these evaluations. Biomarkers of PARP inhibitor sensitivity will be evaluated as exploratory endpoints. Mutation status of genes related to the study disease or PARP inhibitor sensitivity will be evaluated from both circulating cell free DNA (ctDNA)/RNA or genomic material.

DNA/RNA from the blood and tumor samples will be stored and may be used at a later time for testing biomarkers related to study disease or PARP inhibitor sensitivity.

Details on blood and tissue sample collection can be found in the Laboratory Manual.

7. STUDY CONDUCT

7.1. Schedule of Procedures

A schedule of events is provided in Table 6.

Table 6: Schedule of Events

Procedure / Visit[a]	Screening[b]	Cycle 1				Cycle 2	Subsequent Cycles	EOT	Post-Treatment Assessments
Day	-28 to -1	1	8	15	22	1	C(n)/D1[c]	Within 7 days of last dose or discontinuation determination	Every 12 weeks
Informed consent	X[d]								
Demographics and height	X								
Medical, surgical, cancer (including genotyping), and medication history	X	X		X		X	X	X	
Sample collection (tumor) for centralized HRD testing	X[e]								
12-lead ECG	X								
Serum or urine pregnancy test[f]	X	X[g]				X	X[f]		
Physical examination	X	X		X		X	X	X	
Vital signs and weight	X	X		X		X	X	X	
ECOG performance status	X	X				X	X	X	
Adverse event monitoring[h]	X	X		X		X	X	X	X
Concomitant medications	X	X		X		X	X	X	
Serum chemistry	X	X[g]		X		X	X	X	
CBC[i]	X	X[g]	X	X	X	X	X	X	
Serum CA-125[j]	X	X[g]				X	X	X	X
RECIST v.1.1 assessment[j]	X						X	X	X
Chest CT or MRI[k]	X						X	X	X
FOSI, EQ-5D-5L, EORTC-QLQ-C30/ EORTC-QLQ-OV28[l]	X						X	X	X
Randomization	X								
Study treatment dispensed or collected		X[m]				X	X	X	
Blood sample for PK[n]		X				X	X[o]	X[p]	
Blood ctDNA for exploratory biomarker testing		X						X	
Optional sample (tumor) collection								X[q]	

Table 6: Schedule of Events (Continued)

Procedure / Visit[a]	Screening[b]	Cycle 1				Cycle 2	Subsequent Cycles	EOT	Post-Treatment Assessments
Anticancer therapies assessment[r]									X
Survival assessment									X
Bone marrow aspirate and biopsy		X[s]							

Abbreviations: 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, EQ-5D-5L = European Quality of Life scale, 5-Dimensions, EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, EORTC-QLQ-OV28 = EORTC-QLQ ovarian module, FOSI = Functional Assessment of Cancer Therapy – Ovarian Symptom Index, HRD = homologous recombination deficiency, MDS = myelodysplastic syndrome, MRI = magnetic resonance imaging, PK = pharmacokinetics, RECIST = Response Evaluation Criteria in Solid Tumors

[a] Treatment cycles are 28 days long. Study visits are scheduled every 28 days (±3 days), except Cycle 1 (every week).

[b] Screening tests that are considered standard of care (i.e., CT/MRI, physical examination) that were performed within the 28-day screening 'window' may be used as part of the patient's screening assessment even if they were performed prior to the patient providing informed consent. In this case those assessments dates become start date of screening 'window'.

[c] A new cycle will begin every 28 days ±3 days.

[d] Depending on local site requirements, patients may sign a HRD testing ICF prior to the screening period to facilitate early HRD testing only. After a Main ICF is signed all other study tests and procedures must be done in the screening window (Day -28 to Day -1).

[e] For patients with known documented gBRCA or sBRCA mutation, randomization may occur prior to receipt of centralized HRD testing. For patients without known gBRCA or sBRCA mutation, centralized HRD testing of tumor sample must be completed with results reported prior to randomization for stratification. For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained. Additional testing related to HRD may be performed on these samples post randomization. If there is inadequate tissue remaining subsequent to the analysis performed at screening, sites may be requested to provide additional tissue from the block used for screening purposes.

[f] For women of childbearing potential, a negative serum or urine pregnancy test is required within 7 days of the first dose of study treatment. In addition, a negative urine pregnancy test is required monthly (CnD1) thereafter.

[g] Screening assessments completed within 7 days of the first dose do not need to be repeated.

[h] All AEs will be collected and recorded in the eCRF for each patient from the day of signed informed consent until 30 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen. The Investigator should report the SAE to the Sponsor's Pharmacovigilance Department within 24 hours of becoming aware of the SAE according to timelines for reporting SAEs described in Section 6.3.5.

[i] 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.

[j] RECIST tumor assessment via CT or MRI scan of abdomen/pelvis and clinically indicated areas required at screening, then every 12 weeks (±7 days) until centrally confirmed disease progression. For patients who stayed on study treatment for over 2 years (approx. 26 cycles) the CT/MRI will be required every 24 weeks (6 cycles). Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of

whether study treatment is interrupted. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals until progression is centrally confirmed.

[k] 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.

[l] PROs will be collected every 8 weeks (± 7 days) for 56 weeks beginning on C1D1, then every 12 weeks (± 7days), while on study treatment). PROs should be completed by the patient before conducting any other procedures. During the follow-up period, if a patient discontinues study treatment, assessments will occur at 4 weeks, 8 weeks,12 weeks, and 24 weeks (± 1 week for each timepoint) after EOT, regardless of the status of subsequent treatment.

[m] Dosing must occur within 7 days from randomization.

[n] Blood samples for PK on Cycle 1/Day 1 and Cycle 2/Day 1 collected predose (within 30 minutes before scheduled dose) and 2 hours postdose (± 15 minutes) Note: The exact time of the PK blood draw will be recorded. If study drug is held one day prior to and on C2D1, PK sample collection on that day is not required.

[o] Additional blood samples for PK on Cycle 4/Day 1 and Cycle 8/Day 1 will be collected at predose (trough, within 30 minutes before scheduled dose). If study drug is held on C4D1 or C8D1, PK sample collection on those days is not required.

[p] A PK sample should only be collected at EOT if the patient discontinues before completing the Cycle 8/Day 1 blood sample collection for PK.

[q] If the patient has experienced progression.

[r] In addition to survival and anticancer assessment, these assessments include any new malignancy information.

[s] For any suspected MDS/AML case reported while on study, a bone marrow aspirate/biopsy must be completed by a local hematologist

7.2. Procedures by Visit

After screening, visits are organized by treatment cycles. Treatment cycles are 28 days long; the visit for the end of a cycle (Day 29) and the beginning of a new cycle (Day 1) are combined (e.g., C1/29 = C2/D1).

Visits should occur within ±3 days of the scheduled visit. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 PM).

7.2.1. Screening (Visit 1, Day -28 to Day -1)

During screening, the following procedures/tests will be performed

- Informed consent
  - Depending on local site requirements, patients may sign an HRD testing ICF prior to the screening period to facilitate early HRD testing only
  - Screening tests that are considered standard of care (i.e., CT/MRI, physical examination, vital signs, height, weight, and serum chemistry, CBC, pregnancy testing, and serum CA-125) that were performed within the protocol-required timelines (i.e., within the 28-day screening window; within 7 days prior to first dose [i.e., Cycle 1/Day 1] where required) but prior to informed consent being obtained may be used as part of the patient's screening assessment
- Demographics
- Height
- Medical, surgical, cancer (including genotyping, such as g*BRCA* or s*BRCA* status if known) and medication history
  - Complete assessment, including history of prior myelosuppression (thrombocytopenia, neutropenia, leukopenia, or anemia) that occurred within the 1 year prior to signing the main ICF
- Sample collection (tumor) for centralized HRD testing
  - For patients with known g*BRCA* or s*BRCA* mutation, randomization may occur prior to receipt of centralized HRD testing results, but a sample must be submitted for central testing. For patients without known g*BRCA* or s*BRCA* mutation, centralized HRD testing of tumor sample must be completed with results reported prior to randomization for stratification. The sample may be sent after the HRD testing ICF has been signed but in advance of the protocol-defined screening period in order to facilitate the screening and enrollment process. For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained. Additional testing related to HRD may be performed on these samples post randomization. If there is inadequate tissue remaining subsequent to the analysis performed at screening, sites may be requested to provide additional tissue from the block used for screening purposes.

- 12-lead ECG
- Serum or urine pregnancy test for women of childbearing potential
  - A negative serum or urine pregnancy test is required within 7 days of the first dose of treatment drug. Screening assessments completed within 7 days of the first dose do not need to be repeated
- Physical examination
  - Complete assessment
- Vital signs
- Weight
- ECOG performance status
- AE monitoring
- Concomitant medications
  - Complete assessment of medications taken in last 30 days prior to signing the main ICF
- Serum chemistry
- CBC
- Serum CA-125
- RECIST v. 1.1 assessment
  - CT or MRI scan of abdomen/pelvis and clinically indicated areas. PET/CT may be used according to RECIST guidelines, but its use is not a study requirement
- Chest CT or MRI
  - If not done as part of RECIST tumor assessment
- PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30/QLQ-OV28)

Except for HRD testing when an HRD testing ICF has been signed by the patient, study tests and procedures must be done in the screening window (Day -28 to Day -1).

- Randomization occurs after all screening procedures are performed and patient eligibility is confirmed

7.2.2. Cycle 1, Day 1

- Serum or urine pregnancy test for women of childbearing potential
  - A negative serum or urine pregnancy test is required within 7 days of the first dose of treatment drug. Screening assessments completed within 7 days of the first dose do not need to be repeated.

- Physical examination
  - Assessment of change since screening
- Vital signs
- Weight
- ECOG performance status
- AE monitoring
- Concomitant medications
  - Assessment of change since screening
- Serum chemistry
  - Screening assessments completed within 7 days of the first dose do not need to be repeated
- CBC
  - Screening assessments completed within 7 days of the first dose do not need to be repeated
- Serum CA-125
  - Screening assessments completed within 7 days of the first dose do not need to be repeated
- Blood sample for PK
  - Predose (within 30 minutes before scheduled dose)
  - 2 hours postdose (± 15 minutes)

  Note: The exact time of PK blood draw must be recorded.
- Blood sample for ctDNA for exploratory biomarker testing collected predose
- Study treatment dispensed. First dose administered at the site must occur within 7 days from randomization.

7.2.3. Cycle 1, Day 8

- CBC

7.2.4. Cycle 1, Day 15

- Physical examination
  - Assessment of change since previous assessment
- Vital signs
- Weight
- AE monitoring

- Concomitant medications
  - Assessment of change since previous assessment
- Serum chemistry
- CBC

7.2.5. Cycle 1, Day 22

- CBC

7.2.6. Cycle 2, Day 1 (Cycle 1, Day 29)

- Serum or urine pregnancy test for women of childbearing potential
- Physical examination
  - Assessment of change since previous assessment
- Vital signs
- Weight
- ECOG performance status
- AE monitoring
- Concomitant medications
  - Assessment of change since previous assessment
- Serum chemistry
- CBC
- Serum CA-125
- Blood sample for PK
  - Predose (within 30 minutes before scheduled dose)
  - 2 hours postdose (± 15 minutes)
  - Note: The exact time of the PK blood draw must be recorded.
  - If study drug is held one day prior to and on C2D1, PK sample collection on that day is not required.
- Study treatment collected (capsules remaining from Cycle 1) and dispensed (capsules needed for Cycle 2)

7.2.7. Day 1, Subsequent Cycles

- Serum or urine pregnancy test for women of childbearing potential
  - Monthly (from Cycle 1/Day 1)

- Physical examination
  - Assessment of change since previous assessment
- Vital signs
- Weight
- ECOG performance status
- AE monitoring
- Concomitant medications
  - Assessment of change since previous assessment
- Serum chemistry
- CBC
- Serum CA-125
- Blood sample for PK
  - Cycle 4/Day 1, Cycle 8/Day 1 only
  - Predose (within 30 minutes before scheduled dose)

  Note: The exact time of the PK blood draw must be recorded. If study drug is held on C4D1 or C8D1, PK sample collection on those days is not required.
- RECIST version 1.1 assessment
  - CT or MRI scan of abdomen/pelvis and clinically indicated areas. PET/CT may be used according to RECIST guidelines, but its use is not a study requirement
  - Every 12 weeks (± 7 days) from Cycle 1/Day 1 until progression confirmation by blinded central independent review
  - Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted
- PROs
  - PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30/QLQ-OV28) will be collected every 8 weeks (± 7 days) for 56 weeks, then every12 weeks (± 7 days) while on study treatment. PROs should be administered before conducting any other procedures
- Study treatment collected (capsules remaining from previous cycle) and dispensed (capsules needed for next cycle)

7.2.8. End of Treatment (within 7 days of last dose or discontinuation determination)

- Medical, surgical, cancer (including genotyping), and medication history
  - Assessment of change since previous assessment

- Physical examination
  - Assessment of change since previous assessment
- Vital signs
- Weight
- ECOG performance status
- AE monitoring
  - All AEs will be collected and recorded in the eCRF for each patient from the day of signed informed consent until 30 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen
  - Any AEs, irrespective of the suspected causality, will be monitored until the AE has resolved, abnormal laboratory values have returned to baseline or normalized, there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient has died
- Concomitant medications
  - Assessment of change since previous assessment
- Serum chemistry
- CBC
- Serum CA-125
- Blood sample for PK
  - Only collected if the patient discontinues before completing the Cycle 8/Day 1 blood sample collection for PK (see Section 7.2.7)
  - Note: The exact time of the PK blood draw must be recorded.
- Blood sample for ctDNA for exploratory biomarker testing
- RECIST v.1.1 assessment
  - CT or MRI scan of abdomen/pelvis and clinically indicated areas. PET/CT may be used according to RECIST guidelines, but its use is not a study requirement
- PROs
  - PROs must always be completed by the patient using the study forms. At the EOT Visit, patients can be provided hard copies so that follow-up assessments can be completed remotely for return to the study site.
- Study treatment collected
- Optional sample (tumor) collection
  - If the patient has experienced progression

7.2.9. Post-Treatment Assessments

- Post-treatment assessments can be conducted remotely (i.e., by phone) except where noted otherwise. AE monitoring
  - All AEs will be collected and recorded in the eCRF for each patient from the day of signed informed consent until 30 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen
  - Any AEs, irrespective of the suspected causality, will be monitored until the AE has resolved, abnormal laboratory values have returned to baseline or normalized, there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient has died
- RECIST v.1.1 assessment and serum CA-125
  - If a patient discontinues treatment for progression that is not confirmed by BICR , scans and CA-125 testing should continue every 12 weeks (± 2 weeks) until progression is confirmed
  - CT or MRI scan of abdomen/pelvis and clinically indicated areas. PET/CT may be used according to RECIST v1.1 guidelines, but its use is not a study requirement
- PROs
  - If a patient discontinues study treatment, PROs should be collected at 4 weeks, 8 weeks, 12 weeks, and 24 weeks (± 1 week for each timepoint) after EOT, regardless of the status of subsequent treatment
  - PROs must always be completed by the patient using the study forms. Patients may complete the hard copies provided at EOT and return to the study site at the respective collection timepoints (these can be mailed)
- Anticancer therapies assessment will be collected every 12 weeks (± 2 weeks)
- Survival assessment, including new malignancy information will be collected every 12 weeks (± 2 weeks)

7.2.10. Unscheduled Assessments

- SAE monitoring
  - If, at any time after the study is completed, an Investigator becomes aware of an SAE that is considered related to the investigational product, or an AESI regardless of causality, the Investigator should report the SAE/AESI to the Sponsor's Pharmacovigilance Department within 24 hours of becoming aware of the SAE. Note: MDS/AML and secondary cancers (new malignancies other than MDS or AML) must be reported until death or loss to follow-up. Pneumonitis must be reported for up to 90 days after the last dose of study treatment and

pregnancy must be reported for up to 180 days after the last dose of study treatment.

  - CBC
  - 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 also will 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

- Chest CT or MRI
  - 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
- Bone marrow aspirate and biopsy
  - For any suspected case of MDS/AML or secondary cancer (new malignancies other than MDS/AML) reported while a patient is receiving treatment or being followed for post-treatment assessments. See Section 6.5 for details

8. STATISTICAL METHODS

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.

Patients will be randomized according to the following stratification factors: administration of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), HRD status (HRDpos [includes g*BRCA*mut and s*BRCA*mut patients] or HRDneg/nd).

8.1. Study Populations

The intent-to-treat (ITT) population is defined as all patients randomized into the study. The ITT population is the primary analysis population for the efficacy analysis. For this analysis, patients will be analyzed as randomized.

Efficacy will also be analyzed using a per-protocol (PP) population. The PP population will consist of all patients randomized in the study who do not have protocol deviations that may significantly impact the interpretation of efficacy results. A detailed specification of the PP population will be provided prior to the database lock. Patients will be analyzed according to the treatment they actually receive.

The safety population includes all patients who received at least 1 dose of study medication. The safety population will be the primary analysis population for the safety analyses. Patients will be analyzed as treated.

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

Patient disposition will be summarized, including the number of patients treated with niraparib, the number who discontinue and reason for discontinuation, and the number included for analysis. Patient demographics will be summarized descriptively, for the overall ITT population and by subgroup.

8.3. Efficacy Analyses

Primary analyses of efficacy endpoints are described below. Supportive analyses, including any sensitivity analyses that may be performed are detailed in the SAP.

8.3.1. Primary Efficacy Parameter

The PFS is defined as the time from the date of treatment randomization to the date of first documentation of progression (by blinded central review) or death by any cause in the absence of documented progression, whichever occurs first. A hierarchical testing for the PFS endpoint will be used to control the overall Type I error rate. First, PFS analysis will be conducted in the HRDpos patients (including g*BRCA*mut and s*BRCA*mut patients) at the 1-sided alpha level of 0.025. If the result is positive, PFS analysis will be conducted in the overall ITT population with

the 1-sided alpha level of 0.025; otherwise, PFS analysis becomes exploratory in the overall ITT population. PFS data may be censored according to criteria provided in the SAP.

The PFS analysis will be performed using a 1-sided stratified log-rank test. Stratification factors will include administration of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), and HRD status (HRDpos [includes g*BRCA*mut and s*BRCA*mut] or HRDneg/nd). In addition, a stratified Cox proportional hazards model will be used to estimate the treatment effect by HR and its 95% CI. PFS will also be descriptively summarized using Kaplan-Meier methodology.

Subgroups will also be explored for the primary efficacy endpoint based on age, race, geographic region, HRD status, neoadjuvant chemotherapy (yes or no), and best response to first platinum regimen (CR or PR). Subgroups involving *BRCA* mutation markers may also be explored for the primary efficacy endpoint. Details of these subgroup analyses (including exploring subgroups for any other study endpoints) will be detailed in the SAP.

8.3.2. Secondary Efficacy Parameter

OS is a key secondary endpoint and defined as the time from the date of randomization to the date of death by any cause. The analysis of OS is also included in the hierarchical testing to ensure a strong control of the overall Type I error. OS will be only tested if statistical significance is both shown for PFS in HRDpos and ITT populations. OS will be analyzed sequentially using the full alpha first in the ITT population and then in HRDpos population.

An interim analysis of OS will be performed at the time of the final PFS analysis. A Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundaries will be used to determine the significance levels for interim and final OS analyses.

The PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28) will be analyzed descriptively by changes from baseline in overall score, sub-scores, and individual items when applicable. A repeated measures model adjusting for covariates may be conducted. Time to symptom worsening on the FOSI will be analyzed using time-to-event methodology.

Other secondary time to event endpoints (PFS2/TFST) will be analyzed using a stratified log-rank test. The stratified Cox proportional hazards models will be used to estimate the treatment effect by HR and its 95% CI. In addition, Kaplan-Meier methodology will be used to descriptively summarize the data. The details of the analysis will be specified in the SAP.

8.4. Safety Analyses

Safety parameters will be summarized descriptively, for the overall ITT population and by subgroup. No inferential statistical analyses are planned.

8.5. Post-Treatment Analyses

Descriptive summary statistics will be used to summarize post study treatment data (OS, subsequent anticancer therapy, and any new malignancy).

8.6. Pharmacokinetic Analyses

Plasma samples for population PK assessment will be analyzed for concentrations of niraparib and its primary metabolite and time of measurement. A population PK modeling approach will be used to describe plasma concentrations of niraparib and its metabolite in patients. In the analysis, a number of covariates will be evaluated to determine if they contribute to differences in the PK estimates among individuals.

In addition, the PK/PDy relationship between concentrations of niraparib and its metabolite and efficacy and safety measures will be investigated. The exposure to niraparib and its metabolite will be correlated with safety (selected AEs) and efficacy variables.

8.7. Biomarker Analyses

Any biomarker analyses will be specified in the SAP.

8.8. Interim Analyses

No interim analysis for PFS efficacy is planned for the study. An interim analysis of OS will be performed at the time of the final PFS analysis. Periodic safety analyses will be conducted by the IDMC.

8.9. Determination of Sample Size

In the studies of the maintenance therapy following first line chemotherapy for advanced ovarian cancer, the median PFS has been shown to be up to approximately 14 months in the broad population of patients.[1-3] In addition, several studies showed that patients with gBRCA mutation had a longer median PFS (approximately 30 months) than those without the mutation.[4,5] Therefore the median PFS for all placebo patients is assumed as 14 months and the median PFS for placebo patients with BRCAmut is assumed as 30 months. As the data are limited for the prognostic role of HRD in BRCAwt patients in the first line maintenance, median PFS for BRCAwt/HRDpos and HRDneg placebo patients is assumed to be the same.

The median PFS for HRDpos placebo patients is calculated as follows: Assuming an exponential distribution, the PFS for all placebo patients has a mixture of exponential distributions (35% with BRCAmut and 65% with BRCAwt) with the median PFS of 14 months. Since the median PFS for BRCAmut placebo patients is assumed to be 30 months, data simulation yields a median PFS of 10 months for BRCAwt placebo patients and 21 months for HRDpos placebo patients.

Assuming a median PFS of 21 months for HRDpos placebo group, to detect an expected benefit corresponding to hazard ratio of 0.5 with 90% power and a 2:1 randomization ratio, 99 PFS events are required. Current projections suggest that approximately 50% of all patients randomized will be HRDpos. Therefore enrollment of approximately 620 patients (310 with HRDpos) will be needed to compete the study in about 44 months. This assumes that 15% of patients will not provide a PFS event for the primary endpoint (lost-to-follow-up, discordance between investigator and central reviewer, etc.).

The key secondary endpoint is the PFS for all randomized patients regardless of their HRD status. The final analyses for the primary and key secondary endpoints will be performed in a

sequential manner when approximately 99 HRDpos PFS events are reached. The analysis of the key secondary endpoint will include all PFS events at the time of the final analysis. Assuming a median PFS of 14 months for all placebo patients, a total of approximately 270 PFS events are expected for the final analysis. This will provide at least 90% power to detect a true HR of 0.65 in all patients.

If a statistically significant PFS treatment difference is observed in the ITT population, the sequential testing will continue for OS endpoint first in the ITT population and then in HRDpos population. The analysis of OS will include an interim analysis of OS at the time of the final analysis of PFS and a final analysis of OS when approximately 440 deaths have occurred in the ITT population (60% data maturity). A Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundaries will be used to determine the significance levels for interim and final analyses based on the observed fraction of OS events.The final analysis of OS is expected to occur approximately 70 months after first patient randomized. To detect a statistically significant OS treatment difference at 1-sided 0.025 Type I error, the analysis of OS with 440 events will have at least 80% power if the true HR is 0.75 or less in the ITT population. Although this study is not powered for OS analysis in HRDpos population, about one third of deaths in the ITT population are estimated to be HRDpos patients at the time of final analysis of OS, thus the analysis of OS with 150 HRDpos events will have at least 70% power if the true HR is 0.65 or less in HRDpos population.

Sample size was calculated using simulations with R software (version 3.4.2).

9. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1. Data Quality Assurance

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be monitored with respect to the protocol and standard operating procedures for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

9.2. Access to Source Data/Documents

An EDC system to manage data collection will be utilized during this trial. The EDC system is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials. The system is fully compliant with Code of Federal Regulations 21 Part 11.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (e.g., medical records, ECGs, AE, and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient receiving study treatment.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

9.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

9.4. Good Clinical Practice

This study will be conducted in accordance with the ICH E6(R2) for GCP and the Declaration of Helsinki (Version 2013). The clinical study will also be carried out in accordance with national and local regulatory requirement(s).

9.5. Informed Consent

Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study treatment in such a manner that the patient is aware of the potential risks, inconveniences, or AEs that may occur. The patient should be informed that he/she is free to withdraw from the study at any time. The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB/IEC-approved ICF prior to the start of the study.

The main ICF must be signed and dated; 1 copy will be given to the patient and the Investigator will retain the original document as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

Depending on local site requirements, patients may sign an HRD testing ICF prior to the screening period to facilitate early HRD testing only. This ICF should allow HRD testing procedures only. The informed consent process and documentation of informed consent will be the same for the HRD testing ICF as for the main ICF.

If a protocol amendment is required, then the ICFs may need to be revised to reflect the changes to the protocol. If the ICFs are revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

9.6. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the United States, following approval, the

protocol amendment(s) will be submitted to the investigational new drug (IND) under which the study is being conducted. Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.7. Subject Confidentiality and Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, Investigator Brochures, and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating patients must be maintained. Patients will be specified on study documents by their enrollment number or birth date (per country specific data privacy laws), not by name. Documents that identify the patient (e.g., a signed ICF) must be maintained in confidence by the Investigator.

9.8. Study Monitoring

Monitoring and auditing procedures approved by the Sponsor will be followed in order to comply with GCP guidelines. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by onsite visits from a representative of the sponsor (site monitor) who will review the eCRFs and source documents. The drug accountability and destruction forms will be verified during monitoring visits. The site monitor will reconcile the drug accountability log with products stored in the pharmacy. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements through frequent site visits and by communications (letter, telephone, and fax).

9.9. Audits and Inspections

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

9.10. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

9.11. Publication Policy

Information regarding publication of study results is contained in the Steering Committee Charter.

10. REFERENCE LIST

1. du Bois A, Floquet A, Kim JW, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. *J Clin Oncol.* 2014;32(30):3374-3382.
2. Sabbatini P HP, Scambia G et al. Abagovomab As Maintenance Therapy in Patients With Epithelial Ovarian Cancer: A Phase III Trial of the AGO OVAR, COGI, GINECO, and GEICO—The MIMOSA Study. *J Clin Oncol.* 2013;31:1554-1561.
3. Berek J TP, McGuire W et al. Oregovomab Maintenance Monoimmunotherapy Does Not Improve Outcomes in Advanced Ovarian Cancer. *J Clin Oncol.* 2009;27:418-425.
4. Harter P, Johnson T, Berton-Rigaud D, et al. BRCA1/2 mutations associated with progression-free survival in ovarian cancer patients in the AGO-OVAR 16 study. *Gynecol Oncol.* 2016;140(3):443-449.
5. Bookman M, Tyczynski, JE, Espirito JL, Wilson, TW, Fernandes, AW. Impact of primary platinum-free interval and BRCA1/2 mutation status on treatment and survival in patients with recurrent ovarian cancer. *Gynecol Oncol.* 2017(146):58-63.
6. Seidman JD, Zhao P, Yemelyanova A. "Primary peritoneal" high-grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma: assessing the new paradigm of ovarian and pelvic serous carcinogenesis and its implications for screening for ovarian cancer. *Gynecol Oncol.* 2011;120(3):470-473.
7. Mutch DG, Prat J. 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. *Gynecol Oncol.* 2014;133(3):401-404.
8. National Cancer Institute The Surveillance E, and End Results (SEER) Program SEER Stat Fact Sheets: Ovary Cancer. 2016.
9. WHO. EUCAN fact sheet: ovarian cancer estimated incidence, mortality and prevalence. 2012. http://eco.iarc.fr/eucan/CancerOne.aspx?Cancer=27&Gender=2. .
10. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006;354(1):34-43.
11. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med.* 2010;363(10):943-953.
12. du Bois A, Quinn M, Thigpen T, et al. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol.* 2005;16 Suppl 8:viii7-viii12.
13. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol.* 2006;24(29):4699-4707.
14. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol.* 2014;15(8):852-861.
15. Hess LM, Rong N, Monahan PO, Gupta P, Thomaskutty C, Matei D. Continued chemotherapy after complete response to primary therapy among women with advanced ovarian cancer: a meta-analysis. *Cancer.* 2010;116(22):5251-5260.

16. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365(26):2473-2483.
17. Oza AM, Castonguay V, Tsoref D, et al. Progression-free survival in advanced ovarian cancer: a Canadian review and expert panel perspective. *Curr Oncol.* 2011;18 Suppl 2:S20-27.
18. Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol.* 2003;21(13):2460-2465.
19. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011;365(26):2484-2496.
20. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol.* 2015;16(8):928-936.
21. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet.* 2010;376(9737):245-251.
22. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. *Nat Rev Cancer.* 2004;4(10):814-819.
23. TCGA. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474(7353):609-615.
24. Al Hilli M, Weroha S, Becker M, Hou X, Harrington S, McKinstrey S. In vivo antitumor activity of the PARP inhibitor niraparib (MK-4827) in homologous recombination deficient and proficient ovarian cancer. *Clin Cancer Res.* 2013;19(19 Suppl):PR05.
25. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med.* 2016.
26. Timms KM, Abkevich V, Hughes E, et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. *Breast Cancer Res.* 2014;16(6):475.
27. Holstege H, Horlings HM, Velds A, et al. BRCA1-mutated and basal-like breast cancers have similar aCGH profiles and a high incidence of protein truncating TP53 mutations. *BMC Cancer.* 2010;10:654.
28. Stefansson OA, Jonasson JG, Johannsson OT, et al. Genomic profiling of breast tumours in relation to BRCA abnormalities and phenotypes. *Breast Cancer Res.* 2009;11(4):R47.
29. Abkevich V, Timms KM, Hennessy BT, et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. *Br J Cancer.* 2012;107(10):1776-1782.
30. Birkbak NJ, Wang ZC, Kim JY, et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. *Cancer Discov.* 2012;2(4):366-375.
31. Popova T, Manie E, Rieunier G, et al. Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation. *Cancer Res.* 2012;72(21):5454-5462.

32. Timms K, Reid J, Abkevich V, Neff C, Morris B, Potter J. Association between BRCA1/2 status and DNA-based assays for homologous recombination deficiency. *Cancer Res.* 2013;73(24 Suppl):P6-05-10.
33. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
34. Beaumont J, Yount S, Lalla D, et al. Validation of the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Symptom Index (FOSI) in a Phase II Clinical Trial of Pertuzumab in Patients with Advanced Ovarian Cancer. *Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition).* 2007;25(18S):16021.
35. Conner-Spady B, Cumming C, Nabholtz JM, Jacobs P, Stewart D. Responsiveness of the EuroQol in breast cancer patients undergoing high dose chemotherapy. *Qual Life Res.* 2001;10(6):479-486.
36. Greimel E, Bottomley A, Cull A, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. *Eur J Cancer.* 2003;39(10):1402-1408.
37. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001;33(5):337-343.
38. Pickard AS, Wilke CT, Lin HW, Lloyd A. Health utilities using the EQ-5D in studies of cancer. *Pharmacoeconomics.* 2007;25(5):365-384.
39. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.

APPENDIX A. 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 (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence, if the preferred and usual lifestyle of the subject

APPENDIX B. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST), V.1.1

Response Criteria by RECIST v. 1.1

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 7: For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response[1]	Best Overall Response when Confirmation is Required[2]
CR	CR	No	CR	> 4 wks. Confirmation[3]
CR	Non-CR/Non-PD	No	PR	> 4 wks. Confirmation[3]
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[3]
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD[4]	Yes or No	PD	
Any	Any	Yes	PD	

[1] 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 "clinical progression." Every effort should be made to document the objective progression even after discontinuation of treatment.
[2] See RECIST v. 1.1 manuscript for further details on what is evidence of a new lesion.
[3] Only for non-randomized trials with response as primary endpoint.
[4] In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Table 8: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

[1]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 stable disease: Stable disease 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 C. SAMPLE FUNCTIONAL ASSESSMEN 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 past 7 days**.

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.

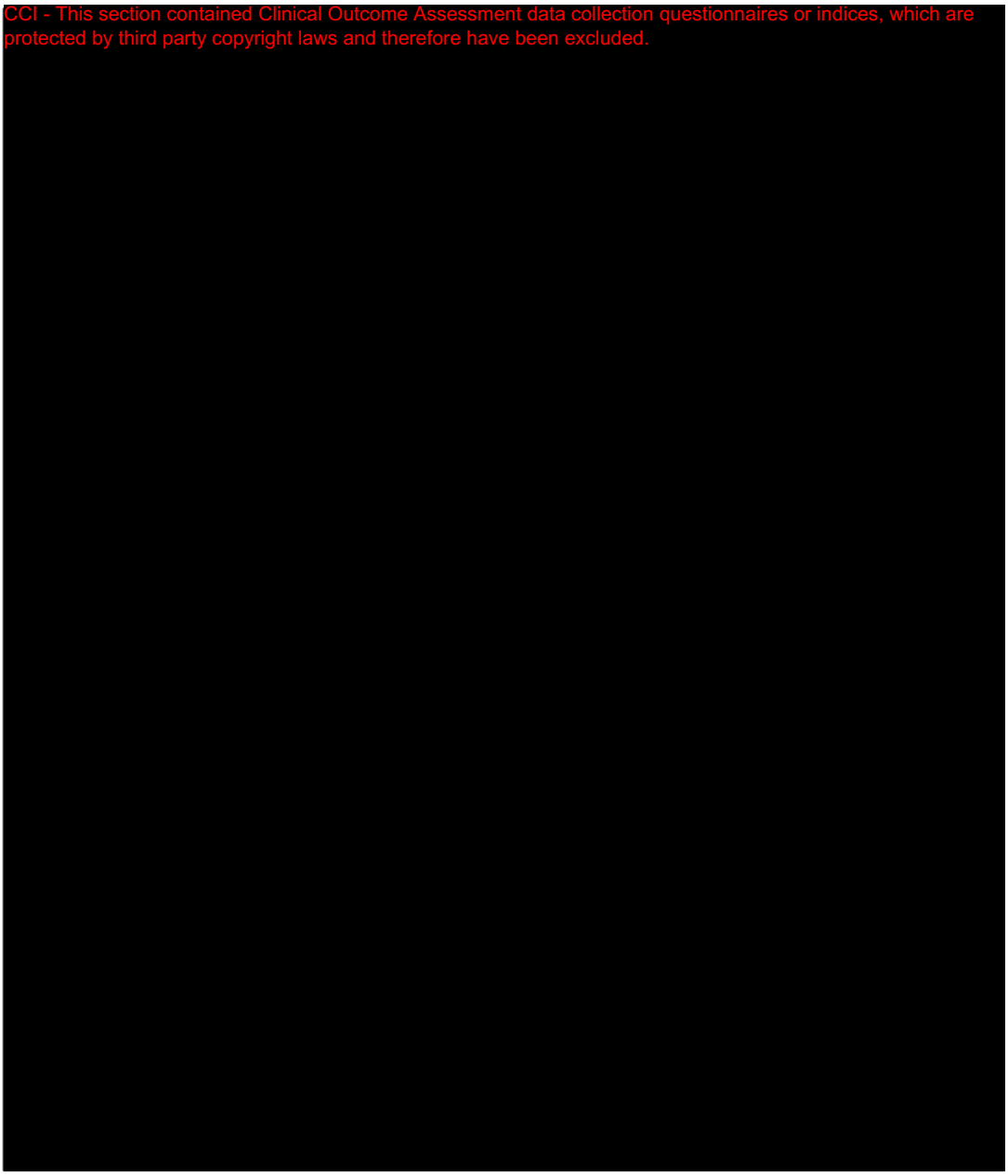
Source: FOSI manuscript[34]

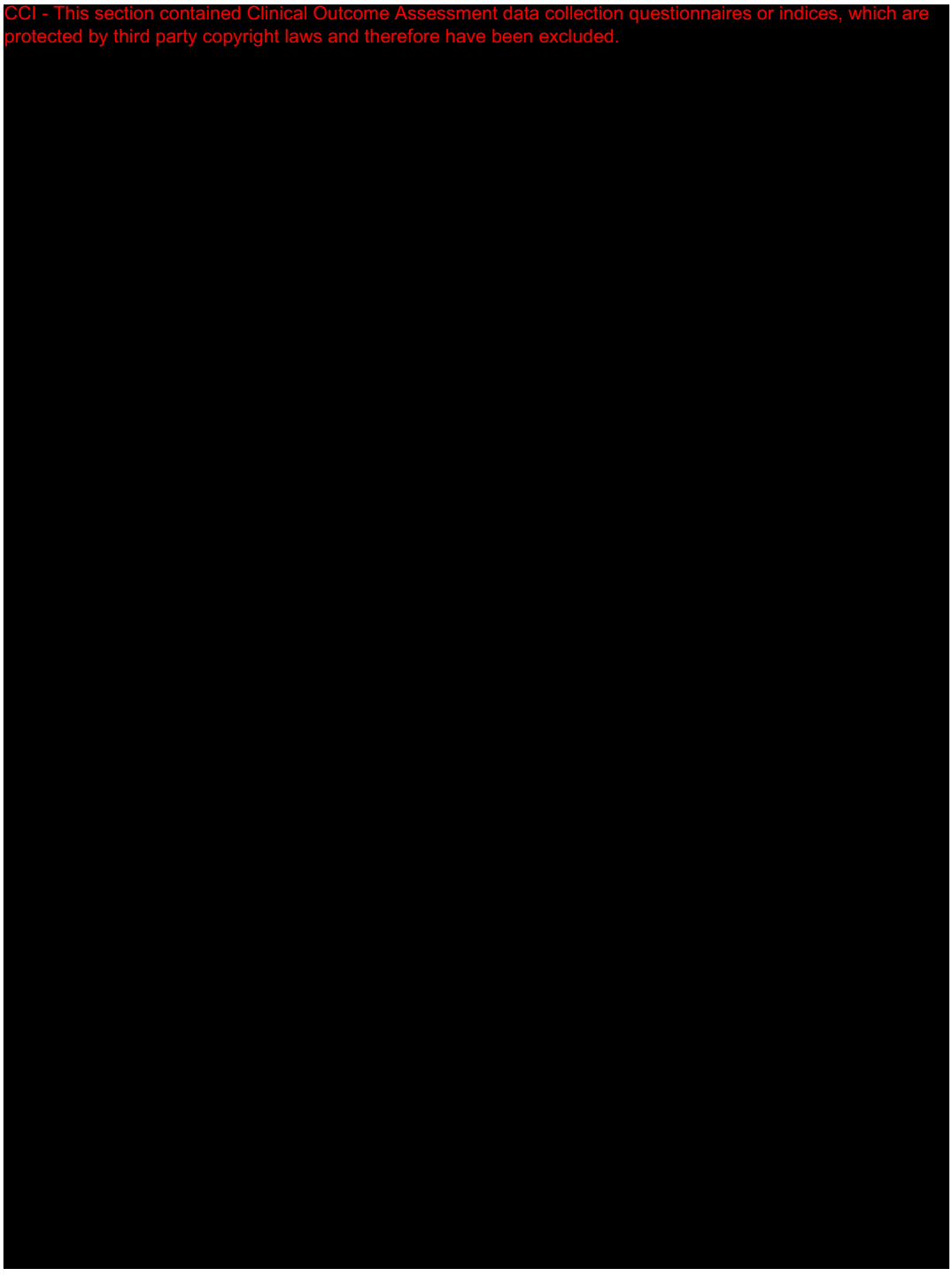
APPENDIX D. SAMPLE EUROPEAN QUALITY OF LIFE SCALE, 5-DIMENSIONS (EQ-5D-5L)

Health Questionnaire

English version for the USA

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: EQ-5D: A Measure of Health Status from the EuroQoL Group[37] Health Utilities Using the EQ-5D in Studies of Cancer[38]

APPENDIX E. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE C30 (EORTC-QLQ-C30)

EORTC QLQ-C30 (version 3)

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.

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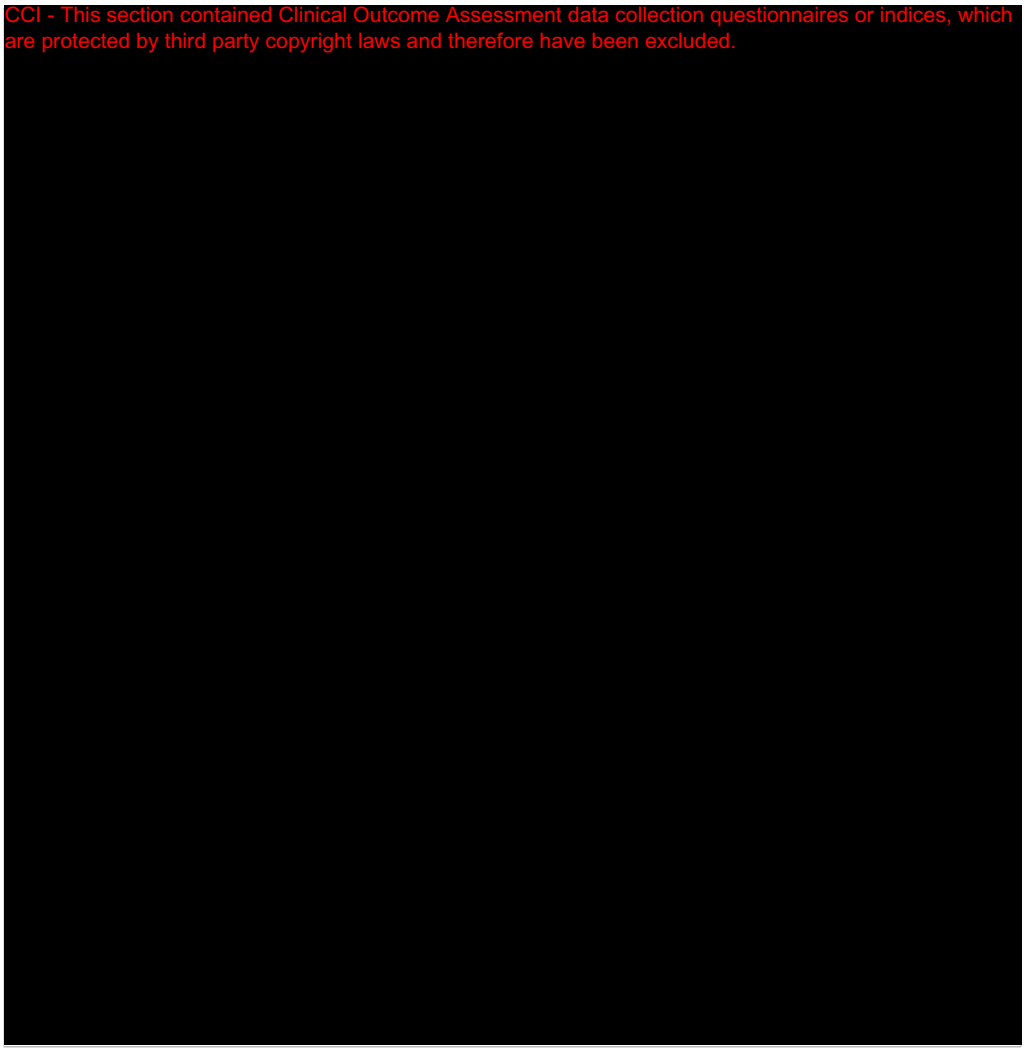
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

APPENDIX F. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITYOF LIFE QUESTIONNAIRE OVARIAN CANCER MODULE OV28 (EORTC-QLQ-OV28)

ENGLISH

EORTC QLQ - OV28

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.



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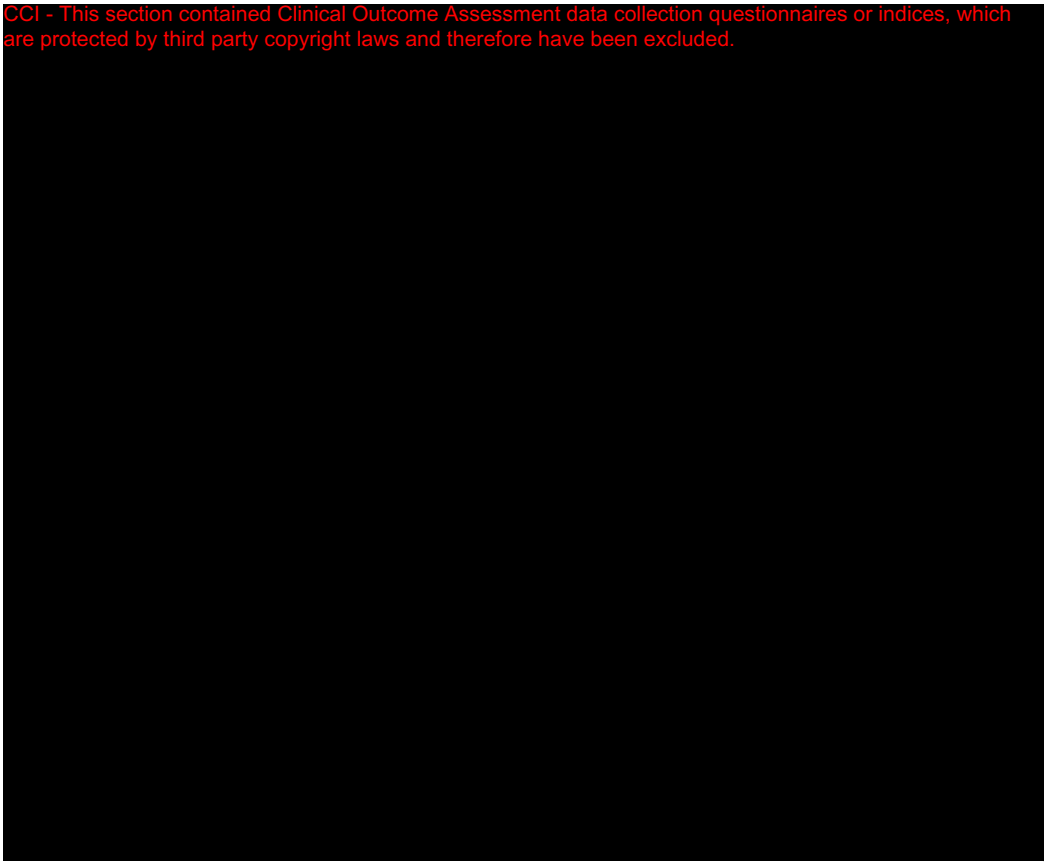
ENGLISH



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

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e., light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Source: Oken et al.[39]