STATISTICAL ANALYSIS PLAN

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

Protocol PR-30-5017-C

Protocol Number:	PR-30-5017-C
Protocol Version and Date:	Version 4.0: 12 February 2018 (Amendment 3) Version 3.0: 16 November 2017 (Amendment 2) Version 2.0: 22 November 2016 (Amendment 1) Version 1.0: 26 October 2015 (Original)
Name of Test Drug:	Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt])
Phase:	Phase 3
Methodology:	Double-Blind, Placebo-Controlled
Sponsor:	TESARO, Inc. 1000 Winter Street Waltham MA 02451 Tel: PPD
Sponsor Representative:	PPD, MD Senior Medical Director
Analysis Plan Date:	19 June 2019
Analysis Plan Version:	Final Version 1.0

APPROVAL SIGNATURE PAGE

Protocol 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
Protocol Number:	PR-30-5017-C
Sponsor:	TESARO, Inc. 1000 Winter Street Waltham MA 02451
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Author Signatory:
PPD
Principal Biostatistician

Signature: PPD

Date: 21 June 2019

Sponsor Approval:

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:
PPD, MD
Senior Medical Director

Signature: PPD

Date:

PPD, PhD
Senior Director, Biostatistics

Signature:

Date:

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PPD, MD
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Date:_____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event(s) of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BER	Base excision repair
BMI	Body mass index
BRCA	Breast cancer gene
CA-125	Cancer antigen 125
CBC	Complete blood count
CFI	Chemotherapy-free interval
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
EORTC-QLQ-OV28	Ovarian Cancer Module OV28
EQ-5D-5L	European Quality of Life scale, 5-Dimensions
eCRF	Electronic case report form
EOT	End of treatment
FUACT	Follow up anti-cancer treatment
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy–Ovarian Symptom Index
g*BRCA*mut	Germline breast cancer gene mutation
GCIG	Gynecologic Cancer Intergroup
GGT	Gamma glutamyl transferase
HEENT	Head, Eyes, Ears, Neck, and Throat
HLT	High level term
HRD	Homologous recombination deficiency
HRDnd	Homologous recombination deficiency not determined
HRDneg	Homologous recombination deficiency negative

Abbreviation	Definition
HRDpos	Homologous recombination deficiency positive
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
KM	Kaplan-Meier
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
OS	Overall survival
PARP	Poly(ADP-ribose) polymerase
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per-protocol
PR	Partial response
PRO	Patient reported outcome
PT	Preferred Term (MedDRA)
Q_1	First quartile
Q_3	Third quartile
QD	Once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R0	No residual disease
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety
SAP	Statistical analysis plan
s*BRCA*mut	Somatic breast cancer gene mutation
SD	Standard deviation
SDF	Survival distribution function
SMQ	Standardized MedDRA queries
SOC	System Organ Class (MedDRA)
t*BRCA*mut	Tumor breast cancer gene mutation

Abbreviation	Definition
t*BRCA*nd	Tumor breast cancer gene not determined
t*BRCA*wt	Tumor breast cancer gene wild type
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent therapy
ULN	Upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

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

PARP-1 and -2 are zinc-finger 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 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 represents an 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."[1] 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.[2] A subset of these tumors

had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib.

1.1.2. Study Objectives

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.

The secondary objectives of the study are as follows:

- To evaluate additional measures of clinical benefit for niraparib versus placebo as maintenance treatment, such as overall survival (OS), patient-reported outcomes (PROs), outcomes for next anti-cancer therapy following study treatment, time to first subsequent therapy (TFST), time to progression on the next anticancer therapy (PFS2) and time to cancer antigen-125 (CA-125) progression.
- To evaluate the safety and tolerability of niraparib versus placebo.

The exploratory objectives of the study are as follows:

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

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analyses of study data in order to answer the study objectives. Patient populations to be used for analyses, data handling rules, statistical methods, and formats for data presentation are identified and provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

The SAP is based upon the following study documents:

- Study Protocol v4.0 dated 12 February 2018
- Electronic Case Report Form (eCRF) v.7.154 dated 04 April 2018

Analyses of PK data are described in a separate SAP.

1.2. Study Design

1.2.1. Synopsis of Study Design

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. 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 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 somatic breast cancer gene mutation [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.

Prior to Protocol Amendment 2, all patients were required to start with 300mg niraparib (3 x 100 mg capsules) or placebo (3 capsules) daily (Fixed Starting Dose) and dose modifications were allowed to reduce the dose to 200mg and 100mg daily. Starting in Protocol Amendment 2, the starting dose of study treatment will be based upon the patient's baseline body weight or baseline platelet count (Individualized Starting Dose). Patients with a baseline body weight ≥77 kg and baseline platelet count ≥150,000/μL will be administered niraparib 300 mg or placebo daily. Patients with a baseline body weight <77 kg or baseline platelet count <150,000/μL will be administered niraparib 200 mg (2 ×100 mg capsules) or placebo (2 capsules) daily. Dose modifications of study treatment are still allowed based on tolerability but 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. 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 Blinded Independent Central Review (BICR). 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 (PD), provision of a tumor sample for exploratory biomarker analyses will be optional. All patients will continue to be followed for OS and other secondary objectives as outlined in Section 1.1.2.

Patient-Reported Outcomes (PROs, including 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 adverse events (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. If, at any time after the study is completed (or as otherwise indicated below), 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.

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.

1.2.2. Randomization Methodology

Patients who meet the entry 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 based on the local test result, then randomization may proceed).

The investigative staff will enter the clinical stratification factors of chemotherapy regimen (neoadjuvant or not), and best response to front-line platinum therapy into the 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.

1.2.3. Stopping Rules and Unblinding

There are no pre-specified stopping rules for the study.

The patient, Investigator, study staff, and the Sponsor study team and its representatives will be blinded to the patients' tumor HRD status and identity of the assigned treatment from the time of randomization until 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.

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.

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

No study sites will be provided with all of the treatment codes within that site until completion of the study following the final analysis and reporting of the CSR.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-1.

Table 1-1 Schedule of Assessments (Protocol Amendment 3)

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

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**
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]	
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 an 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 g*BRCA* or s*BRCA* mutation, randomization may occur prior to receipt of centralized HRD 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. For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained.

[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 protocol 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 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.
[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. 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 (±7 days) 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 1 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 outcomes for subsequent anticancer therapies and 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.

1.2.5. Efficacy, Pharmacokinetic, and Safety Parameters

1.2.5.1. PFS (Progression-Free Survival)

PFS assessed by the blinded independent central review (BICR) is the primary efficacy endpoint and defined as the time from the date of treatment randomization to the date of first documentation of progression or death due to any cause in the absence of documented progression, whichever occurs first.

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 (± 1 week) from Cycle 1/Day 1 visit until progression is confirmed by BICR.

BICR will assess study imaging and available clinical data to determine overall tumor assessment for each patient at each timepoint by data cut-off date for the primary analysis of PFS. After the primary analysis of PFS, BICR may no longer be required.

The original RECIST 1.1 criteria applies unless specifically clarified in the Independent Review Charter (IRC) for this particular indication and patient population. Patients for this trial may have minimal or no disease at baseline. If a subject has no disease (measurable or non-measurable) at baseline the radiologist will assign 'No Disease' (ND) as the overall tumor assessment for any available follow-up timepoints unless a new unequivocal lesion is identified, in which case the assessment will be PD, or imaging is not assessable in which case the assessment will be NE.

BICR includes:

- Radiology Review: two blinded independent radiologists and adjudication radiology review by a third blinded radiologist if required
- Oncology Review: one blinded independent oncologist when the radiology review does not meet the criteria for PD and clinical judgment is required (clinical PD). For date of progression the oncologist will use the earliest date among radiographic and clinical information.

Because of the pelvic location of the primary tumor and the frequent occurrence of peritoneal disease, imaging may not always be reliable for documentation of PD. Therefore, PD will be determined if at least 1 of the following criteria is met:

- Tumor assessment by computed tomography/magnetic resonance imaging (CT/MRI) unequivocally shows PD according to RECIST 1.1 criteria.
- CA-125 progression according to Gynecologic Cancer Intergroup (GCIG) criteria (Section 1.2.5.5) AND additional diagnostic tests (e.g., histology/cytology, ultrasound techniques, endoscopy, positron emission tomography [PET]) may identify new lesions or determine existing lesions qualify for unequivocal PD.
- CA-125 progression according to GCIG criteria (Section 1.2.5.5) 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.

Determination of the PD date for the primary analysis of PFS is shown in Table 1-2.

Table 1-2 Determination of Disease Progression Date

BICR		Investigator	Date of PD
Radiology	**Oncology**		
PD	PD	PD	Earliest date of BICR and Investigator
PD	Non-PD	PD	BICR (Radiology)
PD	PD	Non-PD	BICR (Radiology)
PD	Non-PD	Non-PD	BICR (Radiology)
Non-PD	PD	PD	Earliest date of BICR and Investigator
Non-PD	PD	Non-PD	Non-PD
Non-PD	Non-PD	PD	Non-PD

Note, BICR assessed clinical progression (by oncology review) is considered as an event in the primary analysis of PFS only if it is also a PD by Investigator assessment. When a clinical progression is determined by both BICR and Investigator assessment, the date of PD will be determined by the earliest date of BICR and Investigator assessment.

Censoring for the primary endpoint PFS will be determined as follows:

1. No evaluable baseline OR no evaluable post-baseline radiological assessments; PFS is censored at the date of randomization unless death or progression occurred within two visits of randomization (25 weeks allowing for visit window).
2. Patients who have not progressed or died and have not started subsequent anti-cancer therapy are censored at the date of the latest evaluable radiological assessment.
3. Patients who started subsequent anti-cancer therapy are censored at the date of the latest evaluable radiological assessment prior to the start of subsequent anti-cancer therapy, regardless of whether they have progressed or died after the start of subsequent anti-cancer therapy.
4. Patients who have progressed or died after two or more missed radiological assessments (25 weeks allowing for visit window) are censored at the date of the latest evaluable radiological assessment prior to the missed interval.

Unless otherwise specified, PFS and other time-to-event endpoints will be calculated in month as: (event or censoring date – randomization date + 1)/30.4375

Primary analysis of PFS will be performed first in HRDpos population and followed by ITT population. PFS based on the Investigator assessment will be conducted for sensitivity analysis.

1.2.5.2. OS (Overall Survival)

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

Following the treatment discontinuation visit, survival assessment will be collected every 12 weeks (± 2 weeks).

Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

1.2.5.3. PFS2 (Progression-Free Survival-2)

PFS2 is defined as the time from the date of randomization to the date of progression on the next anti-cancer therapy following study treatment or death by any cause, whichever occurs first.

The date of progression on the next anti-cancer therapy is based on the Investigator assessment according to the local standard clinical practice and recorded on the eCRF follow-up anti-cancer therapy form. Following the treatment discontinuation visit, the assessment of follow-up anti-cancer therapy will be collected every 12 weeks (± 2 weeks). The algorithm to define lines of follow-up anti-cancer therapies is specified in Section 4.3.3.4.

Patients who died prior to any follow-up anti-cancer therapy are considered as events in the PFS2 analysis.

Censoring for PFS2 will be determined as follows:

1. Patients who are alive and have not started any follow-up anti-cancer therapy are censored at the last contact date.
2. Patients who have not progressed or died and have not started the second line follow-up anti-cancer therapy are censored at the last contact date.
3. Patients who started the second line follow-up anti-cancer therapy are censored at the start date of the second line follow-up anti-cancer therapy, regardless of whether they have progressed or died after the start of the second line follow-up anti-cancer therapy.
4. Patients who have progressed or died after two or more missed follow-up assessments (26 weeks allowing for visit window) following treatment discontinuation are censored at the latest follow-up assessment prior to the missed interval or treatment discontinuation date if no follow-up assessment was done.

1.2.5.4. TFST (Time to First Subsequent Therapy)

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

Any patient not known to have died at the time of analysis and not known to have had started any subsequent anti-cancer therapy will be censored at the last known time to have not received any subsequent therapy, i.e. the last assessment where this was confirmed.

1.2.5.5. Time to CA-125 Progression

Time to CA-125 Progression (TCA-125) is defined as the time from the date of randomization to the date of the CA-125 progression.

CA-125 progression criteria are defined as follows:

- Patients with elevated CA-125 pretreatment and normalization of CA-125 during treatment with blinded study drug must show evidence of CA-125 ≥ 2 x ULN on 2 occasions at least 1 week apart, OR

- Patients with elevated CA-125 pretreatment, which never normalizes during treatment with blinded study drug must show evidence of CA-125 ≥ 2 x the nadir value in the 28-day period before day 1 on 2 occasions at least 1 week apart, OR
- Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 ≥ 2 x ULN on 2 occasions at least 1 week apart.

The date of CA-125 progression will be the date of the first measurement that meets the above criteria.

Any patient not known to have died at the time of analysis and have not had CA-125 progression will be censored at the date of the last available CA-125 measurement. Patients that do not have any post-randomization CA-125 measurements will be censored at the date of randomization.

1.2.5.6. PROs (Patient Reported Outcomes)

PROs will be collected every 8 weeks (± 1 week) for 56 weeks beginning on C1D1, then every 12 weeks (± 1 week) 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. Note for patients enrolled in the Original Protocol and Protocol Amendment 1, PROs are collected after EOT every 12 weeks (± 2 weeks) until study discontinuation.

1.2.5.6.1. FOSI (Functional Assessment of Cancer Therapy-Ovarian Symptom Index)

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

The FOSI score will be derived in accordance with the FOSI scoring manual (Section 7.1). Negatively stated items are reversed by subtracting the response from CCI After reversing proper items, all subscale items are summed to a total, which is the subscale score. A higher score indicates a better Quality of Life (QOL).

If there are missing items, subscale scores will be prorated as long as more than 50% of the items were answered (i.e. at least 5 of 8 items). The proration is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered.

FOSI score = CCI x CCI

The FOSI score ranges from CCI to CCI A change of 2 points in FOSI score is considered as a minimum clinically important difference (MCID). The FOSI score change from baseline will be categorized at each visit as follows:

- Improved: change from baseline ≥ 2
- Stable: -2 < change from baseline < 2
- Worsened: change from baseline ≤ -2 or "Patient was too ill" is answered as the reason for not completing the FOSI form at visit.

In the reporting of the proportion of patients who have a response of Improved, Stable, or Worsened, the denominator will be all patients with non-missing FOSI scores at baseline and at each corresponding visit.

The Time-to-First-Worsening in FOSI score (TFW-FOSI) will be defined as the time from the date of randomization to the date of first worsened FOSI score (change from baseline ≤ -2).

Any patient without a worsened FOSI score will be censored at the date of the last evaluable FOSI assessment, i.e. FOSI score is not missing. Patients who have no valid baseline FOSI assessment or any post-baseline FOSI assessment will be censored at the date of randomization.

1.2.5.6.2. EQ-5D (European Quality of Life Scale, 5-Dimensions)

EQ-5D was first developed including three levels of severity in each of five dimensions (EQ-5D-3L) by EuroQol Group. This study used a newer version of the EQ-5D including five levels of severity in each of the existing five dimensions (EQ-5D-5L).

The five domains asking patients to rate their perceived health state today include: CCI [redacted] CCI [redacted] Each domain is scored on a Likert-type scale ranging from 1 to 5 with increasing levels of severity (CCI [redacted] 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. [redacted]).

A unique health state, the EQ-5D-5L profile, based on the five dimension is reported as a five-digit code with a possible total of 3,125 health states. For example, state 11111 indicates no problems on any of the five dimensions; versus, state 55555 indicates extreme problems on all five dimensions. Any missing items will be coded as CCI [redacted] in creating patient profiles.

The EQ-5D-5L profile will be converted into a weighted health state utility value, the EQ-5D index, by applying a country-specific valuation set to the profile that represents the comparative value of health states. The EQ-5D index values summarize how good or bad each health state is on a scale from CCI [redacted] to CCI [redacted]. A higher index value indicates a better QOL. The EQ-5D index value is regarded as missing when responses are missing for 1 or more of the 5 dimensions.

For purpose of analysis, the US value set will be used. EQ-5D index values for the data gathered using the EQ-5D-5L descriptive system will be calculated by mapping the 5L descriptive system data onto the 3L valuation set using the EQ-5D-5L crosswalk value set (Section 7.2)

A Visual Analogue Score (EQ-VAS) is collected separately and records the respondent's self-rated health on a vertical, visual analogue scale from CCI [redacted] to CCI [redacted] CCI [redacted]

1.2.5.6.3. EORTC-QLQ-C30 and OV28

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30), Version 3.0, incorporates five functional scales (CCI [redacted]), three symptom scales (CCI [redacted] CCI [redacted]), a global health status/QoL scale (CCI [redacted]), and 6 single items assessing additional symptoms commonly reported by cancer patients (CCI [redacted] CCI [redacted]). Table 1-3 summarizes the QLQ-C30 scales and component items.

Table 1-3 Scoring the QLQ-C30 version 3.0

Scale	Abbr.	Number of Items	Item Range*	Version 3.0 Item Numbers	eCRF Item Numbers
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.					

Scale scores are calculated by averaging items within scales and transforming average scores linearly. All of the scales range in score from CC to CCI. A high score for a functional scale represents a high/healthy level of functioning whereas a high score for a symptom scale or item represents a high level of symptomatology or problems.

The principle for scoring these scales is the same in all cases and detailed below:

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.

For all scales, the *RawScore* (*RS*) is the mean of the component items:

$$RawScore = \text{CCI}$$

For QLQ-C30 Global health status/QoL Scale:

$$Score = \text{CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and}$$

Thus, a higher score represents a higher ("better") level of health status/QoL.

For QLQ-C30 Functional Scales:

$$Score =$$ CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws

Thus, a higher score represents a higher ("better") level of functioning.

For QLQ-C30 Symptom Scales/Items:

$$Score =$$ CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices,

Thus, a higher score represents a higher ("worse") level of symptoms.

If there are missing items in a scale, the scale score will be calculated on the completed items if at least 50% of the component items have been completed; otherwise the scale score is regarded as missing.

A change of 10 points in QLQ-C30 scale score is considered conventionally as a minimum clinically important difference (MCID).

For QLQ-C30 Global health status/QoL and Functional Scales, the scale score change from baseline will be categorized as follows:

- Improved: change from baseline ≥ 10
- Stable: -10 < change from baseline < 10
- Worsened: change from baseline ≤ -10 or "Patient was too ill" is answered as the reason for not completing the QLQ-C30 form at visit.

For QLQ-C30 Symptom Scales (CCI), the scale score change from baseline will be categorized as follows:

- Improved: change from baseline ≤ -10
- Stable: -10 < change from baseline < 10
- Worsened: change from baseline ≥ 10 or "Patient was too ill" is answered as the reason for not completing the QLQ-C30 form at visit.

In the reporting of the proportion of patients who have a response of Improved, Stable, or Worsened, the denominator will be all patients with non-missing corresponding QLQ-C30 scale scores at baseline and at each corresponding visit.

The Ovarian Cancer Module (QLQ-OV28) supplements to the QLQ-C30. It includes three functional scales (CCI) and five symptom scales/items (CCI CCI). Table 1-4 summarizes the QLQ-OV28 scales and component items.

Table 1-4 Scoring the QLQ-OV28

Scale	Abbr.	Number of Items	Item Range	QLQ-OV28 Item	eCRF Item Numbers
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.					

Overall, the scoring approach for the QLQ-OV28 is identical to that used for the QLQ-C30. A few additional rules include:

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.

For all scales, the *RawScore* (*RS*) is the mean of the component items:

$$RawScore = \text{CCI}$$

For OV-28 Functional Scales (CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third):

$$Score = \text{CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party}$$

For OV-28 Functional Scales (CCI - This section):

$$Score = \text{CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third}$$

Thus, a higher score represents a higher ("b oning.

For OV-28 Symptom Scales/Items:

$$Score = \text{CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices,}$$

Thus, a higher score represents a higher ("worse") level of symptoms.

If there are missing items in a scale, the scale score will be calculated on the completed items if at least 50% of the component items have been completed; otherwise the scale score is regarded as missing.

A change of 10 points in QLQ-OV28 scale score is considered conventionally as a minimum clinically important difference (MCID).

For QLQ-OV28 Symptom Scales (CCI [redacted]), the scale score change from baseline will be categorized as follows:

- Improved: change from baseline ≤ -10
- Stable: -10 < change from baseline < 10
- Worsened: change from baseline ≥ 10 or "Patient was too ill" is answered as the reason for not completing the QLQ-OV28 form at visit.

For QLQ-OV28 Symptom Scales (CCI [redacted]), a Time-to-First-Worsening in the QLQ-OV28-AG scale (TFW-OV28-AG) will be defined as the time from the date of randomization to the date of first worsened OV28-AG scale score (change from baseline ≥ 10).

Any patient without a worsened OV28-AG scale score will be censored at the date of the last evaluable OV28-AG scale assessment, i.e. OV28-AG scale score is not missing. Patients who have no baseline OV28-AG scale score or any post-baseline OV28-AG scale assessment will be censored at the date of randomization.

1.2.5.6.4. Overall compliance of Patient Reported Outcomes

For each of the PROs (FOSI, EQ-5D-5L, QLQ-C30/OV28), overall compliance and compliance by visit will be summarized, based on the following definitions.

- Expected forms: number of patients expected to complete PRO form. Date of study discontinuation and/or date of death will be used to determine the last visit at which a patient is still expected under PRO follow-up.
- Received forms: number of PRO forms received back.
- Evaluable forms: number of Received forms with at least one non-missing scale value plus number of forms not received back for reasons of "Patient was too ill".

The overall compliance rate is defined as the number of patients with an evaluable baseline and at least one evaluable post-baseline form, divided by the number of patients expected to complete the baseline form.

Compliance by visit will be calculated as the number of patients with an evaluable form at that visit, divided by the number of patients expected to complete the form at that visit.

The distribution of forms received and the reasons for forms not received back will be reported at each visit. To ensure the representativeness of the reported PRO data, a comparison of baseline characteristics for compliant vs. non-compliant patients may be performed if compliance is considered inadequate.

1.2.5.7. Pharmacokinetic Parameters

A separate analysis plan will describe PK parameters and analyses.

1.2.5.8. Safety Parameters

Safety parameters evaluated during the conduct of the study include: treatment-emergent AEs (TEAEs), clinical laboratory (hematology, chemistry), vital signs, electrocardiogram (ECG), physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, and use of concomitant medications. The safety endpoints are:

- TEAEs
- Clinical laboratory:
    - Complete blood count (CBC): hemoglobin, platelets, mean corpuscular volume, white blood cell count, differential white cell count (at least absolute neutrophil count)
    - Serum chemistry assessments for safety include: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea or blood urea nitrogen (BUN), total protein, albumin
    - Serum CA-125
    - Serum or urine pregnancy testing
- Physical examination, which includes assessments of the following body systems:
    - General Appearance
    - Dermatologic
    - Head, Eyes, Ears, Nose, and Throat (HEENT)
    - Thyroid
    - Lymph Nodes
    - Respiratory
    - Cardiovascular
    - Gastrointestinal
    - Extremities
    - Musculoskeletal
    - Psychiatric
- Vital signs:
    - Height (at screening only)
    - Weight
    - Systolic and diastolic blood pressure
    - Pulse
    - Temperature
- ECOG performance status

- ECG (screening only)
- Concomitant medications

Additional safety parameters include study treatment exposure and compliance.

2. PATIENT POPULATION

2.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

- 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. Patients who were incorrectly stratified during randomization will be analyzed and presented under the stratum assigned during randomization.
- Per-protocol (PP) population is defined as all patients randomized and treated in the study who do not have protocol deviations that could significantly impact the interpretation of efficacy results. Patients will be analyzed according to the treatment they actually receive. Patients who were incorrectly stratified during randomization will be analyzed and presented under the correct stratum based on the clinical database.
- Safety (SAF) population is defined as all patients who receive at least 1 dose of study drug. Patients will be analyzed as treated. Patients receiving treatment from more than one treatment arm will be accounted for based on their first study treatment.

The ITT population is the primary analysis population for the efficacy analysis. The PP population will be used for supportive analysis as needed. The SAF population will be the primary analysis population for the safety analysis.

2.2. Protocol Deviations

Protocol deviations will be assessed as important or significant per Sponsor's SOP.

- A protocol deviation is classified as important if there is the potential to impact the completeness, accuracy, and/or reliability of the study data, or affect a patient's rights, safety, or well-being.
- An important protocol deviation is classified as significant if it is confirmed to adversely impact the completeness, accuracy, and/or reliability of the study data, or affect a patient's rights, safety, or well-being.

All protocol deviations will be identified and finalized prior to database lock. Patients excluded from the PP population due to a protocol deviation will be identified prior to database lock. If the deviations are serious enough to have the potential to impact the primary analysis, sensitivity analyses may be performed.

The following protocol deviation summaries will be provided:

- Number and percentage of patients with a significant protocol deviation and by category
- Number and percentage of patients with an important protocol deviation and by category
- A data listing of all protocol deviations.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The sample size justification is summarized according to the Protocol Amendment 3 dated 12 February 2018.

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.[3, 4, 5] In addition, several studies showed that patients with g*BRCA* mutation had a longer median PFS (approximately 30 months) than those without the mutation.[6, 7] Therefore the median PFS for all placebo patients is assumed as 14 months and the median PFS for placebo patients with *BRCA*mut is assumed as 30 months. As the data are limited for the prognostic role of HRD in t*BRCA*wt patients in the first line maintenance setting, median PFS for t*BRCA*wt/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 *BRCA*mut and 65% with t*BRCA*wt) with the median PFS of 14 months. Since the median PFS for *BRCA*mut placebo patients is assumed to be 30 months, data simulation yields a median PFS of 10 months for t*BRCA*wt 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 (HR) 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 complete 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.). Since it is an event-driven study, if the actual median PFS for the placebo group in this study is longer or shorter than the assumed median estimate, the time needed to reach the required minimum number of PFS events will be either extended or reduced accordingly.

The final analysis of PFS for HRDpos and ITT population will be performed sequentially after approximately 99 HRDpos PFS events are reached. The PFS analysis in the ITT population will include all PFS events observed 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 of PFS in the ITT population. This will provide at least 90% power to detect a true HR of 0.65.

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 [8]. 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.

First patient was randomized in August 2016 and last patient was randomized in June 2018. By the time of enrollment close, patients who had signed informed consent and still under screening were allowed to continue and be randomized if deemed eligible. A total of 733 patients were randomized into the study. Table 3-1 summarizes the changes in sample size assumptions from all protocol amendments.

Table 3-1 Summary of Sample Size Assumptions in Protocol Amendments

Protocol version	HRDpos population	ITT population	Sample size
Original Protocol	HR 0.65, Placebo mPFS 6m	N/A[1]	305
Amendment 1	HR 0.5, Placebo mPFS 10m	HR 0.65, Placebo mPFS 7m	330
Amendment 2	HR 0.5, Placebo mPFS 13m	HR 0.65, Placebo mPFS 10m	468
Amendment 3	HR 0.5, Placebo mPFS 21m	HR 0.65, Placebo mPFS 14m	620

[1] The original protocol enrolled HRDpos patients only (n=44). HR = Hazard Ratio. mPFS = median PFS.

3.2. General Methods

All safety data listings that contain an evaluation date will also contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study drug is designated with an “L” (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day +1, Day +2, etc. In addition to relative day, cycle and day of treatment within cycle will be calculated and presented.

All output will be incorporated into Microsoft Word or Excel files or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. Unless otherwise stated, all tabulations will be summarized separately for HRDpos population and ITT population.

For categorical variables, summary tabulations of the number and percentage of patients within each category of the parameter will be presented. Percentages will be based on the patients with a non-missing parameter. Percentages will be reported to 1 decimal place. Percentages will not be presented for zero counts.

For continuous variables, the number of patients, mean, standard deviation (SD), median, first quartile (Q_1), third quartile (Q_3), minimum, and maximum values will be presented. Mean,

median, Q_1, and Q_3 will be reported to 1 more decimal place than the raw data, while the SD will be reported to 2 more decimal places than the raw data.

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations.

Formal statistical hypothesis testing will be performed on the efficacy endpoints as described in the SAP.

In addition:

- P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places; p-values less than 0.001 will be presented as "<0.001"
- CIs will be presented to 1 more decimal place than the raw data
- Weeks will be calculated as Number of days divided by 7
- Months will be calculated as Number of days divided by 30.4375
- Years will be calculated as Number of days divided by 365.25
- Day 1 will be considered as the first day of treatment
- End of Study is defined as the last available study assessment
- All tables, figures, and listings will include footers at the bottom of the page reflecting the path of the programs used to generate the tables, figures, and listings, and date and time of the generation of the output

3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software v9.4 or later, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v20.0 or later. Laboratory parameter changes will be described using shift tables, relative to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Concomitant medications will be coded using the latest version of the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) classification (September 2017 or later).

3.4. Baseline Definitions

For all analyses, baseline is defined as the most recent measurement prior to the first administration of study drug (including Cycle 1 Day 1).

3.5. Methods of Pooling Data

Data will be pooled across study sites.

3.6. Adjustments for Covariates

The stratified log-rank test and Cox proportional hazards models will include the randomization stratification factors as "strata". Unless otherwise noted, the randomization stratification factors will be included in the analyses of all primary and secondary efficacy endpoints when appropriate. Stratification factors entered for randomization will be used in the primary analysis.

If there is any mis-stratification, a sensitivity analysis will be performed using the stratification data based on the clinical database.

In the Original Protocol, patients must be HRDpos and were randomized by one stratification factor: best response to platinum therapy (CR or PR). Since Protocol Amendment 1, patients were randomized by three stratification factors: best response to platinum therapy (CR or PR), administration of neoadjuvant therapy (Yes or No), and HRD status (HRDpos or HRDneg/HRDnd).

When analyzing ITT population in a single model, the strata of neoadjuvant therapy and HRD status for patients from the Original Protocol will be based on data in the clinical database. When analyzing HRDpos population, similar approach as in the ITT population will be applied. The HRD status will be removed from the model since it is a constant for HRDpos population.

Table 3-2 summarizes the data sources of stratification factors used for the analysis.

Table 3-2 Data Source of Stratification Factors for Primary and Sensitivity Analysis

	Protocol in which patient was randomized	**Stratification factor**		
		Best response to platinum therapy (CR or PR)	**Administration of neoadjuvant therapy (Yes or No)**	**HRD status (HRDpos or HRDneg/HRDnd)[1]**
Primary Analysis	Original Protocol	Randomization	Clinical database	Clinical database
	Amendments	Randomization	Randomization	Randomization
Sensitivity Analysis	Original Protocol	Clinical database	Clinical database	Clinical database
	Amendments			

[1] HRD status is not applicable in the analysis of HRDpos Population.

Potential influences of other baseline characteristics in addition to the pre-specified stratification factors may be evaluated in an exploratory manner by including them in the models as covariates. For each potential covariate, a statistical test for the presence of a treatment-by-covariate interaction will be performed, by including the interaction term in the analysis model. If any of the treatment-by-covariate interactions are found to be statistically significant at the 2-sided 10% level ($p<0.10$), it will be retained in the final model; otherwise it will be excluded.

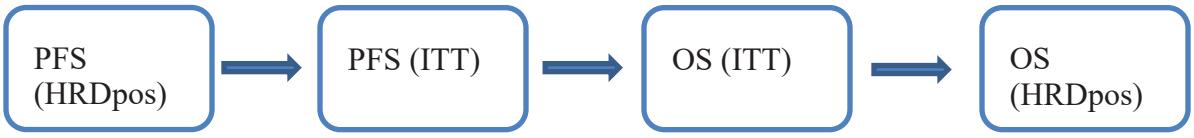
Formal analyses adjusting for possible covariate effects for the PK endpoints are contained in a separate SAP.

3.7. Multiplicity

A hierarchical testing method will be used to control overall Type I error at 1-sided 0.025, where the first statistical test will be performed for the primary endpoint PFS in HRDpos population, followed by a test in the entire ITT population. 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. The testing sequence is shown in the figure below.

Figure 1 Hierarchical Testing Procedure



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.

Results of all statistical analysis will be presented using 95% confidence intervals and two-sided p-values, if applicable.

3.8. Subpopulations

3.8.1. Biomarker Definitions

Germline *BRCA* mutation (g*BRCA*mut): An inherited deleterious or suspected deleterious mutation in either a *BRCA*1 or *BRCA*2 tumor suppressor gene found in blood.

Tumor *BRCA* mutation (t*BRCA*mut): A deleterious or suspected deleterious *BRCA*1 or *BRCA*2 mutation found in a tumor. Somatic *BRCA* mutation (s*BRCA*mut) refers to the presence of t*BRCA*mut but not g*BRCA*mut.

Tumor *BRCA* wild type (t*BRCA*wt): A tumor does not possess either a deleterious or suspected deleterious *BRCA* mutation.

Homologous recombination deficiency (HRD): Dysregulation in the homologous recombination pathway (due to genetic mutations or alterations) leading to cellular genomic instability and an inability to efficiently repair damaged DNA.

HRD positive (HRDpos): HRD positive status may be determined by the myChoice HRD test. Any tumor that scores ≥42 or has a deleterious or suspected deleterious *BRCA* mutation would be considered HRD positive.

HRD negative (HRDneg): HRD negative status may be determined by the myChoice HRD test. Any tumor that scores <42 and does not possess a deleterious or suspected deleterious *BRCA* mutation would be considered HRD negative.

3.8.2. Biomarker Subpopulations

In this study, *BRCA* and HRD status are determined by tumor samples at screening via the myChoice HRD test. Note, g*BRCA*mut status by blood test was initially collected for patients enrolled in the Original Protocol and was removed subsequently in Protocol Amendment 1.

All patients will be summarized by t*BRCA* status as follows:

- t*BRCA*mut
- t*BRCA* wild type (t*BRCA*wt)

- t*BRCA* not determined (t*BRCA*nd): t*BRCA* test result not available (e.g., test canceled, incomplete/inconclusive, or missing)

All patients will be summarized by HRD status as follows:

- HRDpos:
  - t*BRCA*mut
  - non-t*BRCA*mut and HRDpos (i.e. HRD score ≥42)
- HRDneg
- HRD not determined (HRDnd): HRD score not available (e.g., test canceled, incomplete/inconclusive, or missing)

If applicable, other exploratory biomarker subpopulations may be further defined and analyzed.

3.8.3. Fixed and Individualized Starting Dose Subgroups

Prior to Protocol Amendment 2, all patients were required to start with 300mg niraparib or placebo daily (Fixed Starting Dose subgroup). After introduction in Protocol Amendment 2, the starting dose of study treatment will be based upon the patient's baseline body weight or baseline platelet count (Individualized Starting Dose subgroup). With the amendment, patients with a baseline body weight ≥77 kg and baseline platelet count ≥150,000/μL will be administered niraparib 300 mg or placebo daily. Patients with a baseline body weight <77 kg or baseline platelet count <150,000/μL will be administered niraparib 200 mg or placebo daily. Further dose modifications based on tolerability regardless of the starting dose are allowed as described in Section 1.2.1.

NOTE: In conjunction with the Protocol Amendment 2, TESARO sent an administrative letter on 06 December 2017 to inform all sites about the above changes of the starting dose. Based on the guidance in their institutions, some sites started implementing the new starting dose scheme for new patients who were randomized still under Protocol Amendment 1 prior to formal approval of Protocol Amendment 2 by their institution. There is no specific data field flagging those patients enrolled under Protocol Amendment 1 with the new individualized dosing scheme. The following convention will be used to classify the fixed dosing and individualized dosing subgroups.

The effective date for the individualized dosing scheme at each site is defined according to whichever of the following criteria occurs first:

- the date of the first patient randomized after 06 December 2017 with a starting dose of 200 mg/day; or
- the date of the first patient randomized under Amendment 2; or
- the date of the last patient randomized at this site plus 1 day.

Using the site-specific effective date defined above, patients will be classified into one of the two subgroups:

- Fixed Starting Dose subgroup: Patients who were randomized prior to their site's effective date of the individualized dosing scheme.
- Individualized Starting Dose subgroup: Patients who were randomized on or after their site's effective date of the individualized dosing scheme.

For each subgroup, PFS hazard ratio and its 95% confidence interval will be estimated using the stratified Cox proportional hazard (PH) regression model that includes the stratification variables used in randomization as "strata" and treatment as a covariate. In order to evaluate the magnitude of the difference between the subgroup hazard ratios, a stratified Cox PH regression on all patients that includes an indicator variable for the subgroup and a subgroup-by-treatment interaction term will be added to the model. A statistically significant interaction at 2-sided, 0.10 Type I error level may suggest a differential treatment effect between the two starting dose schemes. Other important prognostic baseline characteristics may be included in the models above (with and without interaction) as covariates to account for potentially important imbalances between the subgroups.

3.8.4. Other Study-Specific Subgroups

The following subgroups will be defined according to baseline data:

- Age categories [<65 or ≥65]
- Race [White or non-White]
- ECOG performance status [0 or 1]
- Stage of disease at initial diagnosis [III or IV]
- Primary tumor site [ovarian, primary peritoneal, fallopian tube]
- Neoadjuvant chemotherapy [yes or no] based on the randomization data
- Best response to first platinum regimen [CR or PR] based on the randomization data
- Neoadjuvant chemotherapy [yes or no] derived based on the eCRF data
- Best response to first platinum regimen [CR or PR] derived based on the eCRF data
- Baseline CA-125 level [≤ULN or >ULN]
- Region [North America or Rest of World]

3.9. Withdrawals, Dropouts, Loss to Follow-up

Patients who are withdrawn or discontinue from the study will not be replaced.

3.10. Missing Data

In general, there will be no substitutions made to accommodate missing data points. Methods for handling incomplete PRO instruments are performed according to their scoring manuals. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

When tabulating AE data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution. Imputation of partial dates is

used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. By-visit summaries and analyses will be by nominal visit (all data will be tabulated per the evaluation visit as recorded on the eCRF unless otherwise specified). In data listings, the relative day of all dates will be presented.

For PRO endpoints, visit windows will be applied to PRO assessments after EOT as shown in Table 3-3 when applicable. If multiple assessments are observed in a window, the visit closest to the scheduled assessment date will be used. If equally close, the earlier visit will be used.

Table 3-3 Windows (Inclusive) for PRO Assessments after EOT

Visit after EOT	Scheduled Day after EOT	Window (Days)
4 weeks	28	14 to 42
8 weeks	56	43 to 70
12 weeks	84	71 to 126
24 weeks	168	127 to 210
36 weeks	252	211 to 294
48 weeks	336	295 to 378
60 weeks	420	379 to 462
72 weeks	504	463 to 546
84 weeks	588	547 to 630
96 weeks	672	631 to 714

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated and include the numbers of screened patients (who have signed informed consent) and the numbers of randomized patients in each patient population for analysis, the numbers who discontinued treatment and discontinued study and reason(s) for withdrawal, and the number of patients who died.

Tables will be summarized separately for HRDpos and ITT population. Tables may also be summarized by starting dose subgroup for HRDpos and ITT population, respectively. A by-patient data listing of study completion information including the reasons for treatment discontinuation and/or study discontinuation will be presented.

4.2. Demographics, Baseline Characteristics, and Medical History

Demographics, baseline characteristics, and medical history information will be summarized using descriptive statistics. Tables will be summarized separately for HRDpos and ITT population. Tables may also be summarized by starting dose subgroup for HRDpos and ITT population, respectively. No formal statistical comparisons will be performed.

Demographic and baseline data for each patient will be provided in data listings.

The demographic and baseline characteristics tables will include the following variables:

- Age at time of screening (years) as reported on the eCRF
- Age categories (18 to <65, 65 to <75, ≥75; and ≥65)
- Reproductive status (childbearing/non-childbearing potential)
- Race (White, Black, Asian, American Indian/Alaska native, native Hawaiian or other Pacific Islander, other, unknown, and not reported)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino, unknown, and not reported)
- Time from first diagnosis to first dose (years)
- Primary tumor site (ovarian, primary peritoneal, or fallopian tube)
- International Federation of Gynecology and Obstetrics (FIGO) stage at time of initial diagnosis
- Baseline weight (in kilograms, last value prior to or on Cycle 1 Day 1; if weight is reported in pounds, convert to kilograms by dividing by 2.2)
- Baseline height (in centimeters, last value prior to or on Cycle 1 Day 1; if height is reported in inches, convert to centimeters by multiplying by 2.54)
- Baseline body mass index (BMI) (kg/m^2), calculated using the patient's height and weight at Baseline [BMI (kg/m^2) = weight (kg) / height $(m)^2$]
- ECOG performance status at baseline
- Histology and grade of disease at diagnosis
- History of myelosuppression (thrombocytopenia, leukopenia, anemia, or neutropenia) within the past year

- History of blood transfusion or colony stimulating factors
- History of thrombocytopenia with Grade 3 or 4 (repeated for leukopenia, anemia, and neutropenia) within the past year
- Stratification factors according to the randomization
    - Best response to first platinum regimen (CR or PR)
    - Neoadjuvant chemotherapy (yes or no)
    - HRD status
- Stratification factors according to the eCRF
    - Best response to first platinum regimen (CR or PR)
    - Neoadjuvant chemotherapy (yes or no)
    - HRD status
- Patient randomized by region, country and site
- Prior ovarian cancer treatment, including
    - Any surgeries/procedures related to the study indication
    - Number of surgeries (grouped based on date of surgery if multiple procedures were reported on the same date in the eCRF)
    - Any radiotherapy prior to enrollment
    - Duration of first line platinum therapy (sum of the actual durations of all reported first line platinum regimens, months)
    - Total number of cycles in first line platinum therapy
    - Duration from the end date of first line platinum therapy to the date of randomization (months)
    - Prior chemotherapies
- Other cancer history (yes or no) and type of other cancer
- t*BRCA* status (t*BRCA*mut, t*BRCA*wt, t*BRCA*nd)
- HRD status (HRDpos, HRDneg, HRDnd)
    - HRDpos (t*BRCA*mut, t*BRCA*wt, t*BRCA*nd)
    - HRDneg (t*BRCA*wt, t*BRCA*nd)
- Baseline CA-125 level (≤ULN, >ULN, Missing)
- Baseline platelet count

Countries will be grouped by region according to Table 4-1.

Table 4-1 List of Country by Region

Region	Country Name	Country Code
North America	Canada	124
	United States	840
Eastern Europe	Czechia	203
	Hungary	348
	Poland	616
	Russia	643
	Ukraine	804
Western Europe	Belgium	056
	Denmark	208
	Finland	246
	France	250
	Germany	276
	Ireland	372
	Israel	376
	Italy	380
	Norway	578
	Spain	724
	Sweden	752
	Switzerland	756
	UK	826

Prior chemotherapies will be summarized according to Table 4-2 based on the reported regimens in the eCRF when applicable.

Table 4-2 Reported Anti-cancer Therapies

Therapy	Regimens (Preferred Terms) reported in the eCRF
Platinum	CARBOPLATIN CARBOPLATIN W/GEMCITABINE CARBOPLATIN W/PACLITAXEL CISPLATIN CISPLATIN W/DOXORUBICIN CISPLATIN W/PACLITAXEL OXALIPLATIN

	PACLITAXEL W/CARBOPLATIN
Carboplatin	CARBOPLATIN CARBOPLATIN W/GEMCITABINE CARBOPLATIN W/PACLITAXEL PACLITAXEL W/CARBOPLATIN
Cisplatin	CISPLATIN CISPLATIN W/DOXORUBICIN CISPLATIN W/PACLITAXEL
Taxane	DOCETAXEL PACLITAXEL PACLITAXEL ALBUMIN PACLITAXEL W/CARBOPLATIN CARBOPLATIN W/PACLITAXEL CISPLATIN W/PACLITAXEL
Doxorubicin	DOXORUBICIN DOXORUBICIN HYDROCHLORIDE LIPOSOMAL DOXORUBICIN HYDROCHLORIDE PEGYLATED LIPOSOMAL DOXORUBICIN PEGYLATED LIPOSOMAL DOXORUBICIN HYDROCHLORIDE CYCLOPHOSPHAMIDE W/DOXORUBINCIN CISPLATIN W/DOXORUBICIN
Gemcitabine	GEMCITABINE GEMCITABINE HYDROCHLORIDE CARBOPLATIN W/GEMCITABINE CARBOPLATIN W/GEMCITABINE HYDROCHLORIDE CISPLATIN W/GEMCITABINE HYDROCHLORIDE
Bevacizumab	BEVACIZUMAB
Cyclophosphamide	CYCLOPHOSPHAMIDE CYCLOPHOSPHAMIDE W/DOXORUBINCIN
PARP inhibitor	OLAPARIB NIRAPARIB RUCAPARIB TALAZOPARIB VELIPARIB
PD(L)-1 inhibitor	PEMBROLIZUMAB ATEZOLIZUMAB DURVALUMAB NIVOLUMAB AVELUMAB CEMIPLIMAB

4.3. Efficacy Evaluation

4.3.1. Summary of Primary Analyses and Pre-Specified Sensitivity Analyses

Endpoint	Analysis	Population
PFS	Primary analysis: stratified log-rank test/Cox model using BICR data	HRDpos ITT
	Sensitivity analyses: stratified log-rank test/Cox model • S1: evaluate Investigator data to assess informative censoring • S2: evaluate BICR data to assess attrition bias (using alternative censoring rules) • S3: evaluate BICR data to assess stratification bias (using stratification factors from eCRF) • S4: evaluate BICR data to assess evaluation-time bias (progressions not at the protocol-scheduled scan timepoints) • S5: evaluate BICR data using only radiology (RECIST 1.1) • S6: evaluate BICR data in the per-protocol population • S7: evaluate BICR data to assess subsequent anti-cancer therapy bias • S8: evaluate BICR data using only two stratification factors (best response to platinum therapy and HRD status)	
OS **PFS2** **TFST**	Stratified log-rank test/Cox model	HRDpos ITT
FOSI **EQ-5D** **QLQ-C30/OV38**	Mixed Model for Repeated Measures (MMRM) analysis of the change from baseline	HRDpos ITT

4.3.2. Primary Efficacy Endpoint

The primary endpoint of PFS is based on the Blinded Independent Central Review (BICR).

A hierarchical testing for the PFS endpoint will be used to control the overall Type I error. First, the analysis of PFS will be conducted in HRDpos population at the 1-sided 0.025 Type I error. If the result is positive, PFS analysis will be conducted in the ITT population at the 1-sided 0.025 Type I error; otherwise, PFS analysis becomes exploratory in the ITT population.

A stratified log-rank test on PFS will be performed using SAS PROC LIFETEST with method = PL option (Kaplan-Meier estimates, also known as the product-limit estimates)

In the analysis of HRDpos population, the STRATA statement will include the following variables: administration of neoadjuvant chemotherapy (yes or no) and best response to platinum therapy (CR or PR).

In the analysis of ITT population, the STRATA statement will include the following variables: administration of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), and HRD status (HRDpos or HRDneg/HRDnd).

The hazard ratio with 2-sided 95% CI will be estimated from the stratified Cox proportional hazards model using SAS PHREG procedure with ties=EXACT option in the model. In this analysis the baseline hazard function will be allowed to vary across strata; i.e., the MODEL statement will include treatment group variable as the only covariate and the STRATA statement will include the above prespecified variables. The assumption of proportionality will be tested by producing plots of complementary log-log (event times) versus log(time).

Quartiles (i.e., 25th percentile, median, 75th percentile) and associated 95% CIs for PFS time will be estimated from the product-limit (KM) method. The KM estimate of the survival distribution function (SDF) will be computed for comparison of the 2 treatment groups. Estimates of the SDF will be presented at 6 months, 12 months, 24 months, and so on as data allow. Kaplan-Meier plots of the SDF will be presented and will include the number of patients at risk over time by treatment group. Summaries of the number and percentage of subjects experiencing a PFS event, and the type of event (PD or death) will also be provided.

The following sensitivity analyses will be performed.

- S1: The potential impact of informative censoring will be assessed by sensitivity analysis using a stratified log-rank test with the Investigator-assessed PFS. The stratification factors and censoring rules used in the primary analysis will be applied to the Investigator data in this sensitivity analysis. In addition, the distribution of discrepancy in progression assessment between BICR and Investigator will be summarized by treatment group.
- S2: The potential attrition bias will be assessed by using alternative censoring rules for those patients who are censored in the primary analysis due to the following reasons:
    - Patients who have progressed or died after the start of subsequent anti-cancer therapy are censored at the date of the latest evaluable radiological assessment prior to the start of subsequent anti-cancer therapy.
    - Patients who have progressed or died after two or more missed radiological assessments (25 weeks allowing for visit window) are censored at the date of the latest evaluable radiological assessment prior to the missed interval.

In this sensitivity analysis, these patients will be considered as having an event and using their actual PFS event times in the analysis. The stratification factors used in the primary analysis will be applied. The censoring rules in this sensitivity analysis are below:

1. No evaluable baseline OR no evaluable post-baseline radiological assessments; PFS is censored at the date of randomization unless death or progression occurred within two visits of randomization (25 weeks allowing for visit window).
2. Patients who have not progressed or died and have not started subsequent anti-cancer therapy are censored at the date of the latest evaluable radiological assessment.
3. Patients who have not progressed or died and have started subsequent anti-cancer therapy are censored at the date of the latest evaluable radiological assessment prior to the start of subsequent anti-cancer therapy.

- S3: The potential misclassification of randomization stratification factors will be assessed by using the actual values from the eCRF for the randomization stratification factors in this sensitivity analysis. The censoring rules used in the primary analysis will be applied. In addition, the distribution of discrepancy in each stratification factor between randomization data and the derived value from eCRF data will be summarized by treatment group.
- S4: The potential evaluation-time bias for those patients whose disease progressions were determined by scans not performed at the protocol-scheduled timepoints will be assessed by using the midpoint between the time of progression and the previous evaluable RECIST assessment. The stratification factors and censoring rules used in the primary analysis will be applied in this sensitivity analysis.
- S5: The BICR radiology data based on RECIST 1.1 will be assessed in this sensitivity analysis. The stratification factors and censoring rules used in the primary analysis will be applied in this sensitivity analysis.
- S6: The BICR data will be assessed using the per-protocol population in this sensitivity analysis. The stratification factors will be based on the eCRF data. The censoring rules used in the primary analysis will be applied.
- S7: The potential subsequent anti-cancer therapy bias will be assessed by considering patients who started subsequent anti-cancer therapy as having an event at the start of the subsequent anti-cancer therapy, regardless of whether they have progressed or died after the start of the subsequent anti-cancer therapy. The stratification factors used in the primary analysis will be applied. The censoring rules in this sensitivity analysis are below:

    1. No evaluable baseline OR no evaluable post-baseline radiological assessments; PFS is censored at the date of randomization unless death/progression occurred or subsequent anti-cancer therapy started within two visits of randomization (25 weeks allowing for visit window).
    2. Patients who have not progressed or died or started subsequent anti-cancer therapy are censored at the date of the latest evaluable radiological assessment.
    3. Patients who have progressed or died or started subsequent anti-cancer therapy after two or more missed radiological assessments (25 weeks allowing for visit

window) are censored at the date of the latest evaluable radiological assessment prior to the missed interval.

- S8: The number of randomization stratification factors will be adjusted in this sensitivity analysis. The primary analysis in HRDpos population will use one stratification factor from randomization list: best response to platinum therapy. The primary analysis in the ITT population will use two stratification factors from randomization list: best response to platinum therapy and HRD status. The censoring rules used in the primary analysis will be applied.

In addition, to estimate the median PFS follow-up time at the time of analysis, a time-to-censoring analysis will be performed by reversing the censoring indicator used in the primary PFS analysis, i.e. the censored becomes an event and the PFS event becomes censored.

Subgroup analyses will be performed to assess the consistency of treatment effect across potential or expected prognostic factors. If there are too few events in a particular subgroup, i.e. <20 events per subgroup level, only descriptive summaries will be provided. Combining relevant subgroup levels may be considered if necessary.

The following subgroup analyses will be performed on the BICR data in HRDpos and ITT population respectively, unless otherwise indicated:

- Age categories [<65 or ≥65]
- Race [White or non-White]
- ECOG performance status [0 or 1]
- Stage of disease at initial diagnosis [III or IV]
- Primary tumor site [ovarian, primary peritoneal, fallopian tube]
- Neoadjuvant chemotherapy [yes or no], according to randomization
- Best response to first platinum regimen [CR or PR], according to randomization
- Neoadjuvant chemotherapy [yes or no], according to eCRF
- Best response to first platinum regimen [CR or PR], according to eCRF
- Baseline CA-125 level [≤ULN or >ULN]
- Region (North America or Rest of World)
- Starting dose subgroup [Fixed Starting Dose or Individualized Starting Dose]
- t*BRCA* status [t*BRCA*mut, t*BRCA*wt] (ITT population)
- HRD status [t*BRCA*mut, (non-t*BRCA*mut and HRDpos), HRDneg, HRDnd] (ITT population)

For each subgroup, HR and associated CIs will be calculated from a stratified Cox proportional hazards model. The stratification factors in the primary analysis will be used in the subgroup analyses when applicable. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI for the overall group. Summaries of the number and percentage of patients

experiencing a PFS event for each subgroup will be provided along with the median PFS by treatment group.

4.3.3. Secondary Efficacy Endpoints

4.3.3.1. Overall Survival

The OS endpoint will be analyzed in the same manner as for the primary analysis of PFS. An interim analysis of OS will be performed at the time of the primary PFS analysis. The statistical significance will be determined using O'Brien-Fleming methodology based on the actual number of events observed at the time of analysis. it will be performed sequentially first in the ITT population and then in HRDpos population.

To estimate the median OS follow-up time at the time of analysis, a time-to-censoring analysis will be performed by reversing the censoring indicator used in the primary OS analysis, i.e. the censored becomes an event and the OS event becomes censored.

The following subgroup analyses will be performed for OS:

- Neoadjuvant chemotherapy [yes or no], according to the eCRF
- Best response to first platinum regimen [CR or PR], according to the eCRF
- Region (North America or Rest of World)
- Starting dose subgroup [Fixed Starting Dose or Individualized Starting Dose]

4.3.3.2. Other Time to Event Endpoints

The time to event endpoints of PFS2 and TFST will be analyzed in the same manner as for the primary efficacy endpoint of PFS. Given the CA-125 progression is part of the clinical evaluation of PFS, the time to CA-125 progression alone has limited clinical interpretation; therefore, it will only be analyzed if deemed necessary.

The following subgroup analyses will be performed for PFS2 and TFST:

- Neoadjuvant chemotherapy [yes or no], according to the eCRF
- Best response to first platinum regimen [CR or PR], according to the eCRF
- Region (North America or Rest of World)
- Starting dose subgroup [Fixed Starting Dose or Individualized Starting Dose]

A sensitivity analysis will be performed for PFS2 to assess potential attrition bias using alternative censoring rules for those patients who are censored in the primary analysis of PFS2 due to the following reasons:

- Patients who have progressed or died after the start of the second line of follow-up anti-cancer therapy are censored at the start date of the second line follow-up anti-cancer therapy.
- Patients who have progressed or died after two or more missed follow-up assessments (26 weeks allowing for visit window) following treatment discontinuation are censored at the latest follow-up assessment prior to the missed interval or treatment discontinuation date if no follow-up assessment was done.

In this PFS2 sensitivity analysis, these patients will be considered to have an event and their actual PFS2 event times will be used in the analysis. The censoring rules are below:

1. Patients who are alive and have not started any follow-up anti-cancer therapy are censored at the last contact date.
2. Patients who have not progressed or died and have not started the second line of follow-up anti-cancer therapy are censored at the last contact date.
3. Patients who have not progressed or died and have started the second line of follow-up anti-cancer therapy are censored at the start date of second line follow-up anti-cancer therapy.

4.3.3.3. Patient Reported Outcomes

The following PRO continuous variables will be summarized at each time point.

- FOSI: total score
- EQ-5D-5L: VAS score and EQ-5D index value
- EORTC-QLQ-C30: subscale scores
- EORTC-QLQ-OV28: subscale scores

Summary statistics for observed values and changes from baseline will be provided. A mixed-effects model for repeated measures (MMRM) will be performed to compare between-treatment difference adjusting for correlations across multiple time points within a patient and controlling for the baseline value. The MMRM model will analyze data on treatment visits, EOT, and Week 12/24 visits after EOT. Adjusted mean difference and 95% CIs will be presented to illustrate the effect of treatment. Adjusted means and standard error bars will be plotted over time. The analysis visits include baseline, post-baseline visits, unless there is excessive missing data at a visit (defined as >75% missing data).

The MMRM model will include patient, treatment, analysis visit, and treatment-by-visit interaction as explanatory variables, the baseline value as a covariate along with the baseline-by-visit interaction. Treatment, visit, and treatment-by-visit interactions will be fixed effects in the model; patient will be treated as a random effect. An unstructured covariance matrix will be used to model the within subject variance and the Kenward-Roger approximation will be used to estimate the degrees of freedom. Restricted maximum likelihood (REML) estimation will be used. An overall adjusted mean estimates and estimates of the treatment difference will be derived, representing the average treatment effect over visits giving each visit equal weight. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be used in order until convergence is reached: toeplitz with heterogeneity (TOEPH), autoregressive with heterogeneity (ARH(1)), Toeplitz (TOEP), and autoregressive (AR(1)). If there are still issues with the fit of the model or estimation of the treatment effects, SUBJECT will be treated as a fixed effect.

Descriptive summaries by visit and including change from baseline will be reported for QLQ-C30/OV28 subscales. The PRO categorical variables defined according to the MCID levels will be summarized by visit. The time-to-event PRO variables will be summarized using the PFS analysis method. PRO questionnaire compliance (overall compliance and by visit on treatment, EOT, and Week 12/24 after EOT) will be summarized by treatment group. Descriptive

summaries of individual items in each questionnaire and percentage of missing data at each visit will be reported.

The following subgroup analyses will be performed:

- Starting dose subgroup [Fixed Starting Dose or Individualized Starting Dose]

4.3.3.4. Outcomes for Next Anticancer Therapy Following Study Treatment

The following data are collected in the eCRF for the next anticancer therapy following study treatment: Name of drug (and/or class), Start and Stop date, Progression date, Best response and Dose-limiting toxicities.

The lines of follow-up therapy are determined for each patient based on the reported start date(s) of follow-up therapies (excluding hormonal therapy) and the reported progression date(s) after the start of any follow-up therapy.

Hormonal therapy (PT: tamoxifen, tamoxifen citrate, toremifene, raloxifene, ospemifene, bazedoxifene, letrozole, anastrozole, exemestane) will not be considered for lines of follow-up therapy.

If there are one or more progression dates, all the reported follow-up therapies will be grouped into lines of therapies by comparing their reported start dates to the reported progression dates. The follow-up therapies started prior to the first progression date following the start of any follow-up therapy are grouped as the first line of follow-up therapy. The follow-up therapies started after the first progression date and prior to the second progression date are grouped as the second line of follow-up therapy, and so forth. If there is none of progression date reported, the reported follow-up therapies are grouped as the first line of follow-up anticancer therapy.

For each line of follow-up therapy, the start date of the line is the earliest start date of reported therapies in the line; the stop date of the line is the latest stop date of reported therapies in the line. All reported follow-up anticancer treatments will be summarized for overall and by starting dose subgroup, including

- Any follow-up surgeries (yes or no)
- Any follow-up radiotherapy (yes or no)
- Number of lines of follow-up anticancer therapies
- Follow-up anticancer therapies

The follow-up anticancer therapies will be summarized according to Table 4-2 when applicable.

4.4. Safety Analyses

Safety analyses will be conducted using the Safety (SAF) population.

4.4.1. Treatment Exposure and Compliance

Treatment exposure will be summarized as follows:

- Number and percent of patients beginning 1, 2, 3, ..., 12, and >12 cycles.
- Number of cycles started summarized as a continuous variable.
- Overall treatment exposure (months), defined as the [last dose date - first dose date + 1] / 30.4375, will be summarize as a continuous variable.
- Actual treatment exposure (months), defined as the overall treatment exposure minus the duration of dose interruptions, will be summarized as a continuous variable.
- Time on study (months), defined as the [last contact date or date of death - first dose date + 1] / 30.4375, will be summarized as a continuous variable.

Treatment compliance will be summarized using study treatment data up to the last dose date by data cut-off date as follows:

- The total number of capsules consumed is the sum of the number of capsules dispensed minus the sum of the number of capsules returned by the patient during the study. The sum of the daily doses consumed (mg) is the total number of capsules consumed multiplied by 100 mg.
- Dose intensity (mg/day), defined as sum of the daily doses actually consumed divided by overall treatment exposure (converted to days), will be summarized as a continuous variable.
- Relative dose intensity (RDI, %), defined as dose intensity (mg/day) divided by intended dose intensity (mg/day), where intended dose intensity is the intended starting dose of 300 mg/day or 200 mg/day, will be summarized as a continuous variable.

Dose intensity, dose reductions and dose interruptions will be summarized by cycle:

- Number and percentage of patients with a dose reduction, as indicated on the dose modification eCRF, for any reason and due to an AE.
- Number and percentage of patients with a dose interruption, as indicated on the dose modification eCRF, for any reason and due to an AE.

Summary will be provided for overall and by starting dose subgroup.

Dosing information and capsule counts for each patient will be presented in a data listing.

4.4.2. Adverse Events

4.4.2.1. Overview

All AEs will be classified using MedDRA v20.0 or later. The severity of the toxicities will be graded according to the NCI CTCAE v4.03. Any AEs leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade 3 or higher, study treatment-related events, and SAEs will be presented.

Treatment emergent AEs (TEAEs) will be defined for all AEs that occurred on or after the start of treatment through 30 days after the last dose of study treatment or when the patient initiates a new chemotherapy regimen (including participation in a new clinical trial), whichever is earlier. TEAEs are defined as follows:

- Any new AE (one that was not seen prior to the start of treatment) that occurs for the first time after at least 1 dose of study treatment has been administered; or,
- A preexisting condition (one that was seen prior to the start of treatment) that worsens in severity or is deemed by the investigator to be related to study drug after at least 1 dose of study treatment has been administered.
- Note: If the start date is missing for an AE and the actual start date cannot be determined from a partial date, the AE will be considered treatment-emergent.

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.

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.

Any AEs recorded in the database that occur from the time of informed consent to first dose will be listed only and not included in safety analyses. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page. Any AEs recorded in the database that occur on or after first dose and are not defined as TEAEs will be listed separately.

The number and percentage of patients reporting a TEAE will be summarized by system organ class (SOC), preferred term (PT), toxicity grade, and relationship to study drug.

The toxicity grade of AEs as assessed by the investigator will be graded using NCI CTCAE v4.03. Within the same MedDRA PT, only the most severe AE for each patient will be counted in tabulations by severity. Within a MedDRA SOC, patients with more than 1 MedDRA PT will be counted only once for the most severe AE reported.

The relationship of each AE to the study drug will be summarized as assessed by the Investigator. Related TEAEs are defined as TEAEs considered possibly related or related to treatment as judged by the Investigator. Any TEAEs for which the relationship to study drug is missing will be considered as related. Within the same MedDRA PT, only the AE with the highest ranked relationship to treatment for each patient will be counted in tabulations by relationship to treatment. Within a MedDRA SOC, patients with more than 1 MedDRA PT will be counted only once for the AE that is most related to treatment. The imputation for a missing

relationship will take place prior to determining the most related AE within a SOC or PT for a given patient.

A high-level overview of AEs will be presented in a summary table. This table will include the number and percentage of patients for the following categories: any TEAE, any related TEAE, any Grade ≥3 TEAE, any treatment-related Grade ≥3 TEAE, any treatment-emergent serious adverse events (SAEs), any treatment-related serious TEAE, any AE leading to study drug interruption, any AE leading to study drug reduction, any AE leading to study drug withdrawal, any TEAE leading to death, and any pregnancies.

The following AE tables will be provided:

- Overview of AEs
- TEAE by SOC and PT
- TEAE by PT (sorted by frequency)
- Related TEAE by SOC and PT
- Treatment-emergent SAEs by SOC and PT
- Related treatment-emergent SAEs by SOC and PT
- TEAE by SOC, PT, and maximum grade
- Related TEAE by SOC, PT, and maximum grade
- Grade ≥3 TEAEs by SOC and PT
- Grade ≥3 TEAEs by PT (sorted by frequency)
- Related Grade ≥3 TEAEs by SOC and PT
- TEAEs resulting in death by SOC and PT
- TEAEs resulting in study drug dose interruption by SOC and PT
- TEAEs resulting in study drug dose reduction by SOC and PT
- TEAEs resulting in study drug withdrawal by SOC and PT
- Non-serious TEAEs observed in ≥5% of patients in either treatment arm by SOC and PT (for ClinicalTrials.gov)

Tables for adverse events of special interest (AESI) and other AEs of interest, by grouped term and PT within each group:

- All TEAEs
- Grade ≥3 TEAEs
- Serious TEAEs
- TEAEs resulting in dose interruption
- TEAEs resulting in dose reduction
- TEAEs resulting in study drug withdrawal

The following subgroup analyses will be performed:

- Starting dose subgroup [Fixed Starting Dose or Individualized Starting Dose]

Tables structured as listings will be provided for the following:

- Deaths
- SAEs
- TEAEs resulting in study drug interruption
- TEAEs resulting in study drug dose reduction
- TEAEs resulting in study drug withdrawn
- AESI
- Mapping of AE reported term to PT

Adverse event summaries will be ordered in terms of decreasing frequency for SOC (alphabetically for SOCs with the same number of AEs reported) and decreasing frequency for PT within SOC (alphabetically for PTs with the same number of AEs reported within a SOC).

4.4.2.2. Adverse Drug Reactions

Adverse drug reactions will be evaluated by PT using the relative risk assessment for the niraparib treatment arm versus the placebo arm.

The relative risk and 95% CI will be provided for TEAEs reported in ≥1% of patients and Grade ≥3 TEAEs reported in ≥1% of patients in either treatment arm, respectively. Tables will be sorted by the decreasing frequency of PT. Plots of the relative risk and 95% CI for TEAEs reported in ≥10% of patients and Grade ≥3 TEAEs reported in ≥5% of patients in either treatment arm will be provided, respectively. Plots will be sorted by the decreasing magnitude of relative risk estimate.

4.4.2.3. Adverse Events of Special Interest

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.

Table 4-3 outlines the AESI with the criteria of mapping MedDRA PTs for each AESI using Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and/or PTs.

Table 4-3 Adverse Events of Special Interest

Group Term	MedDRA Criteria for Selection of Preferred Terms
AESI (MDS/AML events)	MedDRA PTs associated with MDS/AML
AESI (new malignancies other than MDS/AML)	Malignant tumor SMQ (other than MDS/AML)
AESI (pneumonitis)	Lower respiratory tract inflammatory and immunologic conditions (HLT)
AESI (embryo-fetal toxicity)	Pregnancy and neonatal topics SMQ

Abbreviations: AESI = adverse event of special interest; AML = acute myelogenous leukemia; HLT = high-level term; MDS = myelodysplastic syndrome; MedDRA = medical dictionary for regulatory activities; PT = preferred term; SMQ = Standardized MedDRA Query.

4.4.2.4. Other Adverse Events of Interest

Other AEs of interest such as myelosuppression, hypertension, thromboembolic events will be summarized in the similar manner as the AESIs.

Table 4-4 outlines these grouped events with the criteria of mapping MedDRA PTs for each group using Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and/or PTs.

Table 4-4 Other Adverse Events of Interest

Group Term	MedDRA Criteria for Selection of Preferred Terms
Thrombocytopenia events	Haematopoietic thrombocytopenia SMQ (Broad)
Anemia events	Haematopoietic erythropenia SMQ (Broad)
Leukopenia events	Haematopoietic leukopenia SMQ (Broad)
Neutropenia events	Selected PTs related to neutropenia in the Haematopoietic leukopenia SMQ (Broad)
Pancytopenia events	Haematopoietic cytopenias SMQ (Broad)
Hypertension events	Hypertension SMQ
Thromboembolic events	Embolic and thrombotic events SMQ

Abbreviations: HLT = high-level term; MedDRA = medical dictionary for regulatory activities; PT = preferred term; SMQ = Standardized MedDRA Query. HLGT = high-level group term

4.4.3. Exposure Adjusted Incidence Rate

Since patients' duration of exposure to study treatment will vary, AEs will also be presented as rates normalized for cumulative exposure.

For each PT within SOC, exposure adjusted incidence rates will be calculated as the number of patients experiencing an event in the numerator, and the overall treatment exposure in patient exposure years (PEY) in the denominator. PEY is defined as follows: first, for each patient with the specific AE being analyzed, the exposure-years will be the duration of exposure to the drug in years at the time of first occurrence of the AE; for patients without the AE, the exposure-years will be defined as their overall treatment exposure in years on the study. PEY is the sum over patients of each of their exposure years. For recurring events, the first occurrence of an AE will be reported, with the appropriate corresponding exposure years.

For AESIs and other grouped AEs, exposure adjusted incidence rate will be summarized overall and by cycle as defined by month (28 days) from start of therapy. It will calculate the cumulative exposure in PEY up to the beginning of each interval, and divide the total number of patients with first incidence of the specific event in the interval by this cumulative exposure. The specific event will be assigned to the relevant time period if the start date of the event occurs within the period. For recurrent events during a reporting interval, the first event occurrence is reported. For events that recur in more than 1 reporting interval (event start date is in different reporting intervals), the event will be reported in the first applicable reporting interval.

4.4.4. Laboratory Data

Laboratory assessments will be performed locally at each center's laboratory by means of their established methods. All laboratory values will be converted to SI units and classified as normal, low, or high based on normal ranges supplied by the local laboratories.

Hematologic and chemistry laboratory results will be graded according to the cut points defined in the NCI CTCAE v4.03 severity grade. Laboratory results will be summarized by maximum CTCAE grade as available. Abnormal laboratory findings will be summarized by CTCAE grade 1-4 and grade 3-4, respectively and sorted by frequency of grade 3-4.

Continuous results will be analyzed using change from baseline and shift values. Change from baseline will be summarized and analyzed according to the largest increase, decrease, and at EOT, irrespective of scheduled or unscheduled visit. Graphical line mean changes over time may be provided, but due to the varying visits, no repeated measures analysis will be performed.

Shift from baseline to the smallest value, the largest value, and the EOT value, categorized as low, normal, or high relative to the normal range, will be reported using number and percentage of patients. Shift from baseline CTCAE grade to the post-baseline maximum CTCAE grade will also be reported when applicable.

A listing of potential Hy's Law cases (patients with AST or ALT ≥3 ×upper limit of normal [ULN] in combination with bilirubin ≥2 ×ULN and ALP <2 ×ULN) will be also presented. Additionally, a Hy's Law (DILI) plot will be produced which plots peak ALT and peak total bilirubin in 1 panel and peak AST and peak total bilirubin in a second panel.

A distribution boxplot of liver function test (albumin, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin and gamma glutamyl transferase [GGT]) and selected hematology and other chemistry laboratory test values over time will be presented. A side panel will be added to the plot to show the distribution of maximum values.

A boxplot of platelet count by visit will be provided for overall and by starting dose subgroup. Platelet count decrease post-baseline during study (until 30 days after the last dose of study treatment) will be summarized according to the following categories for overall and by starting dose subgroup:

- <10,000/μL
- <10,000/μL requiring blood transfusion (±7 days)
- ≥10,000 and <25,000/μL
- ≥10,000 and <25,000/μL requiring blood transfusion (±7 days)
- ≥25,000/μL

A by-patient listing of all laboratory data will be provided, with laboratory reference ranges and abnormal values highlighted, CTCAE grade if applicable, and including center, patient identifier, and visit.

4.4.5. Vital Signs and Physical Examination

Summaries of vital signs parameters (systolic and diastolic blood pressures, pulse rate, and temperature) and weight will be presented by visit. Summary statistics will be produced for both observed and change from baseline values, for each parameter.

Change from baseline will be summarized and analyzed according to the largest increase, the largest decrease, and change at the EOT, irrespective of scheduled or unscheduled visit. Graphical line mean changes over time may be provided, but due to the varying visits no repeated measures analysis will be performed.

A summary table of the number and percent of patients categorized as low or high at any time on study after baseline according to the below criteria will be presented.

- SBP (mm Hg):
    - Low: <90 and decrease from baseline ≥20
    - High: >160 and increase from baseline ≥20
- DBP (mm Hg):
    - Low: <50 and decrease from baseline ≥10
    - High: >100 and increase from baseline ≥10

Vital sign measurements will be presented for each patient in a data listing.

The number and percentage of patients experiencing at least 1 abnormal result at the baseline physical examination will be summarized by body system. Subsequent symptom-targeted physical examination findings will be presented for each patient in a data listing.

ECOG performance status will be summarized by visit and reported in a data listing.

Screening ECG data for each patient will be provided in a data listing.

4.4.6. Concomitant Medications

All medications will be coded using the September 2017 or later version of the WHO Drug Dictionary (WHODD). All prior ovarian cancer treatments are summarized separately in Section 4.2.

Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the treatment withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study drug will be classified as Prior only. If a medication starts before the date of first dose of study drug and stops on or after the date of first dose of study drug, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study drug. Concomitant medication will be summarized by ATC

level 3 and PT in frequency tables by treatment. Patients with more than 1 medication in a given ATC level and PT will be counted only once in that category.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study drug. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study drug. If there is clear evidence to suggest that the medication started prior to the first dose of study drug, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study drug. If there is clear evidence to suggest that the medication stopped prior to the first dose of study drug, the medication will be assumed to be Prior only. The following lists the concomitant medication tables to be displayed:

- Number and percentage with at least 1 prior medication by ATC level 3 and PT
- Number and percentage with at least 1 concomitant medication by ATC level 3 and PT
- Number and percentage with at least 1 prior and concomitant medication by ATC level 3 and PT

The use of concomitant medications will be included in a by-patient data listing.

5. CHANGES TO PLANNED ANALYSES

Not applicable.

6. REFERENCES

1 Holstege H, Horlings HM, Velds A, et al. *BRCA*1-mutated and basal-like breast cancers have similar aCGH profiles and a high incidence of protein truncating TP53 mutations. *BMC Cancer.* 2010;10:654.

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3 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.

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6 Harter P, Johnson T, Berton-Rigaud D, et al. *BRCA*1/2 mutations associated with progression-free survival in ovarian cancer patients in the AGO-OVAR 16 study. *Gynecol Oncol.* 2016;140(3):443-449.

7 Bookman M, Tyczynski JE, Espirito JL, Wilson TW, Fernandes AW. Impact of primary platinum-free interval and *BRCA*1/2 mutation status on treatment and survival in patients with recurrent ovarian cancer. *Gynecol Oncol.* 2017(146):58-63.

8 Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika.* 1983;70:659-663.

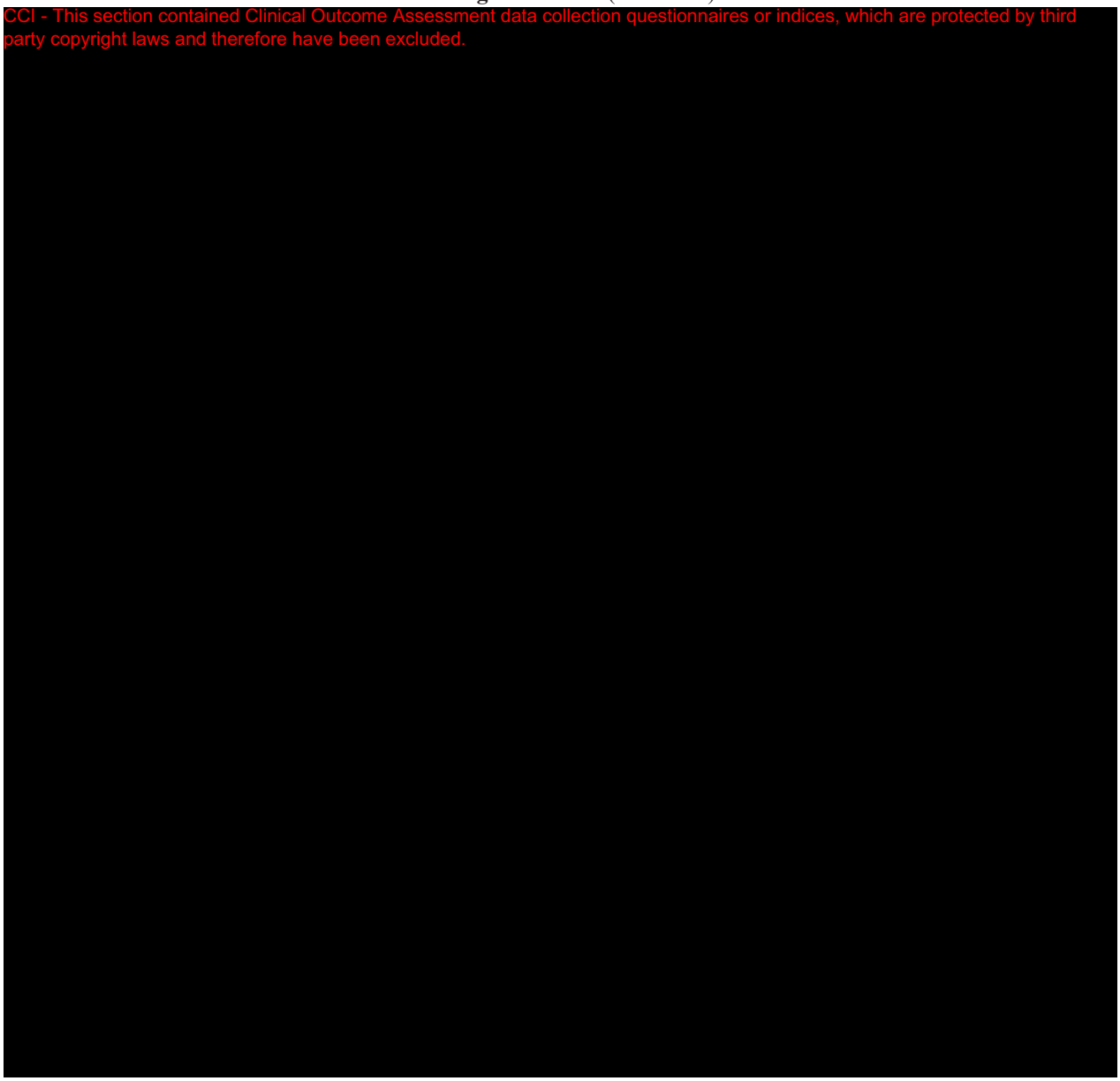
7. APPENDIX

7.1. Scoring Algorithm for the FACT/NCCN Ovarian Symptom Index (FOSI)

FACT/NCCN Ovarian Symptom Index (FOSI)

Scoring Guidelines (Version 4)

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.



7.2. EQ-5D-5L Crosswalk Value Set

EQ-5D-5L_Crosswalk_Value_Sets.xls, retrieved from https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

7.3. MedDRA Preferred Terms for AESIs and Other Grouped Events

The list of terms is provided in a separate document.

8. STATISTICAL OUTPUT SHELLS

The list of statistical output and corresponding table/figure/listing shells are provided in a separate document.