Protocol

213356

A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

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A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

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Clinical Research Organization:	PAREXEL International, LLC 195 West Street Waltham, MA 02451	
Sponsor Protocol No.:	PR-30-5011-C	
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EudraCT No.:	2013-000685-11	
Study Drug Name:	Niraparib capsules	
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Version of Protocol:	8.0	

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

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

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

PPD

PPD

Sebastien Hazard, MD
Senior Medical Director, TESARO

Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Declaration of the Principal Investigator

Title: A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

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

Principal Investigator

_____ _____

Name: Date
Title:
Institution:

PROTOCOL SYNOPSIS

Title	A Phase 3 Randomized Double-blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer
Protocol No.	PR-30-5011-C
Phase	3
Sponsor	TESARO, Inc.
Study Center(s)	Approximately 100 centers worldwide

Objective(s)

Main Study – Double Blind, Placebo Control

The primary objective of this study is to evaluate efficacy of niraparib as maintenance therapy in patients who have platinum sensitive ovarian cancer as assessed by the prolongation of progression-free survival (PFS). This objective will be independently evaluated in a cohort of patients with germline BRCA mutation (gBRCA^{mut}) and in a cohort of patients who have high grade serous or high grade predominantly serous histology but without such gBRCA^{mut} (non-gBRCA^{mut}). In the non-gBRCA^{mut} cohort, the endpoint will be hierarchically evaluated first in a subgroup of patients positive for homologous recombination deficiency HRD^{+} (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) and then in all non-gBRCA^{mut} patients.

Secondary objectives include the following: (1) concordance of a candidate companion BRACanalysis diagnostic test compared to the centralized BRCA mutation test used in this study, if needed; (2) concordance of a candidate companion HRD diagnostic test compared to the HRD test used in this study, if needed (3) to evaluate additional measures of clinical benefit including patient reported outcomes (PROs), time to first subsequent treatment (TFST), time to second subsequent treatment (TSST), time from treatment randomization to the earlier date of assessment of progression on the next anticancer therapy following study treatment or death by any cause (progression-free survival 2; PFS2), chemotherapy-free interval (CFI), and overall survival (OS); (4) to evaluate the safety and tolerability of niraparib compared to placebo in the indicated target population; (5) to evaluate QTc in a subset of niraparib-treated ovarian cancer patients.

Sub-Study – Food Effect

To assess the effect of a high fat meal on the pharmacokinetics (PK) of a single 300 mg dose of niraparib in patients with ovarian cancer.

Design

Main Study

This main study is a double-blind, 2:1 randomized, placebo controlled study in platinum sensitive ovarian cancer patients who have either gBRCA^{mut} or a tumor with high grade serous or high grade predominantly serous histology but without such gBRCA^{mut} (non-gBRCA^{mut}). The patients must have received at least 2 platinum-based regimens with the last treatment course being a platinum containing regimen, must have had a response assessed by a physician as complete response (CR) or partial response (PR) to their last regimen, must not have any measurable lesion > 2 cm, and must have normal cancer antigen (CA)-125 (or > 90% decrease during the last platinum regimen which is stable for at least 7 days). The study will assess whether maintenance with niraparib will extend PFS in this population. There will be 2 independent patient cohorts as determined by the results of Myriad Integrated BRACAnalysis® testing, one with deleterious gBRCA^{mut} and the other with high grade serous or high grade predominantly serous histology but without such gBRCA^{mut} based on the hypothesis that patients with gBRCA^{mut} will be enriched for responsiveness to niraparib. In the non-gBRCA^{mut} cohort, PFS will be hierarchically evaluated first in a subgroup of HRD^{+} (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) patients and then in all non-gBRCA^{mut} patients.

A blood sample will be sent to Myriad for immediate Integrated BRACAnalysis® testing. The sample may be sent in advance of the protocol-defined screening period in order to facilitate the screening and enrollment process.

Patients who have not had Myriad BRCA mutation testing completed in the past must wait for the results from the on-study Myriad Integrated BRACAnalysis® test prior to randomization. Patients who have had a prior Myriad

Integrated BRACAnalysis® test must still provide a sample for testing prior to randomization, but may be randomized based on the results from the prior Myriad test.

Patients with Integrated BRACAnalysis® result will be assigned within a gBRCA^{mut} cohort or a non-gBRCA^{mut} cohort as follows:

MYRIAD Report Results	**Cohort for Randomization**
Positive for a Deleterious Mutation	gBRCA^{mut} cohort
Genetic Variant, Suspected Deleterious	gBRCA^{mut} cohort
Genetic Variant, Favor Polymorphism	Non-gBRCA^{mut} cohort
Genetic Variant of Uncertain Significance	Non-gBRCA^{mut} cohort
No Mutation Detected	Non-gBRCA^{mut} cohort

A separate randomization list will be created for each cohort. Stratification factors will include: time to progression after the penultimate (next to last) platinum therapy before study enrollment (6 to < 12 months and ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (CR and PR). An analysis of outcome by (1) concomitant chemotherapy with platinum in the last and penultimate regimens (yes/no); (2) and number of prior platinum courses (2 and > 2) will also be performed.

A tissue sample will be sent for centralized testing to classify patients by HRD status. Testing may be completed any time prior to database lock. Details on tissue sample collection can be found in the laboratory manual.

Clinic visits will occur in each cycle (every 4 weeks ± 3 days). Response Evaluation Criteria in Solid Tumors (RECIST) will be used for tumor assessment via a computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas, which is required at the end of every 2 cycles (8 weeks with a window of ± 7 days from date of visit) through Cycle 14 (56 weeks), then at the end of every 6 cycles (24 weeks with a window of ± 7 days from date of visit) until 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 a reason other than progression, death, withdrawal of consent, or lost 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 until the start of subsequent anticancer treatment.

PROs (Functional Assessment of Cancer Therapy–Ovarian Symptom Index [FOSI]; European Quality of Life scale, 5-Dimensions [EQ-5D-5L]; and a neuropathy questionnaire) will be collected in a coordinated fashion with RECIST tumor imaging while on study treatment and following discontinuation of treatment, regardless of progression status (at the nearest study visit to the imaging exam, after every 2 cycles through Cycle 14, then after every 3 cycles). If the patient discontinues study treatment, assessment of PROs will be performed at that time and then 8 weeks (± 2 weeks) later, regardless of subsequent treatment. The PROs may be completed remotely. It is estimated that PRO evaluations will take less than 20 minutes at each time point. Since these are questionnaires, their completion will not interfere with, or preclude, future treatment or clinical studies. After treatment discontinuation, study information on PROs, response, tolerability with subsequent anticancer treatment, and survival will continue to be collected.

Patients will continue to receive their assigned treatment until disease progression (determined using RECIST v.1.1 criteria and clinical criteria), unacceptable toxicity, death, withdrawal of consent, or lost to follow-up, whichever comes first. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient.

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 based on their review to continue or stop the trial based on their assessment of efficacy and safety information.

At selected sites in the United States (US), a subset of patients (approximately 36, including 24 patients enrolled in main study and 12 enrolled in the food effect [FE] sub-study) will undergo intensive electrocardiogram (ECG) monitoring to coincide with PK evaluation on Day 1. Triplicate ECGs should be performed between 2 and 5 minutes apart and should be performed prior to blood draws for PK. These patients will remain in the clinic on Day 1 and will have triplicate ECG testing performed predose and at 1, 1.5, 2, 3, 4, 6, and 8 hours postdose (Day 1 only). Patients will be supine and rested for approximately 2 minutes before ECGs are recorded. The average of each of the triplicate measures will be used for analysis. This subset of patients will undergo all other assessments as described above for the main study.

No crossover to niraparib is permitted for patients randomized to placebo. Patient outcome information will be collected during treatment as well as after treatment, including PRO, response, tolerability with subsequent anticancer treatment, and OS.

The study will be conducted in conformance with Good Clinical Practice (GCP).

PRO Instrumentation

The FOSI is an 8-item measure of symptom response to treatment for ovarian cancer.[1] Patients respond to their symptom experience over the past 7 days using a 5-point Likert scale scored from CCI (0) to CCI (4). The average score is calculated as an average of the 8 items. The total symptom index is calculated as the total of the 8 symptoms.

The EQ-5D-5L is a well validated general preference-based health-related quality of life (QoL) instrument in oncology as well as other conditions and is intended to compliment other QoL instruments.[2] It was developed to assess health outcomes from a wide variety of interventions on a common scale for purposes of evaluation, allocation, and monitoring. The EQ-5D-5L encompasses 5 domains asking patients to rate their perceived health state today on the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L domains are scored on a Likert-type scale with scores ranging from 1 to 3, with 1 associated with CCI, 2 associated with CCI and 3 associated with CCI. In addition, a visual analog scale (VAS) is included in the EQ-5D-5L. The VAS measures current health status from 0 to 100, where 0 represents CCI and 100 represents CCI CCI

An additional neuropathy questionnaire will be included.

Food Effect Sub-Study (Study Completed)

Note: As of Amendment 3, enrollment on the FE sub-study has been completed; preliminary results indicate that the PK profile of niraparib is not affected by food intake. The description of planned assessments for these patients is retained in the protocol for completeness.

At selected sites in the US, approximately 12 patients will be enrolled into a 14-day, open-label, 2-treatment, crossover sub-study to evaluate the effect of a high fat meal on niraparib (single dose) exposure. For this sub-study, entry criteria will be broadened to include patients with ovarian cancer regardless of platinum sensitivity and burden of disease as long as no standard therapy exists or the patient has refused standard therapy. Patients will be randomized to either Group A or Group B with 6 patients assigned to each group. In Group A, patients will fast (nothing to eat or drink except water) for at least 10 hours before receiving a single dose of 300 mg niraparib; patients will continue to fast for at least 2 hours following the dose. In Group B, patients will fast for at least 10 hours before consuming a high fat meal. Within 5 minutes of finishing the meal, a single dose of 300 mg niraparib will be administered orally and patients will resume fasting for at least 4 hours. After a 7-day PK assessment and wash-out period, all patients will receive their second single dose of niraparib on Day 8 under the opposite (fasting vs high fat meal) circumstance: the previous 6 patients in Group A will receive their single dose of niraparib after a high fat meal and patients in Group B will receive their second single dose of niraparib under fasting conditions.

FE sub-study patients will undergo intensive (triplicate) ECG monitoring on FE Days 1 and 8 at baseline (predose) and 1, 1.5, 2, 3, 4, 6, and 8 hours postdose to coincide with blood sampling for PK determination. Triplicate ECGs should be performed between 2 and 5 minutes apart and should be performed prior to blood draws for PK. Patients will be supine and rested for approximately 2 minutes before ECGs are recorded. The average of each of the triplicate measures will be used for analysis. Additional blood samples for PK will be collected at 12, 24, 48, 72, 96, and 120 hours postdose on FE Days 1 and 8; predose and 2 hours postdose on Cycle 1/Day 1 and Cycle 2/Day 1; and predose (only) on Cycle 4/Day 1 and Cycle 8/Day 1. Following completion of the 14-day FE sub-study, participating patients will conform to the visit schedule for all safety evaluations in the main study beginning on Cycle 1/Day 1 (approximately 2 weeks after the start of the FE sub-study) and will begin dosing with open-label

niraparib at 300 mg once daily (QD). These 12 patients will only be assessed for safety for the duration of the study and may continue until Investigator-determined progression.

Criteria for Discontinuation of Treatment and Discontinuation from Study

Discontinuation from treatment

Patients may be discontinued from study treatment at any time. Specific reasons for discontinuing treatment are given below:

- Any treatment-related Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 events (see separate guidelines for platelets below) that have not reverted to CTCAE Grade 1 or better within 4 weeks (28 days) of dose interruption. At the Investigator's discretion, following dose interruption (no longer than 28 days), patients may be considered for dose reductions, providing they have not already undergone the maximum number of 2 dose reductions allowed. If upon re-challenging with study treatment at the lowest allowable dose, any CTCAE Grade 3 or 4 adverse events (AEs) recur, the patient must be discontinued.
- If the platelet count has not reverted to > 100,000 within 4 weeks (28 days) of dose interruption, the patient should be discontinued.
- Disease progression according to RECIST v.1.1 criteria or clinical criteria
- Risk to patients as judged by the Investigator and/or Sponsor
- Severe non-compliance to protocol as judged by the Investigator and/or Sponsor
- Patient request
- The patient becomes pregnant

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

Patients who discontinue from treatment will continue to receive follow-up assessments (eg, PRO, treatment outcome with next therapy, and OS) as part of the study unless they are discontinued from study by one of the following events:

Discontinuation from the study

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

Unblinding Procedures

Patients and Investigators will not be unblinded to study treatment except in a situation where knowledge of treatment arm is required as determined necessary by the Investigator..

After the blind is broken, the Investigator (or designee) must document the reason for breaking the blind on the appropriate electronic case report form (eCRF) page. Patients who require unblinding will be discontinued from study treatment permanently but will enter long-term follow-up and will be followed for Overall Survival (OS).

Treatment

Main Study

Blinded study treatment (niraparib or placebo capsules) will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Study treatment will be dispensed to patients on Cycle 1/Day 1 and every cycle (28 days) thereafter until the patient discontinues study treatment.

Study treatment will be administered orally QD continuously. Three capsules of 100 mg strength will be taken at each dose administration. Dose interruption (no longer than 28 days) will be allowed. In addition, dose reduction will be allowed based on treatment side effects. Dose reductions to 2 capsules daily (200 mg) and subsequently to 1 capsule daily (100 mg) will be allowed. No further dose reductions will be allowed. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions.

Food Effect Sub-Study

For the approximately 12 FE sub-study patients, a single dose of 300 mg niraparib (3 x 100 mg) will be given each on FE Days 1 and 8. After the completion of the 14-day FE sub-study, patients will begin 300 mg QD niraparib on Cycle 1/Day 1, approximately 2 weeks after the start of the FE sub-study.

Number of Patients

The primary analysis of PFS will be based on 180 patients randomized in the gBRCA^{mut} cohort and up to 310 patients randomized in the non-gBRCA^{mut} cohort, for a total of 490 patients. Enrollment is expected to occur over approximately 24 months for gBRCA^{mut} and 20 months for non-gBRCA^{mut}. An additional approximately 12 patients will be enrolled into the open-label, crossover, FE sub-study. Thus, a total of approximately 502 patients is the target for enrollment in this study.

Population

Inclusion Criteria – Main Study:

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

1. Female, age at least 18 years
2. Patient agrees to undergo analysis of their gBRCA status. (Testing must be completed prior to randomization. The sample may be submitted at any time prior to the screening period if it appears that the patient is likely to meet other eligibility requirements. To facilitate early testing, a separate informed consent form [ICF] specific for genotyping will be available to be signed prior to gBRCA status testing.)
3. Histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
4. High grade (or Grade 3) serous or high grade predominantly serous histology or known to have gBRCA^{mut}
5. Patients must have completed at least 2 previous courses of platinum-containing therapy (eg, carboplatin, oxaliplatin, or cisplatin):
    a. For the penultimate (next to last) platinum-based chemotherapy course prior to enrollment on the study:
        i. A patient must have platinum sensitive disease after this treatment; defined as achieving a response (CR or PR) and disease progression > 6 months after completion of their last dose of platinum chemotherapy (document 6-12 months or > 12 months). (Source documentation required and may include physician or clinic notes.)
    b. For the last chemotherapy course prior to being randomized in the study:
        i. Patients must have received a platinum-containing regimen for a minimum of 4 cycles
        ii. Patients must have achieved a partial or complete tumor response

iii. Following the last regimen, patients must have either
   1. CA-125 in the normal range OR
   2. CA-125 decrease by more than 90% during their last platinum regimen which is stable for at least 7 days (ie, no increase > 15%)

iv. Following the last regimen, patients must not have any measurable lesion > 2 cm at the time of study entry

c. Patients must be randomized within 8 weeks after completion of their final dose of the platinum-containing regimen.

Note: The last platinum regimen does not necessarily have to immediately follow the next to last (penultimate) platinum regimen. For example, if a patient received a non-platinum regimen between the penultimate platinum regimen and last platinum regimen, they could be eligible, so long as they meet all entry criteria.

6. The patient agrees to complete PROs during study treatment and at 1 additional time point 8 weeks following study treatment discontinuation. It is estimated that completion of PROs will take less than 20 minutes at each time point. Since these are questionnaires, their completion will not interfere with, or preclude, future treatment or clinical studies.
7. Formalin fixed, paraffin-embedded archival tumor available from the primary or recurrent cancer required for all patients
8. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
9. Adequate organ function
   a. Absolute neutrophil count (ANC) ≥ 1,500/μL
   b. Platelets ≥ 100,000/μL
   c. Hemoglobin ≥ 9 g/dL
   d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation
   e. Total bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ 1 x ULN
   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN
10. Able to take oral medications
11. Women of childbearing potential must use adequate birth control for the duration of study participation.

Additional Inclusion Criteria for Food Effect Sub-Study:

With the exception of inclusion criteria 2, 4, 5, 6, 7, and 8 (above), all main study inclusion criteria apply. In addition, the following inclusion criteria apply to the FE sub-study only:

1. Entry criteria are broadened to include patients with ovarian cancer regardless of platinum sensitivity and burden of disease as long as no standard therapy exists or the patient has refused standard therapy.
2. ECOG 0-2
3. Must be able to eat a high fat meal and fast for 12 hours

Exclusion Criteria – Main Study:

Patients will not be eligible for study entry if any of the following criteria are met:

1. Drainage of ascites during last 2 cycles of last chemotherapy
2. Palliative radiotherapy within 1 week encompassing > 20% of the bone marrow
3. Persistent > Grade 2 toxicity from prior cancer therapy

4. Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [eg, radiation or chemotherapy] at least 1 month prior to study entry. The patient must not have any new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids.) A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease (SD) for 28 days.
5. Known hypersensitivity to the components of niraparib
6. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery
7. Diagnosis, detection, or treatment of invasive cancer other than ovarian cancer ≤ 2 years prior to randomization (except basal or squamous cell carcinoma of the skin that has been definitively treated)
8. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
9. History or current evidence of any condition, therapy, or lab abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study treatment, or is not in the best interest of the patient to participate
    - Patients must not have received a transfusion (platelets or red blood cells) within 4 weeks of the first dose of study treatment
10. Patient is pregnant or breast feeding, or expecting to conceive children within the projected duration of the study treatment.
11. Immunocompromised patients (Note: patients with splenectomy are allowed.)
12. Patients with known active hepatic disease (ie, Hepatitis B or C)
13. Prior treatment with a known poly(ADP-ribose) polymerases (PARP) inhibitor
14. Patients with a baseline QT prolongation > 470 milliseconds
15. Patients are receiving concomitant medications that prolong QTc and are unable to discontinue use for the duration of the study (see Appendix 8 for a list).

Additional Exclusion Criteria for Food Effect Sub-Study:

With the exception of exclusion criteria 1 and 13 (above), all main study exclusion criteria apply. In addition, the following exclusion criteria apply to the FE sub-study only:

1. Chemotherapy within 3 weeks of study start
2. Patient taking a proton pump inhibitor, antacids, or H2 blocker within 48 hours of dose

Criteria for Evaluation of Efficacy

Primary Efficacy Endpoint: Progression-Free Survival

PFS is defined as the time from treatment randomization to the earlier date of assessment of progression or death by any cause in the absence of progression. Progression will be assessed by RECIST v.1.1 criteria and clinical criteria using blinded central review by 2 independent radiologists and an arbiter, if necessary, as well as per blinded central clinician review. In the non-gBRCA^{mut} cohort, the endpoint will be hierarchically evaluated first in HRD^{+} (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) patients and then in all non-gBRCA^{mut} patients.

Secondary Endpoints:

1. Concordance of a candidate companion BRACanalysis diagnostic test compared to the centralized BRCA mutation test used in this study, if needed
2. Concordance of a candidate companion HRD diagnostic test compared to the HRD test used in this study, if needed
3. Observed changes from baseline in the following PROs:
    a. FOSI
    b. EQ-5D-5L
    c. Neuropathy questionnaire
4. Outcomes for the next anticancer therapy following study treatment (best response, dose limiting toxicities, and date of progression) will be collected using source documentation.
5. PFS2 is defined as the time from treatment randomization to the earlier date of assessment of progression on the next anticancer therapy following study treatment or death by any cause. Determination of progression will be by site physician clinical and radiographic assessment (clinic and radiology notes may serve as source documentation).
6. Time to first subsequent therapy (TFST) is defined as the date of randomization in the current study to the start date of the first subsequent anticancer therapy.
7. Time to second subsequent therapy (TSST) is defined as the date of randomization in the current study to the start date of the second subsequent anticancer therapy.
8. Chemotherapy-free interval (CFI) the time from last platinum dose until initiation of next anticancer therapy (excluding maintenance therapy). CFI relative to CFI from prior chemotherapy regimens will be evaluated (clinic notes may serve as source documentation).
9. OS as measured from the date of randomization to the date of death by any cause
10. Time to CA-125 progression from time of randomization
11. Evaluation of the effects of food on the PK of niraparib

Criteria for Evaluation of Safety

Safety endpoints include the incidence of treatment-emergent AEs (TEAEs), changes in clinical laboratory parameters (hematology, chemistry), vital signs, ECG parameters, physical examinations, and usage of concomitant medications. Any Adverse Events of Special Interest (AESI) must be reported as Serious Adverse Events (SAEs) to the Sponsor as soon as the Investigator becomes aware of them.

Biomarkers

A biomarker classifier of DNA repair will be evaluated in tumor samples.

Pharmacokinetics

For all patients in the main study, blood samples for measurements of plasma levels of niraparib and the major metabolite M1 will be obtained on Cycle 1/Day 1 and on Cycle 2/ Day 1 at the following time points: 0 (predose within 30 minutes) and 2 hours (± 15 minutes) postdose. In subsequent cycles, blood samples for measurement of plasma levels of niraparib and the major metabolite M1 will be obtained on Cycle 4/Day 1 and Cycle 8/Day 1 predose (within 30 minutes) only.

In addition, a subset of patients (approximately 24, selected sites in the US) will undergo intensive PK evaluation on Day 1. In these patients, blood samples for measurements of plasma levels of niraparib and the major metabolite M1 will be obtained at predose (within 30 minutes) and at 1, 1.5, 2, 3, 4, 6, and 8 hours postdose (± 2 minutes at all postdose time points).

For patients in the FE sub-study, blood samples for PK determination will be taken at baseline (predose) and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours postdose on FE Days 1 and 8. Additional blood samples for PK will be collected predose (within 30 minutes) and 2 hours (± 15 minutes) postdose on Cycle 1/Day 1 and Cycle 2/Day 1 and predose only (within 30 minutes) on Cycle 4/Day 1 and Cycle 8/Day 1.

Statistical Methods

Within each cohort, the overall family-wise error rate will be controlled at 1-sided alpha=0.025.

For the gBRCA^{mut} cohort, superiority of niraparib relative to placebo for PFS will be tested at a 1-sided alpha=0.025.

Within the non-gBRCA^{mut} cohort, PFS will be hierarchically evaluated first in the subgroup of HRD^{+} (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) patients and then in all non-gBRCA^{mut} patients. If the treatment effect is significant in the non-gBRCA^{mut} HRD^{+} subgroup, then PFS will be tested in the full non-gBRCA^{mut} cohort. The overall 1-sided alpha level for both tests in the non-gBRCA^{mut} cohort will be 0.025.

HRD classification HRD^{+} (gBRCA^{mut}, somatic BRCA^{mut} and HRD positive/BRCA^{wt}) or HRD^{-} will be based on results from tissue testing.).Details of this testing are provided in the SAP.

For each cohort, separately, PFS will be analyzed using a 1-sided log-rank test stratifying for time to progression after the penultimate platinum therapy before study enrollment, prior use of bevacizumab in conjunction with the penultimate or last platinum regimen, and best response during the last platinum regimen.

Overall survival will be collected and monitored throughout the study duration.

Analysis of Food Effect Sub-Study

The effect of a high fat meal on the PK of niraparib in the FE sub-study will be estimated by point estimates and 90% confidence intervals (CI) for the ratios of geometric means for niraparib maximum concentration (C_{max}), area under the curve from time zero to time t (AUC_{0-t}), and area under the curve from time zero extrapolated to infinity ($AUC_{0-\infty}$).

Sample Size Considerations:

The main study is sized to address the PFS endpoint and to ensure adequate data to monitor safety and OS. The gBRCA^{mut} cohort sample size is determined based on the assumption that niraparib will result in an improvement in median PFS of 4.8 to 9.6 months (corresponding to a hazard ratio [HR] = 0.50) (niraparib relative to placebo). For a true HR = 0.50, 100 PFS events will provide > 90% power assuming a 2:1 randomization (1-sided alpha = 0.025). It is assumed that 180 gBCRA^{mut} patients will be enrolled over approximately 24 months.

The non-gBCRA^{mut} sample size was determined to maintain consistency with the intended hierarchical testing procedure under the assumption that approximately 40% of the non-gBRCA^{mut} cohort is expected to be classified as HRD^{+}. PFS sample size for the HRD^{+} (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) subgroup is determined based on the same PFS assumption used for the gBRCA^{mut} cohort. For a true HR = 0.50, based on a median PFS of 9.6 months for the niraparib-treated patients and 4.8 months for

placebo patients, in the non-gBRCA^{mut} cohort who are HRD^{+}, 98 PFS events will provide 90% power assuming a 2:1 randomization (1-sided alpha = 0.025). A total of approximately 310 patients will be enrolled into the non-gBRCA^{mut} cohort in order to obtain a sufficient number of events in the HRD^{+} subset(somatic BRCA^{mut} and HRD positive/BRCA^{wt}).

At selected sites in the US, a subset of approximately 36 patients will undergo intensive PK/ECG monitoring on Day 1 only; 24 of these patients will be enrolled from the main study and 12 patients from the open-label FE sub-study.

At least 10 fully evaluable patients (defined as completing both the fasted and fed portion) are targeted to appropriately test for comparison between the fasted and fed states. If the number of evaluable patients falls below 10, replacement patients may be used at the discretion of the Sponsor. This is a descriptive sub-study and no formal sample size calculations were performed.

Schedule of Procedures

See Table 7, Table 8, and Table 9 .

LIST OF STUDY PERSONNEL AND CONTACT INFORMATION

Sponsor	PPD , MD PPD TESARO Inc. 1000 Winter Street Waltham, MA 02451
Contract Research Organization	PAREXEL International, LLC 195 West Street Waltham, MA 02451
Serious Adverse Event Reporting	UBC Fax: 1-866-750-6823 Email: tesaropv@ubc.com

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	activities of daily living
AE	adverse event
AESI	Adverse Event of Special Interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [Classification System]
AUC	area under the curve
AUC_{0-t}	area under the curve from time 0 to time t
$AUC_{0-\infty}$	area under the curve from time 0 extrapolated to infinity
BER	base excision repair
BUN	blood urea nitrogen
CBC	complete blood cell count
CFI	chemotherapy-free interval
CFR	Code of Federal Regulations
CI	confidence interval
CL	Clearance
CNS	central nervous system
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture system
EQ-5D-5L	European Quality of Life Scale, 5-Dimensions
FE	food effect

FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
$gBRCA^{mut}$	germline BRCA mutation
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GCSF	granulocyte colony-stimulating factor
GGT	gamma glutamyl transferase
HDPE	high-density polyethylene
HR	hazard ratio
HRD	homologous recombination deficiency
ICF	informed consent form
IDMC	independent data monitoring committee
IEC	independent ethics committee
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
LDH	lactic dehydrogenase
LOH	loss of heterozygosity
LST	large-scale state transitions
MCV	mean corpuscular volume
MPV	mean platelet volume
NHEJ	non-homologous end joining
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
OS	overall survival
PARP	poly(ADP-ribose) polymerases
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetics
PP	per-protocol

PR	partial response
PRO	patient reported outcomes
QD	once daily
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
TAI	telomeric allelic imbalance
TEAE	treatment-emergent adverse event
TFST	Time to First Subsequent Therapy
TSST	Time to Second Subsequent Therapy
ULN	upper limit of normal
US	United States
UV	Ultraviolet
VAS	visual analog scale
WBC	white blood cells
WHO	World Health Organization

1. INTRODUCTION

1.1. Background of PARP and PARP Inhibition

Poly(ADP-ribose) polymerases (PARP1 and PARP2) are zinc-finger deoxyribonucleic acid (DNA)-binding enzymes that play a crucial role in DNA repair. Upon formation of single-strand DNA breaks, PARP binds at the end of broken DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones and various DNA repair proteins including PARP itself. 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 BER pathway, or those treated with PARP inhibitors, 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 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 (eg, due to inactivation of genes required for homologous recombination, such as BRCA1 or BRCA2) 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 non-homologous end joining (NHEJ) pathway 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.

A hypothesis is that treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline BRCA mutation (gBRCA^{mut}) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on BER, a pathway blocked by PARP inhibitors, for maintenance of genomic integrity. DNA-repair defects can be caused by germline or somatic alterations to the homologous recombination DNA repair pathway. In a recent analysis of ~500 HGS-OvCa tumors, approximately 50% contained homologous recombination defects.[3] A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib. This concept of inducing tumor cell death by use of PARP inhibitors to block one DNA repair pathway in tumors with pre-existing deficiencies in a complementary DNA repair pathways is called synthetic lethality[4]; the 2 insults together induce cell death when neither alone would have this effect.

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

tumors without a gBRCA^{mut} (non-gBRCA^{mut}) is they share distinctive DNA repair defects with gBRCA^{mut} carriers, a phenomenon broadly described as "BRCAness."[5] A tumor arising in a non-gBRCA^{mut} patient that has a homologous recombination deficiency (HRD^{+}; ie, deficiencies in homologous recombination DNA repair genes) could also enhance tumor cell sensitivity to PARP inhibitors. In a recent study, the patterns of genome-wide loss of heterozygosity (LOH) were analyzed in 3 different epithelial ovarian cancer data sets extensively characterized for BRCA1 and BRCA2 defects by evaluating HRD status.[6] The HRD analysis is a DNA-based assay that is capable of detecting HRD independent of its etiology based on genome-wide single nucleotide polymorphism data. An HRD-(LOH) score was developed that is strongly associated with functional defects in BRCA1 and BRCA2. This score also strongly correlated with promoter methylation of RAD51C, a gene implicated in the homologous recombination pathway. Additional DNA-based algorithms of HRD have been developed based on whole genome tumor telomeric allelic imbalance, HRD-(TAI),[7] and large-scale state transitions, HRD-(LST).[8]

In a subsequent study, all 3 HRD algorithms were independently associated with BRCA1/2 deficiency and response to cisplatin treatment in triple-negative breast cancer.[9] The arithmetic mean of the 3 HRD algorithms was significantly associated with BRCA1/2 status in a breast all-comers cohort and with cisplatin response in a second independent triple-negative breast cancer cohort. The final clinical HRD score results from the sum of HRD-LOH, HRD-TAI and HRD-LST scores, and is a single value along a continuous scale from 0 to 100. Analysis of more than 1,000 breast and ovarian cancer tumor samples have identified 2 distinct HRD populations, HRD^{-} and HRD^{+}, with 95% of all gBRCA^{mut} tumors with concomitant LOH at the BRCA gene in the sample classified as HRD^{+}. Details of procedures used to classify patients in this study are provided in the statistical analysis plan (SAP).

Clinical studies have shown that PARP inhibitors are active for recurrent ovarian cancer.[10-14] Clinical anticancer activity has been observed in patients with and without gBRCA^{mut} and in patients who are platinum sensitive and platinum resistant. However, PARP inhibition appears to be most active in patients with gBRCA^{mut} platinum sensitive disease.[11,12,14] This clinical experience to date is largely in patients who have received multiple prior treatments (median ~3; range, 1-10) in multiple Phase 1 and 2 clinical studies. In a Phase 2 study of maintenance therapy in 265 patients with relapsed, platinum sensitive ovarian cancer, daily olaparib therapy compared to placebo treatment was associated with a progression-free survival (PFS) benefit (hazard ratio [HR] = 0.35) and prolongation of the median PFS from 4.8 months to 8.4 months.[14] The subset of patients with known gBRCA^{mut} had a PFS HR of 0.18.[15] Patient reported outcomes (PROs), including the Functional Assessment of Cancer Therapy–Ovarian Symptoms Index (FOSI), were measured and did not show a significant difference between the placebo and treatment groups; suggesting that maintenance treatment did not decrease functioning or quality of life (QoL) in these patients.

1.2. Background of Niraparib

Niraparib is an orally active PARP1/2 inhibitor with nanomolar potency being developed as a monotherapy agent for tumors with defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors.

In nonclinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with homologous recombination

defects. In a BRCA1 mutant xenograft study, niraparib dosed orally caused tumor regression which was mirrored by > 90% reduction in tumor weight compared to control; in a BRCA2 mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Additional nonclinical data on niraparib in ovarian cancer are described in the Investigator's Brochure.

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

Table 1 shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, g*BRCA*mut cohort, HRDpos cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRD negative (HRDneg) tumors was 6.9 months (95% CI: 5.6, 9.6) in the niraparib arm compared to 3.8 months (95% CI: 3.7, 5.6) in the placebo arm with an HR of 0.58 (95% CI: 0.361, 0.922) (p=0.0226).

Table 1: Progression-Free Survival in Ovarian Cancer Patients in NOVA

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

The primary data to support the safety of treatment with niraparib in the proposed indication are derived from the NOVA main study in which a total of 546 patients received study treatment. Niraparib appears to have a predictable adverse event (AE) profile that is readily managed through routine laboratory testing (i.e., complete blood count [CBC]) and clinical monitoring (i.e., blood pressure monitoring and adherence to the recommended dose modifications). In the NOVA study, both all grade and high grade treatment emergent adverse events (TEAE) tend to decrease over time. Most TEAEs following one year of study treatment are readily managed with dose modifications and/or widely available supportive measures; events occurring in ≥ 5% of patients after one year of niraparib treatment include nausea, constipation, vomiting, diarrhea, nasopharyngitis, arthralgia and cough. TEAEs in the NOVA study of clinical significance

following one year of treatment include ≥ Grade 3 hypertension and MDS/AML, both of which are routinely monitored for all patients on study.

The niraparib clinical safety data reported to date, including Phase 1 results, dose limiting toxicities, and toxicity profile are provided in detail in the Investigator's Brochure.

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Blood pressure will be monitored at each study visit. Hypertension should be medically managed with antihypertensive medications as well as adjustment of the niraparib dose, if necessary.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML is provided in Section 6.3.5 and Section 7.1.

1.3. Rationale for Current Trial

Collectively, the data from multiple published Phase 1 and 2 clinical studies of PARP inhibitors used as monotherapy to treat patients with recurrent ovarian cancer suggest that the agents are active in this population; the strongest activity being observed in the platinum sensitive, $gBRCA^{mut}$ subgroup. Data from a randomized Phase 2 study of olaparib vs placebo in patients with relapsed, platinum sensitive ovarian cancer, in response to their most recent platinum regimen showed a significant prolongation of PFS, this effect being strongest in patients with known $gBRCA^{mut}$.[14]

The niraparib Phase 3 study is designed to address certain deficiencies in the design of the olaparib maintenance study[14] and to document and power for PFS benefit in this setting. Improvements include: (1) prospective identification, enrichment, and randomization of patients with $gBRCA^{mut}$; (2) prospective identification and randomization of non-$gBRCA^{mut}$ patients to enable assessment of niraparib activity in the group without enrichment; (3) prespecified and adequately powered statistical analyses that enable a primary endpoint analysis on the enriched $gBRCA^{mut}$ cohort and the non-$gBRCA^{mut}$ HRD^{+} subgroup (somatic $BRCA^{mut}$ and HRD positive/$BRCA^{wt}$); (4) support of PFS data with PRO data that extends beyond progression to enable data collection during subsequent chemotherapy; (5) collection of tumor and blood samples to enable analyses with different molecular classifiers that may further identify or enrich for those patients that could benefit from niraparib treatment, or those patients in either cohort who may not benefit from niraparib treatment; and (6) ongoing follow-up to provide overall survival (OS) information.

At selected sites in the United States (US), this study will include a 14-day, open-label, crossover FE sub-study in approximately 12 patients with ovarian cancer to assess the effect of a high fat meal on the single-dose pharmacokinetics (PK) of niraparib 300 mg.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate efficacy of niraparib as maintenance therapy in patients who have platinum sensitive ovarian cancer as assessed by the prolongation of PFS. This objective will be independently evaluated in a cohort of patients with germline BRCA mutation ($gBRCA^{mut}$) and in a cohort of patients who have high grade serous or high grade predominantly serous histology but without such $gBRCA^{mut}$ (non-$gBRCA^{mut}$). The statistical analysis of the primary endpoint of PFS for the non-$gBRCA^{mut}$ cohort in the NOVA study will be performed in a hierarchical manner, with a test for the HRD positive subset (somatic $BRCA^{mut}$ and HRD positive/$BRCA^{wt}$) performed first, followed by a test of the overall non-$gBRCA^{mut}$ cohort if the first test is statistically significant.

2.2. Secondary Objectives

Secondary objectives include the following:

1. Concordance of a candidate companion BRACanalysis diagnostic test compared to the centralized BRCA mutation test used in this study, if needed.
2. Concordance of a candidate companion HRD diagnostic test compared to the HRD test used in this study, if needed
3. To evaluate additional measures of clinical benefit, including PROs, time to first subsequent treatment (TFST), time to second subsequent treatment (TSST), time from treatment randomization to the earlier date of assessment of progression on the next anti-cancer therapy following study treatment or death by any cause (PFS2), chemotherapy-free interval (CFI) and OS.
4. To evaluate the safety and tolerability of niraparib compared to placebo in the indicated target population.
5. To evaluate QTc in a subset of niraparib-treated ovarian cancer patients.

2.3. Food Effect Sub-Study Objective

To assess the effect of a high fat meal on the PK of a single 300 mg dose of niraparib in patients with ovarian cancer.

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1. Overview

Niraparib is a potent inhibitor of PARP, a clinically validated target in breast and ovarian cancer. Current standard of care for patients with platinum sensitive, recurrent ovarian cancer that has responded to the last platinum regimen is close follow-up with no treatment.

3.1.1. Main Study

The main study is a double-blind, 2:1 randomized, placebo controlled study in platinum sensitive ovarian cancer patients who have either gBRCA^{mut} or a tumor with high grade serous or high grade predominantly serous histology but without such gBRCA^{mut} (non-gBRCA^{mut}). The patients must have received at least 2 platinum-based regimens with the last regimen prior to being randomized in the study being platinum-based, had a response assessed by a physician of complete response (CR) or partial response (PR) to their last regimen, must not have any measurable lesion > 2 cm, and must have normal cancer antigen (CA)-125 (or >90% decrease) following their last treatment. The study will assess whether maintenance with niraparib will extend PFS in this population. There will be 2 independent patient cohorts as determined by the results of Myriad Integrated BRACAnalysis® testing, one cohort of patients with results indicating either a positive deleterious gBRCA mutation or genetic variant or a suspected deleterious mutation (gBRCA^{mut}) and the other with high grade serous or high grade predominantly serous histology but without such gBRCA^{mut}(non-gBRCA^{mut}) based on the hypothesis that patients with gBRCA^{mut} will be enriched for responsiveness to niraparib. The statistical analysis of the primary endpoint of PFS for the non-gBRCA^{mut} cohort in the NOVA study will be performed in a hierarchical manner, with a test for the HRD positive subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) performed first, followed by a test of the overall non-gBRCA^{mut} cohort if the first test is statistically significant.

A blood sample will be sent to Myriad for immediate Integrated BRACAnalysis® testing. The sample may be sent in advance of the protocol-defined screening period in order to facilitate the screening and enrollment process.

Patients who have not had Myriad BRCA mutation testing completed in the past must wait for the results from the on-study Myriad Integrated BRACAnalysis® test prior to randomization. Patients who have had a prior Myriad Integrated BRACAnalysis® test must still provide a sample for testing prior to randomization, but may be randomized based on the results from the prior Myriad test.

Patients with Integrated BRACAnalysis® result will be assigned within a gBRCA^{mut} cohort or a non-gBRCA^{mut} cohort as per Table 2.

Table 2: Cohort Assignment Based on Myriad Report

MYRIAD Report Results	Cohort for Randomization
Positive for a Deleterious Mutation	gBRCA^{mut} cohort
Genetic Variant, Suspected Deleterious	gBRCA^{mut} cohort
Genetic Variant, Favor Polymorphism	Non-gBRCA^{mut} cohort
Genetic Variant of Uncertain Significance	Non-gBRCA^{mut} cohort
No Mutation Detected	Non-gBRCA^{mut} cohort

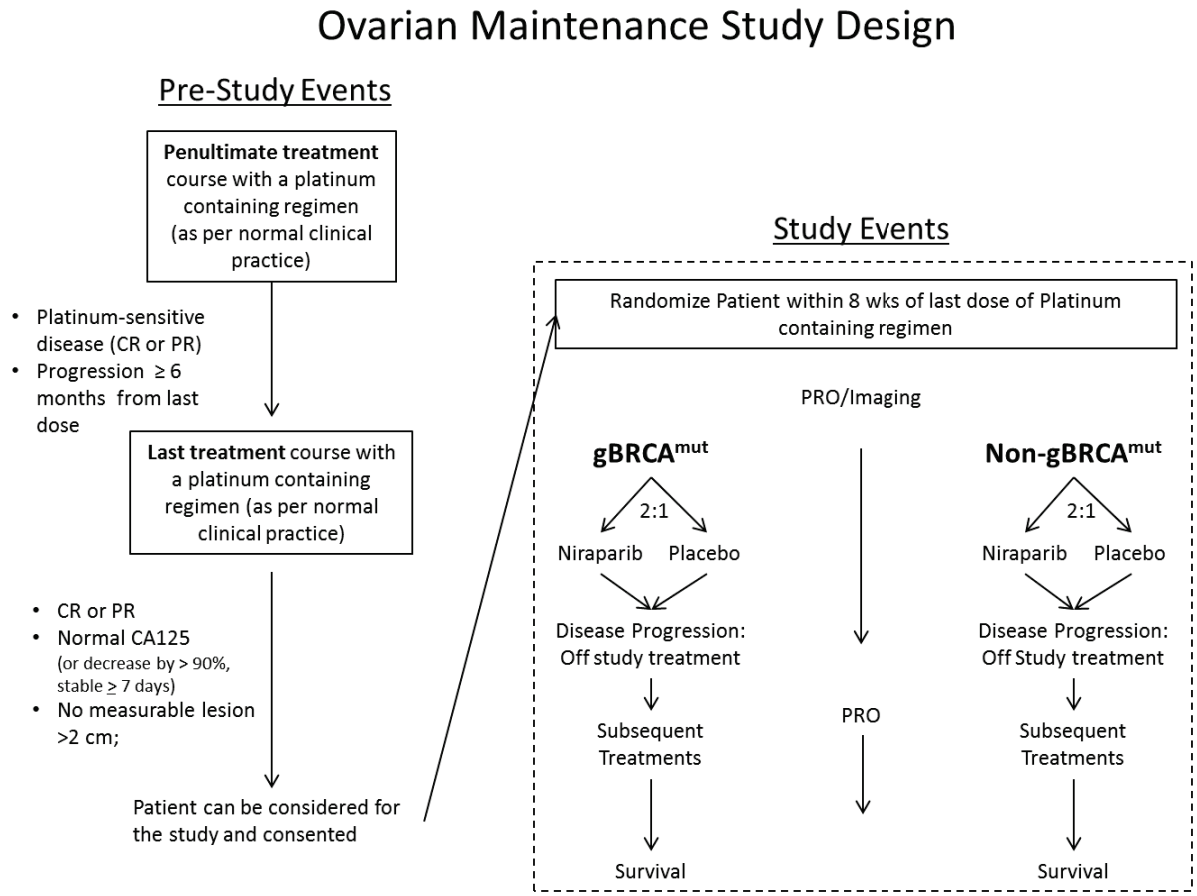
A separate randomization list will be created for each cohort. Stratification factors will include time to progression after the penultimate (next to last) platinum therapy before study enrollment (6 to < 12 months and ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no) and best response during the last platinum regimen (CR and PR). An analysis of outcome by (1) concomitant chemotherapy with platinum in the last and penultimate regimens (yes/no), and (2) number of prior platinum courses (2 and > 2) will also be performed.

A tissue sample will be sent for centralized testing to classify patients by HRD status. Testing may be completed any time prior to database lock. Details on tissue sample collection can be found in the laboratory manual.

Clinic visits will occur in each cycle (4 weeks ± 3 days). Response Evaluation Criteria in Solid Tumors (RECIST) will be used for tumor assessment via a computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas, which is required at the end of every 2 cycles (8 weeks with a window of ± 7 days from date of visit) through Cycle 14 (56 weeks), then at the end of every 6 cycles (24 weeks with a window of ± 7 days) until 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 a reason other than progression or death, withdrawal of consent, or lost 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 until the start of subsequent anticancer treatment.

PROs (FOSI; European Quality of Life scale, 5-Dimensions [EQ-5D-5L]; and a neuropathy questionnaire) will be collected in a coordinated fashion with RECIST tumor imaging while on study treatment and following discontinuation of treatment, regardless of progression status (at the nearest study visit to the imaging exam, and after every 2 cycles through Cycle 14, then after every 3 cycles). If the patient discontinues study treatment, assessment of PROs will be performed at that time and then 8 weeks (±2 weeks) later, regardless of subsequent treatment. The PROs may be completed remotely. It is estimated that PRO evaluations will take less than 20 minutes at each time point. Since these are questionnaires, their completion will not interfere with, or preclude, future treatment or clinical studies. After treatment discontinuation, study information on PROs, response, tolerability with subsequent anticancer treatment, and survival will continue to be collected (see Figure 1).

Figure 1: Study Schema



Patients will continue to receive their assigned treatment until disease progression (determined using RECIST v.1.1 criteria and clinical criteria), unacceptable toxicity, death, withdrawal of consent, or lost to follow-up, whichever comes first. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient.

At selected sites in the US, a subset of patients (approximately 36, including 24 patients enrolled in the main study and 12 enrolled in the food effect [FE] sub-study) will undergo intensive ECG monitoring to coincide with PK evaluation on Day 1. Triplicate ECGs should be performed between 2 and 5 minutes apart and should be performed prior to blood draws for PK. These patients will remain in the clinic on Day 1 and will have triplicate ECGs taken predose and at 1, 1.5, 2, 3, 4, 6, and 8 hours postdose (Day 1 only). Patients will be supine and rested for approximately 2 minutes before ECGs are recorded. The average of each of the triplicate measures will be used for analysis. This subset of patients will undergo all other assessments in the main study.

To lessen the burden of travel to the clinic site and to allow patients to continue receiving study treatment and undergo assessments on the NOVA study, the frequency of in-clinic assessments is reduced in Amendment 7. As of May 2017, there are approximately 70 patients remaining on study treatment and 210 patients in the long term follow up for the NOVA study. With the introduction of this amendment, patients who have completed at least 20 cycles of study

treatment and remain on study treatment will have an Extended Visit Cycle, which allow for the patient to have in-clinic visits approximately every 84 days, rather than every 28 days. All study procedures and assessments for the in-home visits will be completed through telephone contact and home nursing visits. The study specific procedures and assessments are not reduced with the introduction of the Extended Visit Cycle; thus there will be no impact on the collection or evaluation of safety and efficacy data for these patients.

The study sponsor, TESARO, will offer the in-home nursing visits to mitigate the need for monthly travel to the study site for evaluation. An in-home nurse will travel to the patient's home and perform study procedures on the Extended Visit Cycle; the nurse will measure vital signs, confirm that the specimens from the previous visit have been tested per protocol, collect and prepare new laboratory specimens for testing and dispense study medication. For patients who live greater than two hours from the study clinic, the Sponsor will offer the option to courier the study drug to the patient's home. The in-home nurse will ensure that the patient specimens arrive at the laboratory for testing and that the data from the patient evaluation is provided to the study site. In alignment with the timeframe of the in-home nurse visits, the site staff will contact the patient by phone to obtain the evaluation for the ECOG performance status, adverse event monitoring and concomitant medications.

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 based on their review 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. Patient outcome information will be collected during treatment as well as after treatment, including PRO, response, tolerability with subsequent anticancer treatment, and OS.

3.1.2. Food Effect Sub-Study (Study Completed)

Note: As of Amendment 3, enrollment on the FE sub-study has been completed; preliminary results indicate that the PK profile of niraparib is not affected by food intake. The description of planned assessments for these patients is retained in the protocol for completeness.

At selected sites in the US, approximately 12 patients will be enrolled into a 14-day, open-label, 2-treatment, crossover sub-study to evaluate the effect of a high fat meal on niraparib (single dose) exposure. For this FE sub-study, entry criteria will be broadened to include patients with ovarian cancer regardless of platinum sensitivity and burden of disease as long as no standard therapy exists or the patient has refused standard therapy.

Patients will be randomized to either Group A or Group B with 6 patients assigned to each group. In Group A, patients will fast (nothing to eat or drink except water) for at least 10 hours before receiving a single dose of 300 mg niraparib; patients will continue to fast for at least 2 hours following the dose. In Group B, patients will fast for at least 10 hours before consuming a high fat meal. Within 5 minutes of finishing the meal, a single dose of 300 mg niraparib will be

administered orally and patients will resume fasting for at least 4 hours. After a 7-day PK assessment and wash-out period, all patients will receive their second single dose of niraparib on Day 8 under the opposite (fasting vs high fat meal) circumstance: the previous 6 patients in Group A will receive their single dose of niraparib after a high fat meal and patients in Group B will receive their second single dose of niraparib under fasting conditions (Section 5.2).

The high fat meal (approximately 50% of total caloric content of the meal) and high calorie (approximately 800–1,000 calories) is recommended as for food-effect bioavailability and fed bioequivalence studies. This meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. An example high fat breakfast meal is 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.[16]

Niraparib will be administered in the clinical facility. After administration of niraparib, an examination of the oral cavity is required to verify that a patient has swallowed the capsules. The patient should drink the entire aliquot of water given to swallow the capsules. The examiner should have the patient open the mouth and stick out the tongue far enough to permit visualization of the posterior most part of the tongue. A light source should be used to ensure complete visualization and in some cases it may be necessary to use a tongue blade. The patient should be directed to move the tongue up and then from side to side. It may be necessary to use a tongue blade to move the tongue far enough to permit full visualization of the area under the tongue. The tongue blade should then be used to inspect the sulcus between the gums and the inner cheeks in all 4 quadrants. The patient should then be asked to lift the upper and lower lips to permit visualization of the sulcus between the inner lip and the gums.

For the FE sub-study, if emesis should occur within 4 hours of dosing, this patient will be considered non-evaluable from a PK perspective and will need to be replaced.

FE sub-study patients will undergo intensive (triplicate) ECG monitoring on FE Days 1 and 8 at baseline (predose) and 1, 1.5, 2, 3, 4, 6, and 8 hours postdose to coincide with blood sampling for PK determination. Triplicate ECGs should be performed between 2 and 5 minutes apart and should be performed prior to blood draws for PK. Patients will be supine and rested for approximately 2 minutes before ECGs are recorded. The average of each of the triplicate measures will be used for analysis. Additional blood samples for PK will be collected at 12, 24, 48, 72, 96, and 120 hours postdose on FE Days 1 and 8; predose and 2 hours postdose on Cycle 1/Day 1 and Cycle 2/Day 1; and predose (only) on Cycle 4/Day 1 and Cycle 8/Day 1.

Upon completion of the 14-day FE sub-study, participating patients will then conform to the schedule in the main study on Cycle 1/Day 1 (approximately 2 weeks after the start of the FE sub-study) and will begin dosing with open-label niraparib at 300 mg once daily (QD). These 12 patients will only be assessed for safety for the duration of the study and may continue until Investigator-determined progression.

3.2. Justification of Study Design and Choice of Endpoints

Platinum-containing regimens are considered the treatment of choice for recurrent ovarian cancer patients who are platinum sensitive. However, studies demonstrate that the PFS times for

patients are relatively short after treatment, so there is a need to find treatments that will prolong the progression free interval.

The current study design allows patients to complete their platinum-containing regimen prior to enrollment. Niraparib has demonstrated significant anti-tumor activity in patients with platinum sensitive ovarian cancer. In Protocol PN001, a Phase 1 trial of niraparib, anti-tumor activity was observed for monotherapy in patients with advanced platinum sensitive and refractory tumors at various dose levels ranging from 60 to 400 mg. Among the 104 patients enrolled in this study, including diverse malignancies and clinical presentations, 14 patients achieved confirmed or unconfirmed PR by RECIST v.1.1 and/or by CA-125 criteria. Six of 10 patients (60%) with platinum sensitive ovarian cancer achieved response. The 300 mg QD dose was chosen based on the efficacy, PK/pharmacodynamics, safety, and tolerability profiles of niraparib in early clinical testing.

The proposed study design incorporates what has been learned previously in similar studies. A key focus of this study will be on patients with high-grade serous or high-grade predominantly serous ovarian cancer and gBRCA^{mut}. Based on data from the completed dose escalation study with niraparib as well as data from clinical studies with the PARP inhibitor olaparib [11,12,14], it is believed that the subset of patients with gBRCA^{mut} will be enriched for response to PARP inhibition. The Myriad BRACAnalysis® test has been developed to determine gBRCA^{mut} status of individual tumors and identify patients likely to respond to PARP inhibitor treatment. Furthermore, recent studies have demonstrated a high incidence of HRD^{+} in tumors that are responsive to platinum and are non-gBRCA^{mut} from patients with high grade serous histology.[3,17] HRD^{+} status may explain the sensitivity of non-gBRCA^{mut} patients to treatment with PARP inhibitors.[3] A molecular classifier has been developed to determine HRD status of individual tumors and identify patients likely to respond or be resistant to PARP inhibitor treatment. Therefore, the broader population of patients with platinum sensitive, relapsed, high grade serous or high grade predominantly serous ovarian cancer in response to a platinum-based regimen will be evaluated utilizing a design that incorporates a patient enrichment strategy to prospectively identify, independently randomize, and independently evaluate gBRCA^{mut} and non-gBRCA^{mut} cohorts. Within the non-gBRCA^{mut} cohort, the primary PFS analysis will also prospectively identify HRD^{+} patients and hierarchically evaluate the non-gBRCA^{mut} HRD^{+} (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) subgroup and the full non-gBRCA^{mut} cohort.

4. STUDY POPULATION

4.1. Inclusion Criteria

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

1. Female, age at least 18 years
2. Patient agrees to undergo analysis of their gBRCA status. (Testing must be completed prior to randomization. The sample may be submitted at any time prior to the screening period if it appears patient is likely to meet other eligibility requirements. To facilitate early testing, a separate informed consent form [ICF] specific for genotyping will be available to be signed prior to gBRCA status testing.)
3. Histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
4. High grade (or Grade 3) serous or high grade predominantly serous histology or known to have $gBRCA^{mut}$
5. Patients must have completed at least 2 previous courses of platinum-containing therapy (eg, carboplatin, oxaliplatin, or cisplatin):
    a. For the penultimate (next to last) platinum-based chemotherapy course prior to enrollment on the study:
        i. A patient must have platinum sensitive disease after this treatment; defined as achieving a response (CR or PR) and disease progression > 6 months after completion of their last dose of platinum therapy (document 6-12 months or > 12 months). (Source documentation required and may include physician or clinic notes.)
    b. For the last chemotherapy course prior to being randomized in the study:
        i. Patients must have received a platinum-containing regimen for a minimum of 4 cycles
        ii. Patients must have achieved a partial or complete tumor response
        iii. Following the last regimen, patients must have either
            1. CA-125 in the normal range OR
            2. CA-125 decrease by more than 90% during their last platinum regimen which is stable for at least 7 days (ie, no increase > 15%)
        iv. Following the last regimen, patients must not have any measurable lesion > 2 cm at the time of study entry
    c. Patients must be randomized within 8 weeks after completion of their final dose of the platinum-containing regimen.

Note: The last platinum regimen does not necessarily have to immediately follow the next to last (penultimate) platinum regimen. For example, if a patient received a non-platinum regimen between the penultimate platinum regimen and last platinum regimen, they could be eligible, so long as they meet all entry criteria

6. The patient agrees to complete PROs during study treatment and at 1 additional time point 8 weeks following study treatment discontinuation. It is estimated that completion of PROs will take less than 20 minutes at each time point. Since these are questionnaires, their completion will not interfere with, or preclude, future treatment or clinical studies
7. Formalin fixed, paraffin-embedded archival tumor available from the primary or recurrent cancer required for all patients
8. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
9. Adequate organ function
    a. Absolute neutrophil count (ANC) ≥ 1,500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin ≥ 9 g/dL
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation
    e. Total bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ 1 x ULN
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN
10. Able to take oral medications
11. Women of childbearing potential must use adequate birth control for the duration of study participation (Section 4.3)

4.1.1. Additional Inclusion Criteria for Food Effect Sub-Study

With the exception of inclusion criteria 2, 4, 5, 6, 7, and 8 (above), all main study inclusion criteria apply. In addition, the following inclusion criteria apply to the FE sub-study only:

1. Entry criteria are broadened to include patients with ovarian cancer regardless of platinum sensitivity and burden of disease as long as no standard therapy exists or the patient has refused standard therapy.
2. ECOG 0-2
3. Must be able to eat a high fat meal and fast for 12 hours

4.2. Exclusion Criteria

Patients will not be deemed eligible for entry into this study if any of the following criteria are met:

1. Drainage of ascites during last 2 cycles of last chemotherapy
2. Palliative radiotherapy within 1 week encompassing > 20% of the bone marrow
3. Persistent > Grade 2 toxicity from prior cancer therapy
4. Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled", central nervous system (CNS) disease must have undergone treatment [eg, radiation or chemotherapy] at least 1 month prior to study entry. The patient must not have any new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids.) A scan to confirm the absence of brain

metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease (SD) for 28 days.

5. Known hypersensitivity to the components of niraparib
6. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery
7. Diagnosis, detection or treatment of invasive cancer other than ovarian cancer ≤ 2 years prior to randomization (except basal or squamous cell carcinoma of the skin that has been definitively treated)
8. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
9. History or current evidence of any condition, therapy, or lab abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study treatment, or is not in the best interest of the patient to participate
    - Patients must not have received a transfusion (platelets or red blood cells) within 4 weeks of the first dose of study treatment
10. Patient is pregnant or breast feeding, or expecting to conceive children within the projected duration of the study treatment
11. Immunocompromised patients (Note: patients with splenectomy are allowed.)
12. Patients with known active hepatic disease (ie, Hepatitis B or C)
13. Prior treatment with a known PARP inhibitor
14. Patients with a baseline QT prolongation > 470 milliseconds
15. Patients are receiving concomitant medications that prolong QTc and are unable to discontinue use for the duration of the study (see Appendix 8 for a list)

4.2.1. Additional Exclusion Criteria for Food Effect Sub-Study:

With the exception of exclusion criteria 1 and 13 (above), all main study exclusion criteria apply. In addition, the following exclusion criteria apply to the FE sub-study only:

1. Chemotherapy within 3 weeks of study start
2. Patient taking a proton pump inhibitor, antacids, or H2 blocker within 48 hours of dose

4.3. Restrictions During Study

1. Patients of child bearing potential and their partners who are sexually active (exception: abstinence for the total duration of the trial, defined as the time from the patient's signing of the main ICF through the drug washout period which is at least 90 days) must agree to

the use of 2 highly effective forms of contraception throughout their participation during the study treatment and for 90 days after last dose of study treatment(s):

a. Condom with spermicide and 1 of the following:
   - Oral contraceptive or hormonal therapy (eg, hormone implants)
   - Placement of an intrauterine device (IUD)

Acceptable non-hormonal birth control methods include:

a. Total sexual abstinence for the total duration of the trial, defined as the time from the patient's signing of the main ICF through the drug washout period. The washout period for niraparib is at least 90 days
b. Vasectomised sexual partner plus male condom with spermicide and participant assurance that partner received post-vasectomy confirmation of azoospermia
c. Tubal occlusion plus male condom with spermicide
d. IUD plus male condom with spermicide

Acceptable hormonal methods include:

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

2. No other anticancer therapy is permitted during the course of the study treatment for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to enrollment, as per exclusion criteria above). If the patient discontinues study treatment, this restriction no longer applies, however the patient will remain enrolled in the study for the purpose of collecting subsequent outcomes, including tolerance of subsequent anticancer treatments. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present
3. Prophylactic cytokine (granulocyte colony-stimulating factor [GCSF]) administration should not be given in the first cycle of the study, but may be administered in subsequent cycles according to local guidelines
4. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown and therefore they should not be administered to patients in the study
5. Patients participating in the FE sub-study are not permitted to take a proton pump inhibitor, antacids, or H2 blocker within 48 hours of dose (FE Days 1 and 8)
6. Patients who are blood donors should not donate blood during the study and for 90 days after the last dose of study treatment

4.4. Patient Withdrawal and Replacement

4.4.1. Discontinuation from Treatment

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

- Any treatment-related Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 events that have not reverted to CTCAE Grade 1 or better within 4 weeks (28 days) of dose interruption. At the Investigator's discretion, following dose interruption (no longer than 28 days), patients may be considered for dose reductions, providing they have not already undergone the maximum number of 2 dose reductions allowed. If upon re-challenging with study treatment at the lowest allowable dose, any CTCAE Grade 3 or 4 AEs recur, the patient must be discontinued
- If the platelet count has not reverted to > 100,000 within 4 weeks (28 days) of dose interruption, the patient should be discontinued
- Disease progression according to RECIST v.1.1 criteria or clinical criteria
- Risk to patients as judged by the Investigator and/or Sponsor
- Severe non-compliance with the protocol as judged by the Investigator and/or Sponsor
- Patient request
- The patient becomes pregnant

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

4.4.2. Discontinuation from the Study

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

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

Patients who withdraw from the main study will not be replaced. In the FE sub-study, at the discretion of the Sponsor, replacement patients may be used.

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

4.5. Planned Sample Size and Number of Study Centers

The primary analysis of PFS will be based on 180 patients randomized in the gBRCA^{mut} cohort and up to 310 patients randomized in the non-gBRCA^{mut} cohort for a total of 490 patients. Enrollment is expected to occur over approximately 24 months for gBRCA^{mut} and 20 months for non-gBRCA^{mut}. An additional approximately 12 patients will be enrolled into the open-label, crossover, FE sub-study. Thus, a total of approximately 502 patients is the target for enrollment in this study.

At selected sites in the US, a subset of approximately 36 patients will undergo intensive PK/ECG monitoring on Day 1 only; 24 of these patients will be enrolled from the main study and 12 patients from the open-label FE sub-study. There will be approximately 100 centers worldwide.

4.6. Patient Identification and Randomization

4.6.1. Patient Identification

All patients who enter into the Screening Period of the study (defined as the point at which the patient signs the main ICF) will receive a unique patient identification number. This number will be used to identify the patient throughout the study and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the entire study; it must not be changed at the time of enrollment or randomization. This number will not necessarily be the same as the randomization numbers for the study.

4.6.2. Randomization Scheme

For the main study, patients will be randomized (must occur within 72 hours prior to first dose) using a 2:1 allocation ratio to niraparib:placebo. A 2:1 allocation ratio is being used as it is believed it will improve recruitment. A separate randomization list will be created for each cohort. Stratification factors will include time to progression after the penultimate platinum therapy before study enrollment (6 to < 12 months and ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (CR and PR).

Patients with Integrated BRACAnalysis® result will be assigned within a gBRCA^{mut} cohort or a non-gBRCA^{mut} cohort as per Table 2.

For the FE sub-study (selected US sites only), patients will be randomized into 2 sequence groups (Group A or Group B) with 6 patients per group, 12 in total (Section 5.2).

Each patient who completes the study screening assessments, meets all eligibility criteria, and is accepted for the main study will be assigned a unique identification number and will receive the corresponding treatment according to a randomization scheme generated by the interactive web response system (IWRS) vendor. The randomization schedule will be prepared by the IWRS vendor using a validated program. The IWRS will assign a randomization number to patients in the main study, which will be used to link the patient to a treatment group and will specify a unique medication number for the study drug to be dispensed to the patient. Randomized patients who terminate their study participation for any reason, regardless of whether study treatment was taken or not, will retain their randomization number. IWRS personnel not involved with any of

the protocol operations will prepare the randomization schedule. The subset of patients (approximately 24 enrolled from the main study at selected sites) who will undergo intensive PK/ECG testing on Day 1 will be selected at those sites.

Patients in the FE sub-study will be randomized separately.

5. STUDY MEDICATION

5.1. Identity

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP1/2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate.

5.2. Administration

5.2.1. Main Study

In the main study, niraparib 300 mg (3 x 100 mg niraparib capsules) or placebo (3 appearance-matched capsules) will be administered orally QD continuously in a double-blind fashion. Patients will be instructed to take their dose at the same time of the day, preferably in the morning. Patients must swallow and not chew all capsules. The consumption of water is permissible. The first dose will be administered at the site.

Dose interruption (no longer than 28 days) or dose reduction (no more than 2 dose reductions) will be allowed based on treatment side effects. 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. The timing of efficacy or safety evaluations will not be affected by dose interruptions or reductions.

5.2.2. Food Effect Sub-Study (Completed)

In the open-label, crossover, FE sub-study, a single dose of niraparib 300 mg (3 x 100 mg niraparib capsules) will be administered orally on 2 separate occasions (FE Day 1 and FE Day 8) as presented below:

FE Day 1

Group A 3 x 100 mg capsules of niraparib administered orally with 240 mL of water following a minimum 10-hour overnight fast. Patients will continue to fast for at least 2 hours following the dose.

Group B 3 x 100 mg capsules of niraparib administered orally with 240 mL of water following a minimum 10-hour overnight fast. Patients will then consume a high fat meal. The dose of niraparib will be administered orally within 5 minutes of finishing the meal and they will resume fasting for at least 4 hours.

FE Day 8

Group A 3 x 100 mg capsules of niraparib administered orally with 240 mL of water following a minimum 10-hour overnight fast. Patients will then consume a high fat meal. The dose of niraparib will be administered orally within 5 minutes of finishing the meal and they will resume fasting for at least 4 hours.

Group B 3 x 100 mg capsules of niraparib administered orally with 240 mL of water following a minimum 10-hour overnight fast. Patients will continue to fast for at least 2 hours following the dose.

A 7-day PK evaluation and washout period will occur between the 2 single dose administrations. Upon completion of the 14-day FE sub-study, participating patients will begin daily dosing with niraparib 300 mg, approximately 2 weeks after the start of the FE sub-study. These patients will be assessed for safety for the duration of the study and may continue until Investigator-determined progression.

5.3. Dose Modification

Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient. Treatment must be interrupted for any non-hematologic National Cancer Institute (NCI)-CTCAE (v.4.02) Grade 3 or 4 AE which the Investigator considers to be related to administration of niraparib or matching placebo. If toxicity is appropriately resolved to baseline or Grade 1 or less within 28 days, the patient may restart treatment with niraparib or matching placebo, but with a dose level reduction according to Table 3 if prophylaxis is not considered feasible. If the event recurs at similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted.

Table 3: Dose Reductions for Non-Hematologic Toxicities

Event[1]	**Dose**[2]
Initial dose	300 mg QD
1st dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
2nd dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE ≥ 28 days	Discontinue study medication

Abbreviations: AE=adverse event; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; QD=once daily; SAE=serious adverse events

[1] Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient.

[2] Dose not to be decreased below 100 mg QD

If the toxicity requiring dose interruption has not resolved completely or to NCI-CTCAE Grade 1 during the maximum 4 week (28 day) dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib or matching placebo.

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

Table 4: Dose Modification/Reduction for Hematologic Toxicities

Finding	**Modification**
Platelet count 75,000-99,999/µL	Study medications must be interrupted until platelet counts are ≥ 100,000/µL, with weekly

	blood counts for CBC monitored until recovery. Study medication may then be resumed at same dose or reduced dose based on clinical judgment.
2nd occurrence of platelet count 75,000-99,999/µL	Study medications must be interrupted until platelet counts are ≥ 100,000/µL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at a reduced dose.
Platelet count < 75,000/µL*	Study medications must be interrupted until platelet counts are ≥ 100,000/µL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at a reduced dose.
Neutrophil < 1,000/µL	Study medications must be interrupted until neutrophil counts ≥ 1,500/µL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at a reduced dose.
Hemoglobin < 8 g/dL	Study medications must be interrupted until hemoglobin is ≥ 9 g/dL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at a reduced dose.

Abbreviation: CBC = complete blood cell count
*For patients with platelet count ≤ 10,000/µL prophylactic platelet transfusion per guidelines may be considered.[18 19] For patients taking anticoagulation or antiplatelet drugs consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤ 20,000/µL.

If dose interruption or modification is required at any point on study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for complete blood cell count (CBC) 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. Weekly blood draws for CBC can be collected either at study site or local laboratories. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib or matching placebo.

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

The patient must be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue study treatment.

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

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

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

5.4. Packaging, Labeling and Storage

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

Study treatment will be dispensed to patients on Cycle 1/Day 1 and every cycle (28 days) thereafter until the patient discontinues study treatment.

For the approximate 12 FE sub-study patients, a single dose of 300 mg niraparib will be given each on FE Days 1 and 8. After the completion of the 14-day FE sub-study, participating patients will begin dosing with niraparib at 300 mg QD on Cycle 1/Day 1, approximately 2 weeks after the start of the FE sub-study. These patients will then receive a supply of open-label niraparib on Cycle 1/Day 1 and then every cycle (28 days) thereafter until the patient discontinues study treatment.

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

5.5. Blinding and Breaking the Blind

The patient, Investigator, study coordinator(s), and the Sponsor study team and its representatives will be blinded to the identity of the assigned treatment in the main study from the time of randomization until database lock. Study treatment assignment will be available to the investigator upon request for post-study treatment planning.

The identity of the treatments will be concealed by the use of study treatments that are all identical in packaging, labeling, and schedule of administration.

Patients and investigators will not be unblinded to study treatment except in cases as determined necessary by the Investigator. The process for unblinding the identity of the assigned treatment is outlined in the Pharmacy Manual.

After the blind is broken, the Investigator (or designee) must document the reason for breaking the blind on the appropriate eCRF page. Patients who require unblinding will be discontinued from study treatment permanently but will enter long-term follow-up including overall survival.

5.6. Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study. The drug accountability log includes information including the enrollment number, amount dispensed, and amount returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as “returned” and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. The study monitor will assume the responsibility to reconcile the drug accountability log. The pharmacist will dispense study drug for each patient according to the protocol and pharmacy manual, if applicable.

5.7. Previous and Concomitant Medications

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

At Screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking. Patients must not be receiving medications that prolong QTc at Screening and for the duration of the study (see Appendix 8).

Niraparib has potential to induce cytochrome P450 (CYP)1A2; therefore, use caution with drugs metabolized by CYP1A2 (see Appendix 1). Niraparib is a substrate for P-glycoprotein; therefore, use caution with drugs that are inhibitors or substrates of P-glycoprotein. Niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs.

6. VARIABLES AND METHODS OF ASSESSMENT

A schedule of procedures is provided in Table 7, Table 8, and Table 9 .

6.1. Primary Efficacy: Progression Free Survival

Determination of the date of progressive disease (PD) will be determined by central blinded review. This review will be based first, but not exclusively, on imaging assessment according to RECIST v.1.1 (Appendix 2, Table 5) criteria. 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.

Criteria other than RECIST may be applicable to define PD; thus, PD will be determined if at least 1 of the following criteria is met:

1. Tumor assessment by CT/MRI unequivocally shows PD according to RECIST v.1.1 criteria (Appendix 2, Table 5)
    a. If a patient had a CT/MRI of the abdomen/pelvis and clinically indicated areas within the 28-day screening window before Cycle 1/Day 1 but prior to signing the main ICF, the patient is not required to complete an additional CT/MRI scan for study screening. CT/MRI scans completed during screening prior to signing the main ICF must have been performed and be able to be submitted per the image acquisition guidelines.
2. Additional diagnostic tests (eg, histology/cytology, ultrasound techniques, endoscopy, positron emission tomography) identify new lesions or determine existing lesions qualify for unequivocal PD **AND** CA-125 progression according to Gynecologic Cancer Intergroup (GCIG)-criteria (below)
3. Definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes ([1] intractable cancer-related pain; [2] malignant bowel obstruction/worsening dysfunction; or [3] unequivocal symptomatic worsening of ascites or pleural effusion) **AND** CA-125 progression according to GCIG criteria (below).

PD will not be diagnosed in case of CA-125 progression in the absence of at least 1 of the criteria defined above.

The investigator will describe why PD was diagnosed in the eCRF. The date of PD is defined as the earliest time point when one of the PD criteria is met. When required to determine progression, CA-125 levels should be evaluated ± 2 weeks from the primary PD assessments (ie, diagnostic test or clinical parameters) and must be confirmed by a second determination ≥ 7 days later. In case assessments of CA-125 levels occur greater than 2 weeks from the primary PD assessments, the date of the primary assessment of PD will be used to define the date of PD. GCIG criteria for CA-125 progression are as follows: (Note: CA-125 progression alone will not be considered disease progression.)

1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 ≥ 2 x ULN on 2 occasions at least 1 week apart, **OR**
2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 ≥ 2 x the nadir value on 2 occasions at least 1 week apart, **OR**

3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 ≥ 2 x ULN on 2 occasions at least 1 week apart.

If CT/MRI shows existing (baseline) lesions which only equivocally suggest PD and additional diagnostic tests are required to determine unequivocal PD, the official date of PD will be the date PD was unequivocally determined. Alternatively with new lesions (except ascites and effusions) that are initially equivocal that are later unequivocally determined, the date of progression will be the date the lesion was initially identified. Note: If the Investigator determines clinical PD, they can consult an imaging clinician prior to receiving results from the central reader. Pursuant to consultation with the clinician, the Investigator can keep the patient on study treatment as long as it is considered safe, or the Investigator can discontinue the patient.

The central review process will be as follows:

1. When the patient discontinues treatment and/or Investigator believes the patient has progressed, all imaging and supportive clinical data will be submitted for central review
2. RECIST imaging assessment by 2 independent radiologists along with adjudicator, if necessary
3. Central blinded clinician will review clinical information for determination of PD
4. Notify site of central PD determination
5. In the case where the Investigator determines PD (eg, RECIST PD), but central review does not determine PD, the patient may continue study treatment as long as it is considered safe and the patient continues to meet other treatment criteria. In any case, the patient should continue to undergo scheduled imaging until central PD is determined or subsequent therapy initiated

Table 5: Determination of Overall Response per Central RECIST and Central Clinical Review

Central RECIST Review	Central Clinical Review	Overall Response
PD	PD	PD
PD	SD or improvement	PD
SD, PR, CR, NE	PD	PD
SD, PR, CR, NE	SD or improvement	Per central RECIST

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

6.1.1. Central Blinded Clinician Review

The central blinded clinician will review clinical and radiographic data supporting clinical progression and will determine if the patient had protocol-defined clinical progression, and at which time points. The central blinded clinician will not provide an opinion on the presence or timing of radiographic progression. The central blinded clinician may not modify lesion selection performed by the independent radiologists. They may not select target lesions from clinical sources, even if no radiographic target lesions are present as determined by the independent radiologists. If lesions assessed by physical exam are documented by the investigator sites and the

assessments provided to the central blinded clinician, they will be assessed qualitatively and incorporated into the central blinded clinician's assessment.

6.1.2. Date of Progression

For the purpose of the primary endpoint, the date of progression will be determined using information from radiology review, the central blinded clinician, and the Investigator at the site. For radiology progression date, the central review will be used. For clinical progression, both the central blinded clinician review and the Investigator review will be used. If the Investigator does not determine clinical PD, this cannot be overturned by the central blinded clinician determination of PD. Alternatively, an Investigator assessment of PD will be invalidated if it is not substantiated by central blinded clinician. The actual date of progression will be designated by either the radiology review or the Investigator; the central blinded clinician cannot specify the date of progression, he/she can only verify whether or not PD occurred at specified dates (± 7 days). For the purpose of determining the date of progression, Table 6 will be used.

Table 6: Reference Table for Determining the Date of Progression

Central Radiology	Central Blinded Clinician	Investigator	Date of PD
PD	PD	Clinical PD	Earliest of Radiology and Investigator
PD	No PD	Clinical PD	Radiology
PD	PD	Non-PD	Radiology
PD	No PD	Non-PD	Radiology
Non-PD	PD	Non-PD	No PD
Non-PD	No PD	Clinical PD	No PD
Non-PD	PD	Clinical PD	Investigator

Abbreviations: PD = progressive disease

6.2. Secondary Efficacy

6.2.1. Concordance of BRCA Tests

For each patient in the study, baseline blood samples will be prospectively collected and archived to support the possibility of bridging the centralized BRCA mutation test used in this study to a candidate companion BRACanalysis diagnostic test. Before any of these archived samples are assayed, the single candidate companion BRACanalysis diagnostic test will be specified. These archived samples will then be evaluated by that specific candidate companion diagnostic test in a laboratory that is blinded to treatment outcomes. The concordance of the candidate companion BRACanalysis diagnostic test and the centralized BRCA mutation test used in this study, with respect to identification of $gBRCA^{mut}$ patients, will be assessed.

6.2.2. Concordance of HRD Tests

For each patient in the study, baseline archival samples will be prospectively collected and archived to support the possibility of bridging the HRD test used in this study to a candidate companion HRD diagnostic test.

6.2.3. Patient Reported Outcomes

Observed changes from baseline in the following PROs will be assessed:

1. FOSI (see Appendix 5)
2. EQ-5D-5L (see Appendix 6)
3. Neuropathy questionnaire (see Appendix 7)

The FOSI is a validated 8-item measure of symptom response to treatment for ovarian cancer.[1] Patients respond to their symptom experience over the past 7 days using a 5-point Likert scale scored from CCI (0) to CCI (4). The average score is calculated as an average of the 8 items. The total symptom index is calculated as the total of the 8 symptoms.

The EQ-5D-5L is a well validated general preference-based health-related quality of life (QoL) instrument in oncology as well as other conditions and is intended to compliment other QoL instruments.[2] It was developed to assess health outcomes from a wide variety of interventions on a common scale for purposes of evaluation, allocation, and monitoring. The EQ-5D-5L encompasses 5 domains asking patients to rate their perceived health state today on the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L domains are scored on a Likert-type scale with scores ranging from 1 to 3, with 1 associated with CCI 2 associated with CCI and 3 associated with "extreme CCI In addition, a visual analog scale (VAS) is included in the EQ-5D-5L. The VAS measures current health status on a scale from 0 to 100, where 0 is CCI and 100 is CCI

PROs (FOSI, EQ-5D-5L, and a neuropathy questionnaire) will be collected every 8 weeks for the first year, then every 12 weeks thereafter while the patient is receiving study treatment and throughout the follow-up period. Once a patient discontinues treatment, PRO evaluations will be performed at that time and one additional time 8 weeks following discontinuation.

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

An additional neuropathy questionnaire will be used.

6.2.4. Outcomes for Next Anticancer Therapy Following Study Treatment

Using source documentation (including clinic notes), the following information will be collected for the next anticancer therapy following study treatment:

- Next anticancer therapy (name and/or class)
- Date of start
- Dose limiting toxicities
- Best response (CR, PR, SD, PD)

- Date of progression

6.2.5. PFS2

PFS2 is defined as the time from treatment randomization to the earlier date of assessment of progression on the next anticancer therapy following study treatment or death by any cause.

6.2.6. Time to First Subsequent Therapy (TFST)

TFST is defined as the date of randomization in the current study to the start date of the first subsequent anticancer therapy.

6.2.7. Time to Second Subsequent Therapy (TSST)

TSST is defined as the date of randomization in the current study to the start date of the second subsequent anticancer therapy.

6.2.8. Chemotherapy Free Interval

CFI is defined as the time from last platinum dose until initiation of next anticancer therapy (excluding maintenance therapy). CFIs relative to CFI from prior chemotherapy regimens will be evaluated. Clinic notes may serve as source documentation.

6.2.9. Overall Survival Time

OS is defined as the time of randomization to the date of death by any cause. Following the treatment discontinuation visit, survival status will be collected for all patients using acceptable means including telephone contact. New malignancy information will also be collected as part of this assessment.

6.2.10. Time to CA-125 Progression

Time to CA-125 progression will be measured from time of randomization. CA-125 progression will be defined according to the following (Note: CA-125 progression alone will not be considered disease progression.):

1. Patients with elevated CA-125 pretreatment and normalization of CA-125 during treatment with niraparib/placebo must show evidence of CA-125 ≥ 2 x ULN on 2 occasions at least 1 week apart; OR
2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 ≥ 2 x the nadir value on 2 occasions at least 1 week apart; OR
3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 ≥ 2 x ULN on 2 occasions at least 1 week apart.

CA-125 levels must be normal at screening or have a >90% decrease compared to baseline prior to their last platinum-based chemotherapy course. Abnormal CA-125 levels on-study do not represent disease progression; however, they may prompt imaging if clinically indicated.

6.3. Safety Variables

6.3.1. Adverse Events

6.3.1.1. Definitions

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

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs, including intercurrent illnesses, occurring from the time of signing the main ICF through study treatment discontinuation visit will be documented in the eCRF. Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the medical history or other appropriate page.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by patient), must be documented.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least 1 dose of study treatment has been administered.

6.3.1.2. Assessment of Adverse Events

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

6.3.1.2.1. Seriousness

Serious adverse events (SAEs) will be collected from the time of signing the main ICF through treatment discontinuation. New SAEs (including deaths) will be collected for 30 days after treatment discontinuation.

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  - This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is an important medical event(s)

Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc) will not be considered an SAE; however, any AE that prolongs hospitalization will be considered an SAE. Planned hospitalizations should be captured in medical history.

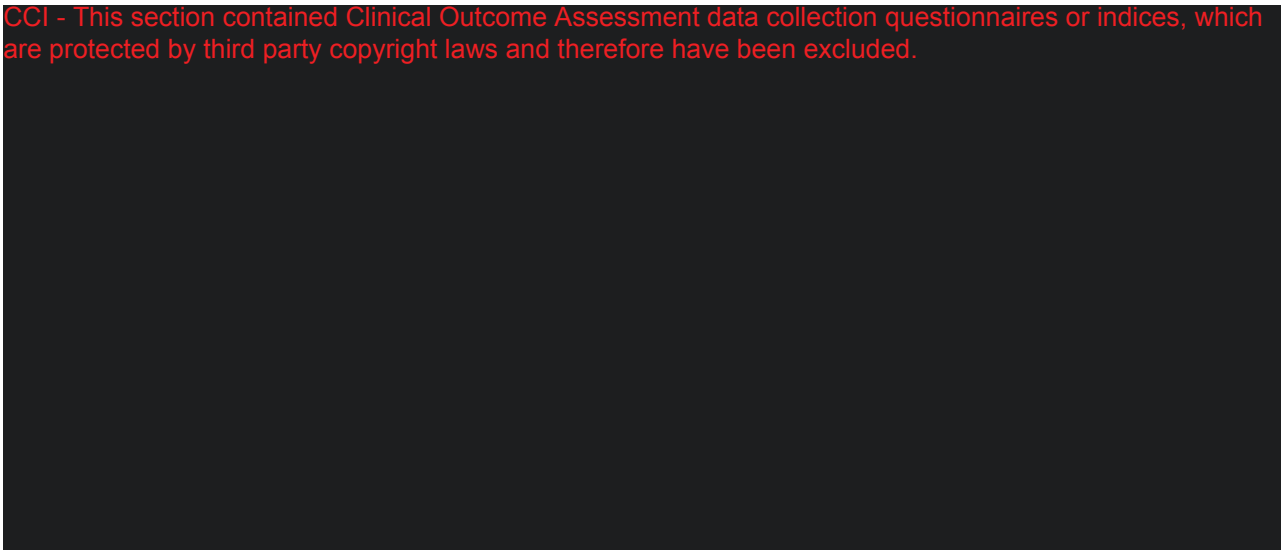
An important medical event may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm;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

A distinction should be drawn between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

6.3.1.2.2. Intensity

Investigators should assess the severity of AEs according to CTCAE (Appendix 3). In general, CTCAE v.4.02 severity grades are:



6.3.1.2.3. Causality

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

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

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

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

6.3.1.3. Recording Adverse Events

AEs and SAEs will be collected from the time of signing the main ICF through treatment discontinuation. New SAEs (including deaths) will be collected for 30 days after treatment discontinuation (see Table 7, Table 8, and Table 9 for schedules of events). SAEs assessed as related to the study medication will be reported through the end of the Post Study Treatment Assessments. SAEs can also be reported, if in the assessment of the Investigator, the SAE is related to the study medication.

AEs may be volunteered spontaneously by the patient or discovered by the study staff during physical examinations or by asking an open, non-leading question such as: "How have you been feeling since you were last asked?" All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE will be documented together with the Investigator's assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure.

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

6.3.1.4. Reporting Disease Progression

The event of disease progression is an efficacy criterion and is therefore not considered an AE. If AEs/SAEs occur in relation to disease progression, the AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 6.3.1.3 and Section 6.3.1.5, respectively.

6.3.1.5. Reporting Serious Adverse Events

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

SAE REPORTING CONTACT INFORMATION

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

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

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

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/contract research organization (CRO) will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference document (Investigator Brochure or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, this information will be reported to the relevant competent authorities and Ethics Committees as required by regulations.

All SAEs will be recorded from signing of the main ICF until 30 days following study treatment discontinuation. SAEs occurring after this 30 day period and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally related to study drug.

6.3.1.6. Follow-up of Adverse Events

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

6.3.1.7. Suspected Unexpected Serious Adverse Reactions

For any AE that is serious, associated with the use of the study treatment, and unexpected (as defined as not listed in the appropriate section of the current Investigator Brochure) additional reporting requirements are described below. These types of reports are referred to as suspected unexpected serious adverse reactions (SUSARs).

- If the SUSAR is fatal or life-threatening, associated with the use of the study treatment, and unexpected, Regulatory Authorities and Independent Ethics Committees (IECs) will be notified within 7 calendar days after the Sponsor or designee learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study treatment, and unexpected, Regulatory Authorities and IECs will be notified within 15 calendar days after the Sponsor or designee learns of the event.

The Sponsor or designee will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of patients. Follow-up information may be submitted if necessary.

The Sponsor or designee will also provide updated safety information for the study to the Regulatory Authorities and IECs responsible for the study in the Development Safety Update Report (DSUR). Information on SUSARs and other relevant safety findings will be included in the DSUR.

6.3.2. Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Each pregnancy must be reported by the Investigator to the Sponsor/CRO on an Initial Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as such in the eCRF unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

The investigator must follow up all pregnancies, document the course and the outcome, and report this information to the Sponsor on a Pregnancy Outcome Report Form within 24 hours of becoming aware - even if the patient was withdrawn from the study or the study has finished.

Elective abortion without complications should not be regarded as an AE, however, it should be reported as the pregnancy outcome on the Pregnancy Outcome Report Form.

Therapeutic abortions should be reported as a treatment procedure and the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE in the eCRF.

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

6.3.3. Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on a Serious Adverse Event Form (Section 6.3.1.5, within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded on the CRF; dosing information is recorded on the CRF.

6.3.4. Adverse Events of Special Interest

Selected non-serious AEs and SAEs are also known as Adverse Events of Special Interest (AESI) and must be recorded as such on the eCRF and reported within 24 hours to the Sponsor as noted for SAEs in Section 6.3.1.5. AESIs must be reported to the Sponsor at any time the Investigator becomes aware of them.

- MDS and AML

- Secondary primary cancers (other than MDS and AML)
- Pneumonitis
- Embryo-fetal toxicity

6.3.5. Laboratory Variables

The following laboratory variables will be determined in accordance with Table 7, Table 8, and Table 9:

Complete Blood Cell Count (CBC):

- hemoglobin
- platelets
- mean platelet volume (MPV), optional (see Section 6.3.7)
- mean corpuscular volume (MCV)
- white blood cells (WBC)
- differential white cell count

Coagulation Factors (not required during the Extended Visit Schedule):

- activated partial thromboplastin time (APTT)
- international normalized ratio (INR)

Serum Chemistry assessments for safety include:

- sodium
- potassium
- calcium
- magnesium
- chloride
- glucose
- creatinine
- total bilirubin
- gamma glutamyl transferase (GGT)
- alkaline phosphatase (ALP)
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- urea or blood urea nitrogen (BUN)
- total protein

- albumin
- lactic dehydrogenase (LDH)
- amylase

Urinalysis:

- specific gravity
- leukocyte esterase
- nitrite
- blood
- protein
- glucose
- ketones
- urobilinogen
- bilirubin

These tests will be performed by the local laboratory at the clinical site or at the laboratory local to the patient home during the Extended Visit Schedule.

In addition, serum CA-125 and serum pregnancy testing will be performed.

Hematological testing may occur more frequently than is specified in Table 7, Table 8, or Table 9 when additional testing is medically indicated per PI judgment. Additional tests may be performed at a laboratory facility other than the study site, but test results must be reported to the study site, the study site must keep a copy of test results with the patient's study file, and the results must be entered into the electronic data capture system (EDC).

For any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization (WHO) criteria[20]) and other sample testing reports related to MDS/AML. Report data will be entered into EDC on the appropriate eCRF pages and the site must keep a copy of all reports with the patient's study file.

6.3.6. Physical Examination and Vital Signs

Physical examinations and vital sign assessments will be performed in accordance with the schedule of events (Table 7, Table 8, and Table 9).

Physical examinations will be performed (including vital signs: BP, pulse, and temperature) at the screening visit and as outlined in the study schedule. If a patient develops hypertension while on study medication, the hypertension should be medically managed with antihypertensive medications as well as adjustment of the niraparib dose, if necessary.

Weight will be measured according to the study schedule. Height will be measured at screening only.

Performance status will be assessed using the ECOG scale (see Appendix 4) at screening and baseline and as outlined in the study schedules. The same observer should assess performance status each time.

6.3.7. Additional Safety Assessments

Standard 12-lead ECGs will be performed for patients in the main study in accordance with the procedures outlined in Table 7. In addition, at selected sites, a subset of patients (approximately 36, including 24 enrolled in the main study and 12 enrolled in the FE sub-study) will undergo intensive ECG monitoring to coincide with PK on Day 1 (Table 7); for this intensive ECG monitoring subset, triplicate ECGs should be performed between 2-5 minutes apart and should be performed prior to blood draws for PK. Patients will be supine and rested for approximately 2 minutes before ECGs are recorded. The average of each of the triplicate measures will be used for analysis. This subset of patients will undergo all other assessments in the main study.

For patients participating in the FE sub-study (approximately 12 at selected sites), in addition to standard 12-lead ECGs (outlined in Table 8), triplicate ECGs will be performed on FE Days 1 and 8 to coincide with PK assessments; ECG monitoring is to be completed prior to PK blood draws.

Although MPV collection is optional (see Section 6.3.5), it is highly encouraged especially for patients with high grade thrombocytopenia.

6.3.8. Concomitant Medication

Previous (within the past month) and concomitant medication will be documented as described in Section 5.7. Medications will be coded using World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification.

6.4. Demographics and Baseline Characteristics

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

6.4.1. Patient Eligibility

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

6.4.2. Patient Demography

Patient demography consists of:

- Age at screening
- Race
- Ethnicity
- Sex

6.4.3. Disease History

For disease history the following will be documented:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy, if additional biopsy performed
- Date of start of first treatment
- Agents in first treatment
- Date of last dose of first treatment
- Dates of start of all subsequent treatments
- Agents in all subsequent treatments
- Dates of last dose of all subsequent treatments
- Best response for each prior treatment
- Date of recurrence for each treatment
- ECOG performance status
- Collection of hematologic events during prior therapy

6.4.4. Medical and Surgical History

Major medical and surgical history (including medication history) will be collected. Details of any prior invasive malignancy will be collected. Medical and surgical history will be obtained by interviewing the patient or by inspecting his/her medical records.

6.5. Pharmacokinetics

In the main study, blood samples for measurements of plasma levels of niraparib and the major metabolite M1 will be obtained on Cycle 1/Day 1 and on Cycle 2, Day 1 at the following time points: 0 (predose within 30 minutes) and 2 hours(± 15 minutes) post dose. In subsequent cycles, a blood sample for measurements of plasma levels of niraparib and the major metabolite M1 will be obtained on Cycle 4/Day 1 and Cycle 8/Day 1 predose (within 30 minutes) only. In addition, a subset of patients (approximately 36, including 24 patients enrolled in the main study and 12 enrolled in the FE sub-study) at selected sites will undergo intensive PK evaluation on Day 1. In these patients blood samples for measurements of plasma levels of niraparib and the major metabolite M1 will be obtained within 30 minutes predose and at 1, 1.5, 2, 3, 4, 6, and 8 hours (± 2 minutes for all time points) postdose.

The time of last dose prior to PK blood draw should be recorded.

Model predicted AUCs will be derived. Parameters of interest are AUC, C_{min}, C_{max}, CL/F and Vz/F, AUC_{ss}, $C_{min,ss}$, $C_{max,ss}$. For the FE sub-study (approximately 12 patients, selected sites), blood samples (1 x 5 mL) will be drawn predose (30 minutes prior to dosing) and at the

following time points after each of the two single doses (FE Days 1 and 8): 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours. Additional samples for PK will be collected predose and 2 hours postdose on Day 1 of Cycles 1 and 2 and predose (only) on Cycle 4/Day 1 and Cycle 8/Day 1. The primary PK parameters for the food effect sub-study include the following: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, t_{max} and $t_{½}$.

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

6.6. Biomarkers

A biomarker classifier of DNA repair will be evaluated in tumor samples.

7. STUDY CONDUCT

7.1. Schedule of Procedures

A schedule of events for the main study is provided in Table 7. A schedule of events for patients participating in the open-label FE sub-study is provided in Table 8. A schedule of events for the extended visit cycle for patients in the main study is provided in Table 9.

Table 7 Schedule of Events – Main Study

Cycle[1]	Screening	1				2	Subsequent Cycles[2]	Study Treatment Discontinuation (visit within 7 days of last dose)	Post Treatment Assessments
Day	**-28 to -1**	**1[3]**	**8**	**15**	**21**	**1**	**Cycle n, Day 1**		
Informed Consent[4]	X								
Demographics	X								
Medical, surgical, cancer, medication history	X								
Record local gBRCA mutation result, if done[5]	X								
Blood sample for centralized gBRCA mutation testing	X[6]								
Blood sample for DNA repair typing		X							
Pregnancy test	X[7]						X[7]		

Abbreviations: C = Cycle; CA = cancer antigen; CBC = complete blood cell count; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EQ-5D-5L = European Quality of Life Scale, 5-Dimensions; FOSI = Functional Assessment of Cancer Therapy – Ovarian Symptom Index; gBRCA = germline BRCA; gBRCA^{mut} = germline BRCA mutation; ICF = informed consent form; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic(s); PRO = patient reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

[1] Treatment cycles are 28 days long, visits on Day 1 of each cycle unless otherwise specified.

[2] Visits continue every 4 weeks until study treatment discontinuation.

[3] C1/D1 is day of first dose.

[4] A separate ICF may be signed prior to the screening period for Myriad Integrated BRACAnalysis® testing in order to facilitate early testing. Depending on local site requirements, patients may sign a single study ICF prior to the screening period to facilitate early gBRCA^{mut} testing only. All other study tests and procedures must be done in the screening window (Day -28 to Day -1).

[5] Local gBRCA^{mut} results that had been performed previously should be entered into eCRF at screening.

[6] Centralized gBRCA^{mut} testing of DNA by Integrated BRACAnalysis® at Myriad must be completed prior to randomization. The sample may be submitted prior to the screening period for patients who are identified for a Screening Visit to occur. DNA from this sample will be stored and may be used at a later time for biomarker testing including potential to bridging to candidate companion diagnostic assays.

[7] Negative serum pregnancy test required within 72 hours from first dose of study treatment for females of childbearing potential; repeated every 3 months for duration of study (ie, Cycle 4, Cycle 7, etc).

Cycle[1]	Screening	1				2	Subsequent Cycles[2]	Study Treatment Discontinuation (visit within 7 days of last dose)	Post Treatment Assessments
Day	**-28 to -1**	**1[3]**	**8**	**15**	**21**	**1**	**Cycle n, Day 1**		
Randomization	X[8]								
Physical examination	X	X		X		X	X	X	
Vital signs, height, [9] weight	X	X		X		X	X	X	
ECOG performance status	X	X				X	X	X	
Adverse event monitoring	X	X		X		X	X	X[10]	
Concomitant medications	X	X		X		X	X	X	
Coagulation/serum chemistry	X	X[11]		X		X	X	X	
CBC[12]	X	X	X	X	X	X	X	X	
Serum CA-125[13,14]	X	X				X	X	X	
Urinalysis[15]	X								
12-lead ECG[16]	X	X				X		X	

[8] Randomization must occur within 72 hours prior to first dose.
[9] Height obtained at screening only.
[10] SAEs recorded up to 30 days after study treatment discontinuation.
[11] If Screening laboratory testing (serum chemistry, CBC, coagulation) performed within 72 hours of Day 1, repeat testing not required.
[12] 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 adverse event resolves, and to ensure safety of the new dose, weekly blood draws for CBC will be also be required for an additional 4 weeks after the adverse event has been resolved to the specified levels, after which monitoring every 4 weeks may resume.
[13] CA-125 levels must be normal at screening or > 90% decrease as compared with baseline prior to last platinum-based chemotherapy course. Abnormal CA-125 levels during study do not represent disease progression; however, they may prompt imaging if clinically indicated. CA-125 sample within 72 hours of dose on Cycle 1/Day 1.
[14] For determination of CA-125 progression, at least 2 CA-125 values at least 1 week apart are required for confirmation (Section 6.1).
[15] Urinalysis parameters must include: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin.
[16] Patients will have a 12-lead ECG at Screening, Baseline (predose, within 30 minutes), 2 hours postdose on Day 1(within 30 minutes), Cycle 2/Day 1, (predose, 2 hours postdose, within 30 minutes) and upon study treatment discontinuation. Note that the ECG is to be completed prior to the PK blood draw.

Cycle[1]	Screening	1				2	Subsequent Cycles[2]	Study Treatment Discontinuation (visit within 7 days of last dose)	Post Treatment Assessments
Day	**-28 to -1**	**1[3]**	**8**	**15**	**21**	**1**	**Cycle n, Day 1**		
Triplicate ECGs (selected sites only)		X[17]							
Tumor sample[18]	X								
Blood sample for PK		X[19,20]				X	X[21]		
Tumor Assessment (RECIST)[22]	X						X	X	X
Chest CT/MRI[23]	X								
FOSI, EQ-5D-5L, neuropathy questionnaire[24]	X						X	X	X

[17] At selected sites, a subset of patients (approximately 24) will undergo triplicate ECG testing on Day 1 only at baseline (predose) and 1, 1.5, 2, 3, 4, 6 and 8 hours postdose. Triplicate ECGs should be performed between 2-5 minutes apart and should be performed prior to blood draws for PK.

[18] Formalin fixed, paraffin-embedded tumor sample (primary or metastatic site) consisting of 100 micron thickness of sections (≥ 80 micron minimum) or unsectioned paraffin block.

[19] Blood samples for PK collected on Cycle 1/Day 1 and Cycle 2/Day 1 collected predose (within 30 minutes) and 2 hours postdose (within 30± 15 minutes Note: The exact time of the PK blood draw will be recorded and ECG monitoring is to be completed prior to the PK blood draw.

[20] At selected sites, a subset of patients (approximately 12) undergoing intensive PK on Day1 will have samples collected at baseline (within 30 minutes predose) and 1, 1.5, 2, 3, 4, 6 and 8 hours (± 2 minutes at all time points) postdose. Note: The exact time of the PK blood draw will be recorded and the ECG monitoring is to be completed prior to the PK blood draw.

[21] Additional blood samples for PK on Cycle 4/Day 1 and Cycle 8/Day 1 will be collected at predose (trough) within 30 minutes only.

[22] RECIST tumor assessment via CT or MRI scan of abdomen/pelvis and clinically indicated areas required at baseline, then after every 2 cycles (ie, 8 weeks with a window of ± 7 days from date of visit) through Cycle 14 (56 weeks), then after every 6 cycles (24 weeks with a window of ± 7 days) until study treatment discontinuation; at this point, a final follow-up set of imaging is required. PET/CT may be used according to RECIST guidelines. 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 confirmed or until the start of subsequent anticancer treatment.

[23] Chest CT/MRI if not done as part of RECIST tumor assessment at Screening. If the chest CT/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.

[24] PROs (FOSI, EQ-5D-5L, neuropathy questionnaire) will be collected while on study treatment every 8 weeks through the first year, then every 12 weeks thereafter. If the patient discontinues study treatment, assessment will occur at that time and then 8 weeks (± 2 weeks) later, regardless of status of subsequent treatment. PROs should be administered before conducting any other procedures.

Cycle[1]	Screening	1				2	Subsequent Cycles[2]	Study Treatment Discontinuation (visit within 7 days of last dose)	Post Treatment Assessments
Day	**-28 to -1**	**1[3]**	**8**	**15**	**21**	**1**	**Cycle n, Day 1**		
Study treatment dispensed/collected		X				X	X	X[25]	
Anti-cancer therapies assessment									X[26]
Survival assessment[27]									X
Bone marrow aspirate and biopsy		X[28]							

[25] No new capsules dispensed
[26] Every 90 days following study treatment discontinuation.
[27] In addition to survival, this assessment includes outcomes for subsequent anticancer therapies including any new malignancy information.
[28] For any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria[20]) and other sample testing results related to MDS/AML.

7.2. Procedures by Visit – Main Study

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

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

At Screening, the following procedures/tests will be performed:

- Written informed consent
  - Based on local site requirements, the following ICF procedures are acceptable:
    - Two separate ICFs will be signed. An ICF for the Myriad Integrated BRACAnalysis® test will be signed before the blood sample is drawn, prior to randomization. A main ICF will be signed prior to any other screening procedures (Day -28 to Day -1).
    - A single study ICF will be signed before any study procedures
- Demographics
- Medical/surgical/medication history, including history of prior myelosuppression (thrombocytopenia, neutropenia, leukopenia, or anemia) within the 1 year prior to signing the main ICF
- Cancer history
- Blood sample for centralized gBRCA mutation testing sent to Myriad for immediate Integrated BRACAnalysis® testing. (Testing must be completed prior to randomization. The sample may be submitted at any time prior to the screening period if it appears that the patient is likely to meet other eligibility requirements). DNA from this sample will be stored and may be used at a later time for biomarker testing including potential to bridging to candidate companion diagnostic assays
- Ascertainment of any prior gBRCA mutation test results, if performed
- Serum pregnancy test (within 72 hours prior to first dose) (for females of child-bearing potential only)
- Randomization (within 72 hours prior to first dose)
- Physical examination
- Vital signs (BP, pulse, temperature) and weight
- Height
- ECOG performance status
- CBC
- Coagulation
- Serum chemistry
- Serum CA-125

- Urinalysis (parameters must include: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen and bilirubin)
- 12-lead ECG
- Formalin fixed paraffin-embedded tumor sections of 100 micron thickness (≥ 80 micron minimum) or unsectioned paraffin block
- RECIST v.1.1 tumor assessment of the abdomen/pelvis and other areas (if clinically indicated)
- Chest CT/MRI if not done as part of RECIST tumor assessment. (If the chest CT/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)
- PROs (FOSI, EQ-5D-5L, neuropathy questionnaire).
  - Note that PROs should be administered before conducting any other procedures.
- AE monitoring
- Concomitant medications

7.2.2. Cycle 1, Day 1

- Physical examination
- Vital signs (BP, pulse, temperature, and weight)
- ECOG performance status
- AEs
- Concomitant medications
- CBC (repeat testing not required if Screening testing was done within 72 hours of Day 1)
- Coagulation (repeat testing not required if Screening testing was done within 72 hours of Day 1)
- Serum chemistry (repeat testing not required if Screening testing was done within 72 hours of Day 1)
- Serum CA-125
- 12-lead ECG predose and 2 hours postdose (prior to blood draws for PK)
- Blood sample for PK determination (predose within 30 minutes and 2 hours ± 15 minutes postdose); blood draws for PK are to be done after ECG monitoring and the exact time of the blood draw is to be recorded
- Blood sample for retrospective analysis of typing markers of DNA repair (eg, BRCA)
- For subset of patients (select sites), triplicate ECGs on Day 1 only at baseline (predose) and 1, 1.5, 2, 3, 4, 6 and 8 hours postdose

- For subset of patients (select sites) undergoing intensive PK on Day 1, blood sample at baseline (within 30 minutes predose) and 1, 1.5, 2, 3, 4, 6 and 8 hours (± 2 minutes at all time points) postdose.
- Study treatment capsules dispensed; first dose administered at the site

7.2.3. Cycle 1, Day 8

- CBC

7.2.4. Cycle 1, Day 15

- Physical examination
- Vital signs (BP, pulse, temperature) and weight
- AEs
- Concomitant medications
- CBC
- Coagulation
- Serum chemistry

7.2.5. Cycle 1, Day 21

- CBC

7.2.6. Cycle 2, Day 1

- Physical examination
- AEs
- Vital signs (BP, pulse, temperature) and weight
- ECOG performance status
- Concomitant medications
- CBC
- Coagulation
- Serum chemistry
- Serum CA-125
- 12-lead ECG predose and 2 hours postdose (prior to blood draws for PK)
- Blood sample for PK determination (predose within 30 minutes and 2 hours ± 15 minutes postdose); blood draws for PK are to be done after ECG monitoring and the exact time of the blood draw is to be recorded.
- Study treatment capsules dispensed/collected, as appropriate

7.2.7. Day 1, Subsequent Cycles

- Physical examination
- AEs
- Vital Signs (BP, pulse, temperature) and weight
- ECOG performance status
- Concomitant medications
- CBC
- Coagulation
- Serum chemistry
- Serum pregnancy test at 3 month intervals from screening (Cycles 4, 7, etc)
- Serum CA-125
- Blood sample for PK determination predose only (within 30 minutes) on Cycle 4/Day 1 and Cycle 8/Day 1 only; the exact time of the PK blood draw will be recorded
- RECIST (v.1.1) tumor assessment of the abdomen/pelvis and other areas (if clinically indicated) after every 2 cycles through Cycle 14 and then after every 3 cycles
- PROs (FOSI, EQ-5D-5L, neuropathy questionnaire) every 2 cycles through Cycle 14, then after every 3 cycles.
  - Note that PROs should be administered before conducting any other procedures
- Study treatment capsules dispensed/collected, as appropriate

7.2.8. Study Treatment Discontinuation (within 7 days of last dose)

- Physical examination
- Vital signs (BP, pulse, temperature) and weight
- ECOG performance status
- AEs (SAEs recorded 30 days post study treatment discontinuation)
- Concomitant medications
- CBC
- Coagulation
- Serum chemistry
- Serum CA-125
- 12-lead ECG
- RECIST (v.1.1) tumor assessment of the abdomen/pelvis and other areas (if clinically indicated) radiographic assessment will continue until progression in the study-specified schedule for patients terminating study for reasons other than disease progression

- PROs (FOSI, EQ-5D-5L, neuropathy questionnaire)
  - Note that PROs should be administered before conducting any other procedures.
- Study treatment capsules collected

7.2.9. Post Study Treatment Assessments (Study Visit Not Required)

- PROs (FOSI, EQ-5D-5L, neuropathy questionnaire) will be completed one additional time at 8 (± 2 weeks) weeks following the study treatment discontinuation visit.
  - Note that PROs should be administered before conducting any other procedures.
- Assessment of next subsequent anticancer therapies will be assessed every 90 days (± 28days) following study treatment discontinuation visit. The following will be collected using source documentation:
  - Next anticancer therapy (name and/or class)
  - Date of start of subsequent therapies
  - Dose limiting toxicities
  - Best response (CR, PR, SD, PD)
  - Date of progression
- Survival status will be assessed every 90 days (± 28days) following study treatment discontinuation visit. New malignancy information will also be collected as part of this assessment.

7.2.10. Unscheduled Assessments

- For any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria[20]) and other sample testing results related to MDS/AML.

Table 8 Schedule of Events – Open-Label Food Effect Sub-Study (Study Completed)

	Screening	14-Day Food Effect		Cycle1			Subsequent Cycles[2]	Treatment Discontinuation (within 7 days of last dose)
				C1		C2		
Day	**-28 to -1**	**FE 1**	**FE 8**	**1**	**15**	**1**	**Cycle n, Day 1**	
Informed Consent	X							
Demographics	X							
Medical, cancer, surgical, medication history	X							
Pregnancy test	X[3]			X[3]				
Randomization	X[4]							
Study treatment dispensed/collected		X[5]	X[5]	X		X	X	X[6]
Consumption of high fat meal, as applicable		X	X					
Physical examination	X	X		X	X	X	X	X
Vital signs, height[7], weight	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X		X	X	X
Hematology/serum chemistry	X	X	X	X	X	X	X	X
Urinalysis[8]	X							
12-lead ECG[9]	X	X[10]	X[10]	X		X		X
Blood sample for PK[11]		X	X	X		X	X	

Abbreviations: C = cycle; FE = food effect; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic(s); QD = once daily.

[1] Treatment cycles are 28 days long, visits on Day 1 of each cycle unless otherwise specified.

[2] Visits continue every 4 weeks until study treatment discontinuation.

[3] Negative serum pregnancy test required within 72 hours prior to study treatment for females of childbearing potential; repeated every 3 months for duration of study (ie, Cycle 4, Cycle 7, etc).

[4] Patients will be randomized in a crossover design within 72 hours prior to FE Day 1 (first single dose).

[5] Patients receive a single oral dose of niraparib 300 mg on FE Days 1 and 8.

[6] No new capsules dispensed.

[7] Height obtained at screening only.

[8] Urinalysis parameters must include: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen and bilirubin.

[9] 12-lead ECG at Screening, Cycle 1/Day 1 (predose and 2 hours postdose), Cycle 2/Day 1 (predose and 2 hours postdose), and at treatment discontinuation. ECG monitoring is to be performed prior to PK blood draws.

[10] Triplicate ECG monitoring to coincide with PK on FE Days 1 and 8 at baseline (predose) and at 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose. Triplicate ECGs should be performed between 2-5 minutes apart and should be performed prior to blood draws for PK.

[11] Blood samples for PK will be taken on FE Days 1 and 8 at baseline (within 30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours postdose. Additional blood samples will be collected predose and 2 hours postdose on Day 1 of Cycles 1 and 2 and predose only on Day 1 of Cycles 4 and 8. The exact time of the PK blood draw will be recorded and PK blood draws are to be completed after ECG monitoring.

Table 8 Schedule of Events – Open-Label Food Effect Sub-Study (Study Completed) (Continued)

	Screening	14-Day Food Effect		Cycle12			Subsequent Cycles[13]	Treatment Discontinuation (within 7 days of last dose)
				C1		C2		
Day	**-28 to -1**	**FE 1**	**FE 8**	**1**	**15**	**1**	**Cycle n, Day 1**	
Adverse event monitoring	X	X	X	X	X	X	X	X[14]
Concomitant medications	X	X	X	X	X	X	X	X
Bone marrow aspirate and biopsy		X[15]						
Note: Patients in food effect sub-study will receive a single oral dose of niraparib 300 mg on FE Days 1 and 8. Upon completion of the 14-day sub-study, patients will then start open-label treatment with daily niraparib (300 mg QD) on Day 1/Cycle 1 (approximately 2 weeks after start of food effect sub-study) and will be followed using the main study visit schedule for safety.								

Abbreviations: C = cycle; FE = food effect; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic(s); QD = once daily.

[12] Treatment cycles are 28 days long, visits on Day 1 of each cycle unless otherwise specified.

[13] Visits continue every 4 weeks until study treatment discontinuation.

[14] SAEs recorded up to 30 days after study treatment discontinuation.

[15] For any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria[20]) and other sample testing results related to MDS/AML.

7.3. Procedures by Visit – Food Effect Study

Visits should occur at the scheduled visit day. All times should be recorded using the 24-hour clock (eg, 23:20, not 11:20 PM).

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

At Screening, the following procedures/tests will be performed:

- Written informed consent
- Demographics
- Medical/surgical/medication history
- Cancer history
- Serum pregnancy test (within 72 hours prior to first dose)
- Physical examination
- Vital signs (BP, pulse, temperature) and weight
- Height
- ECOG performance status
- Hematology
- Serum chemistry
- Urinalysis (parameters must include: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen and bilirubin)
- 12-lead ECG
- AE monitoring
- Concomitant medications

7.3.2. Food Effect, Day 1

- Randomization (within 72 hours prior to first dose)
- Consumption of high fat meal within 30 minutes, as applicable
- Physical examination
- Vital signs (BP, pulse, temperature, and weight)
- ECOG performance status
- AEs
- Concomitant medications
- Hematology
- Serum chemistry

- Triplicate ECGs (prior to blood draws for PK) predose and at 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose (2-5 minutes between ECGs)
- Blood samples for PK determination at baseline (predose within 30 minutes) and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours postdose; blood draws for PK are to be done after ECG monitoring and the exact time of the blood draw is to be recorded
- Study treatment capsules dispensed and doses administered at site

7.3.3. Food Effect, Day 8

- Consumption of high fat meal within 30 minutes, as applicable
- Physical examination
- ECOG performance status
- Vital signs (BP, pulse, temperature) and weight
- Hematology
- Serum chemistry
- Triplicate ECGs (prior to blood draws for PK) predose and at 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose (2-5 minutes between ECGs)
- Blood samples for PK determination at baseline (predose within 30 minutes) and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours postdose; blood draws for PK are to be done after ECG monitoring and the exact time of the blood draw is to be recorded
- AEs
- Concomitant medications
- Study treatment capsules dispensed and doses administered at site

7.3.4. Cycle 1, Day 1 (Approximately 2 Weeks After Start of Food Effect Sub-Study)

- Physical examination
- ECOG performance status
- Vital signs (BP, pulse, temperature) and weight
- AEs
- Concomitant medications
- Hematology
- Serum chemistry
- 12-lead ECG predose and 2 hours postdose (prior to blood draws for PK)
- Blood sample for PK determination (predose within 30 minutes and 2 hours postdose); blood draws for PK are to be done after ECG monitoring and the exact time of the blood draw is to be recorded.
- Study treatment capsules dispensed and first dose administered at site

7.3.5. Cycle 1, Day 15

- Physical examination
- Vital signs
- AEs
- Concomitant medications
- Hematology
- Serum chemistry

7.3.6. Cycle 2, Day 1

- Physical examination
- Vital signs (BP, pulse, temperature) and weight
- ECOG performance status
- AEs
- Concomitant medications
- Hematology
- Serum chemistry
- 12-lead ECG predose and 2 hours postdose (prior to blood draws for PK)
- Blood sample for PK determination (predose within 30 minutes and 2 hours postdose); the exact time of the PK blood draw is to be recorded and is to be done following ECG monitoring
- Study treatment capsules dispensed/collected

7.3.7. Day 1, Subsequent Cycles

- Physical examination
- Vital signs (BP, pulse, temperature) and weight
- ECOG performance status
- Hematology
- Serum chemistry
- Serum pregnancy test at 3 month intervals from screening (Cycle 4, 7, etc)
- Blood sample for PK determination at predose (within 30 minutes) on Cycle 4/Day 1 and Cycle 8/Day 1 only; the exact time of the PK blood draw is to be recorded
- AEs
- Concomitant medications
- Study treatment capsules dispensed/collected, as appropriate

7.3.8. Study Treatment Discontinuation (Within 7 Days of Last Dose)

- Physical examination
- Vital signs (BP, pulse, temperature) and weight
- ECOG
- AEs
- Concomitant medications
- Hematology
- Serum chemistry
- 12-lead ECG
- Study treatment capsules collected

7.3.9. Unscheduled Assessments

- For any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria[20]) and other sample testing results related to MDS/AML.

Table 9: Schedule of Events – Main Study –Extended Visit Cycle

Cycle	Subsequent Cycles[1]	Subsequent Cycles[2]	Subsequent Cycles[3]	Study Treatment Discontinuation (visit within 7 days of last dose)	Post-Treatment Assessments
Day	**Extended Cycle, Day 1**	**Cycle n, Day 1**	**Cycle n, Day 1**		
Location	**In Clinic**	**Site Staff Telephone Contact to Patient**	**Patient Visit to Local Clinic or In-Home Nursing**	**In Clinic**	
Physical examination	X			X	
Vital signs, weight	X		X[4]	X	
ECOG performance status	X	X		X	
Adverse event monitoring	X	X		X[5]	
Concomitant medications	X	X		X	
Serum chemistry	X		X	X	
CBC[6]	X		X	X	
Serum CA-125[7,8]	X		X	X	
12-lead ECG[9]				X	
Tumor Assessment (RECIST)[10]	X			X	X
FOSI, EQ-5D-5L, neuropathy questionnaire[11]	X			X	X
Study treatment dispensed/collected	X		X	X[12]	
Anticancer therapies assessment					X[13]
Survival assessment[14]					X
Bone marrow aspirate and biopsy	X[15]				

[1] During the in-clinic visit extended cycle, all study procedures and assessments required will be performed.
[2] The study coordinator will contact the patient by telephone to obtain information for the ECOG performance status, adverse event monitoring, and concomitant medications when the study assessments are not performed in clinic.
[3] The collection of blood samples for CBC and chemistry analysis, vital signs and weight may be collected during visit to local clinic or at in-home nursing visit when the study assessments are not performed in clinic.

7.4. Procedures by Visit – Main Study Extended Visit Cycles

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

7.4.1. Day 1, Subsequent Cycles

The following study assessments will be performed during the **patient visit to local clinic or in-home nursing visit**:

- Vital Signs (BP, pulse, temperature) and weight
- CBC
- Serum chemistry
- Serum CA-125
- Study treatment capsules dispensed/collected, as appropriate

The following study assessments will be performed during the **study coordinator telephone contact to patient**:

- AEs
- Concomitant medications
- ECOG performance status

7.4.2. Day 1, Extended Cycles (every three cycles, 84 days)

The following study assessments will be performed during the **patient visit to the study site**:

- Physical examination
- AEs
- Vital Signs (BP, pulse, temperature) and weight (only measured during in-clinic visits)
- ECOG performance status
- Concomitant medications
- CBC
- Serum chemistry
- Serum CA-125
- RECIST (v.1.1) tumor assessment of the abdomen/pelvis and other areas (if clinically indicated) after every 2 cycles through Cycle 14 and then after every 3 cycles
- PROs (FOSI, EQ-5D-5L, neuropathy questionnaire) every 3 cycles.
  - Note that PROs should be administered before conducting any other procedures
- Study treatment capsules dispensed/collected, as appropriate

7.4.3. Study Treatment Discontinuation (within 7 days of last dose)

- Physical examination
- Vital signs (BP, pulse, temperature) and weight
- ECOG performance status
- AEs (SAEs recorded 30 days post study treatment discontinuation)
- Concomitant medications
- CBC
- Serum chemistry
- Serum CA-125
- 12-lead ECG
- RECIST (v.1.1) tumor assessment of the abdomen/pelvis and other areas (if clinically indicated) radiographic assessment will continue until progression in the study-specified schedule for patients terminating study for reasons other than disease progression
- PROs (FOSI, EQ-5D-5L, neuropathy questionnaire)
  - Note that PROs should be administered before conducting any other procedures.
- Study treatment capsules collected

7.4.4. Post Study Treatment Assessments (Study Visit Not Required)

- PROs (FOSI, EQ-5D-5L, neuropathy questionnaire) will be completed one additional time at 8 (± 2 weeks) weeks following the study treatment discontinuation visit.
  - Note that PROs should be administered before conducting any other assessments.
- Assessment of next subsequent anticancer therapies will be assessed every 90 days (± 28 days) following study treatment discontinuation visit. The following will be collected using source documentation:
  - Next anticancer therapy (name and/or class)
  - Date of start of subsequent therapies
  - Dose limiting toxicities
  - Best response (CR, PR, SD, PD)
  - Date of progression
- Survival status will be assessed every 90 days (± 28 days) following study treatment discontinuation visit. New malignancy information will also be collected as part of this assessment.

7.4.5. Unscheduled Assessments

- For any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria) and other sample testing results related to MDS/AML.

8. STATISTICAL METHODS

Details of the statistical analyses presented below will be provided in the study's SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report (CSR). The descriptive and analytical statistics outlined in this section will be applied separately and independently to the efficacy data generated within each of the 2 study cohorts unless otherwise indicated; demographic and safety data will be presented for each cohort separately as well as combined. Specification of which analyses and summaries will be performed separately for the gBRCA^{mut} and non-gBRCA^{mut} cohorts (HRD^{+} and full, if necessary) will be provided in the SAP.

8.1. Study Populations

The intent-to-treat (ITT) population will be defined as all patients randomized into the main study (not FE study). The ITT population is the primary analysis population for the efficacy analysis. For this analysis, patients will be analyzed as randomized.

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

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

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

Descriptive statistics will be used to summarize demographics and baseline characteristics.

Medical history, medications used prior to treatment, and concomitant medications will be summarized by treatment group.

8.3. Efficacy Analyses

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

8.3.1. Primary Efficacy Parameter

The primary endpoint is PFS, which is defined as the time from the date of treatment randomization to the date of first documentation of progression (by blinded central review) or death by any cause in the absence of documented progression whichever occurs first. For the primary analysis, PFS data will be censored according to Table 10 .

Table 10: Censoring Rules for Primary PFS Analysis

Situation	Date of Censoring
No baseline radiologic assessment	Date of randomization
No post-baseline radiologic assessment (and no death or clinical progression prior to first scheduled radiologic assessment)	Date of randomization.
No progression or death on study	Date of last radiologic assessment
Documented progression or death after two or more consecutive missing radiologic assessments	Date of last radiologic assessment
New anticancer therapy started prior to progression	Date of last radiologic assessment prior to new anticancer therapy

Within each cohort, the overall family-wise error rate will be controlled at a 1-sided alpha of 0.025.

Within the non-gBRCA^{mut} cohort, PFS will be hierarchically evaluated first in the HRD^{+} subgroup (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) and then in all non-gBRCA^{mut} patients. If the treatment effect is significant in the non-gBRCA^{mut} HRD^{+} subgroup, then PFS will be tested in the full non-gBRCA^{mut} cohort. The overall 1-sided alpha level for both tests in the non-gBRCA^{mut} cohort will be 0.025.

HRD classification HRD^{+} (gBRCA^{mut}, somatic BRCA^{mut} and HRD positive/BRCA^{wt}) or HRD^{-} will be based on results from tissue testing. Details of this testing are provided in the SAP.

The primary PFS analysis will be performed using a 1-sided log-rank test, stratified for time to progression from penultimate platinum therapy before study enrollment, use of bevacizumab in conjunction with the penultimate or last platinum regimen and best response during the last platinum regimen (CR and PR). In addition, a stratified Cox proportional hazards models will be used to estimate the treatment HR and its 95% confidence interval (CI). PFS will also be descriptively summarized using Kaplan-Meier methodology.

Subgroups will also be explored for the primary efficacy endpoint based on: age, race, geographic region, time to progression after the penultimate platinum therapy before study enrollment, use of bevacizumab in conjunction with the penultimate or last platinum regimen, best response during the last platinum regimen (CR and PR), concomitant chemotherapy with platinum in the last and penultimate regimens (yes, no), and the number of prior platinum regimens (2, >2).

8.3.2. Secondary Endpoints Analyses

Concordance of a candidate companion BRACanalysis diagnostic test with the centralized BRCA mutation test used in this study with respect to identifying gBRCA^{mut} patients may be evaluated using archived study samples. If evaluated, the sensitivity and specificity of a candidate companion BRACanalysis test to the centralized test with respect to gBRCA status will be determined along with the corresponding 95% CI.

Concordance of the companion HRD and BRACanalysis diagnostic tests may also be evaluated as described in the SAP.

The FOSI, the EQ-5D-5L, and a neuropathy questionnaire will be used in this study. Changes from baseline in overall score, sub-scores, and individual items will be analyzed descriptively by treatment group. A repeated measures model adjusting for covariates and subject evaluating change in symptoms and QoL as measured by the FOSI and the EQ-5D-5L will be conducted. Time to symptom worsening on the FOSI will be analyzed using time-to-event methodology.

PFS2, OS, CFI, and time to CA-125 progression will be analyzed using a stratified log-rank test. The stratified Cox proportional hazards models will be used to estimate the treatment HR and its 95% CI. In addition, Kaplan-Meier methodology will be used to descriptively summarize the data.

8.4. Safety Analyses

Safety and tolerability of niraparib relative to placebo will be analyzed separately for the gBRCA^{mut}, non-gBRCA^{mut}, and FE cohorts as well as overall. Incidence of TEAEs and usage of concomitant medications will be summarized by treatment group. Clinical laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group and by study visits. Descriptive summary statistics for observed values as well as changes from baseline will be presented. In addition, thresholds of marked abnormalities will be predefined for specific safety parameters. Incidence of marked abnormalities and shift tables will be presented.

8.5. Post-Treatment Analyses

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

8.6. Food Effect Analyses

The effect of a high fat meal on the PK of niraparib will be estimated by point estimates and 90% CI for the ratios of geometric means for niraparib C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. For each of the PK parameters, a general linear model will be used to account for the following sources of variation: sequence, patient nested in sequences, period, and treatment (fasted/fed). C_{max} and AUC will be log-transformed prior to analysis.

8.7. QTc Analyses

Descriptive statistics and categorical analyses of ECG variables will be provided for the subset of patients (approximately 36) with intensive ECG collection.

A separate population PK analysis plan will be written to describe the analyses of ECG variables and PK parameters.

8.8. Interim Analyses

An interim analysis will not be performed for this study.

8.9. Determination of Sample Size

The following hypothesis will be tested for each cohort using a stratified log-rank test:

H_0: $PFS(t)_{placebo} = PFS(t)_{niraparib}$

H_a: $PFS(t)_{placebo} < PFS(t)_{niraparib}$

where PFS(t) represents the progression free survivorship function at time, t.

The gBRCA^{mut} and non-gBRCA^{mut} cohorts are treated as 2 independent cohorts/studies where each cohort is allocated 1-sided alpha = 0.025. Each cohort will have a separate randomization and the primary PFS analysis will be performed separately for each cohort. It is anticipated a priori that niraparib will have a positive effect in each cohort. The gBRCA^{mut} cohort is conservatively powered by assuming an HR of 0.5, to ensure a robust dataset to address the PFS endpoint and ensure adequate data to monitor safety and OS. The sample size assumptions are primarily based on a Phase 2 study of maintenance therapy in 265 patients with relapsed, platinum sensitive ovarian cancer where daily olaparib therapy compared to placebo treatment was associated with a PFS benefit (HR = 0.35).[14] The subset of patients with known gBRCA^{mut} (approximately 22% of the patients) had a PFS HR = 0.18.[15]

The gBRCA^{mut} cohort sample size is determined based on the assumption that niraparib will result in an improvement in median PFS of 4.8 to 9.6 months (corresponding to a HR = 0.50) (niraparib relative to placebo). For a true HR = 0.50, 100 PFS events in the gBRCA cohort, to maintain 90% power assuming a 2:1 randomization (1-sided alpha=0.025). It is assumed that 180 gBCRA^{mut} patients will be enrolled over approximately 24 months.

The non-gBCRA^{mut} sample size was determined to maintain consistency with the intended hierarchical testing procedure under the assumption that approximately 40% of the non-gBRCA^{mut} cohort is expected to be classified as HRD^{+}. PFS sample size for the HRD^{+} subgroup (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) is determined based on the same PFS assumption used for the gBRCA^{mut} cohort. For a true HR = 0.50, based on a median PFS of 9.6 months for the niraparib-treated patients and 4.8 months for placebo patients, in the non-gBRCA^{mut} cohort who are HRD^{+}, 98 PFS events will provide 90% power assuming a 2:1 randomization (1-sided alpha = 0.025). A total of approximately 310 patients will be enrolled into the non-gBRCA^{mut} cohort in order to obtain a sufficient number of events in the HRD^{+} subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}).

In addition, approximately 12 patients will be enrolled into the open-label food effect sub-study. At least 10 fully evaluable patients (defined as completing both the fasted and fed portion) are targeted to appropriately test for comparison between the fasted and fed states. If the number of evaluable patients falls below 10, replacement patients may be used at the discretion of the Sponsor. This is a descriptive sub-study and no formal sample size calculations were performed.

9. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1. Data Quality Assurance

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

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

All aspects of the study will be carefully monitored with respect to Good Clinical Practices (GCP) and standard operating procedures (SOPs) for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator or designee.

9.2. Access to Source Data/Documents

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

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

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

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

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

9.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

9.4. Good Clinical Practice

This study will be conducted in accordance with ICH GCP and the Declaration of Helsinki (Version 2008). The clinical study will also be carried out in keeping with national and local regulatory requirement(s).

9.5. Informed Consent

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

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

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

9.6. Protocol Approval and Amendment

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

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients with appropriate instructions.

9.7. Independent Data Monitoring Committee

An 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 based on their review to continue or stop the trial based on their assessment of efficacy and safety information.

9.8. Study Monitoring

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

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and by communications (letter, telephone, and fax).

All unused study treatment and other study materials will be returned to the Sponsor after the clinical phase of the study has been completed.

9.9. Audits and Inspections

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

9.10. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (Version 2008). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

9.11. Publication Policy

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

10. REFERENCES

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APPENDIX 1. DRUGS KNOWN TO INHIBIT OR INDUCE CYP1A2

Inhibitors of CYP1A2		
Strong ≥ 5-fold increase in AUC or >80% decrease in CL	**Moderate** ≥ 2-fold but < 5-fold increase in AUC or 50% to 80% decrease in CL	**Weak** ≥ 1.25-fold but < 2-fold increase in AUC or 20% to 50% decrease in CL
Ciprofloxacin, enoxacin, fluvoxamine	methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton	acyclovir, allopurinol, caffeine, cimetidine, daidzein, disulfiram, echinacea, famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
Inducers of CY1A2		
Strong 80% decrease in AUC	**Moderate** 50% to 80% decrease in AUC	**Weak** 20% to 50% decrease in AUC
	Montelukast, phenytoin, smokers vs non-smokers	moricizine, omeprazole, phenobarbital
Substrates of CYP1A2		
Sensitive substrates[1]		**Substrates with narrow therapeutic range**[2]
Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine		Theophylline, tizanidine, Warfarin

Abbreviations: AUC=area under the curve; CL=clearance; CYP=Cytochrome P450

[1] *Sensitive CYP substrates* refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor or AUC ratio in poor metabolizers vs extensive metabolizers is greater than 5-fold.

[2] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

Source: [21]

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

Response Criteria by RECIST v.1.1 [22]

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

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

Table 11: For Patients with Measurable Disease (ie, Target Disease)

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

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

Table 12: For Patients with Non-Measurable Disease (ie, Non-Target Disease)

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

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

Duration of Response

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

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

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

APPENDIX 3. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) V.4.02

http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

APPENDIX 4. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

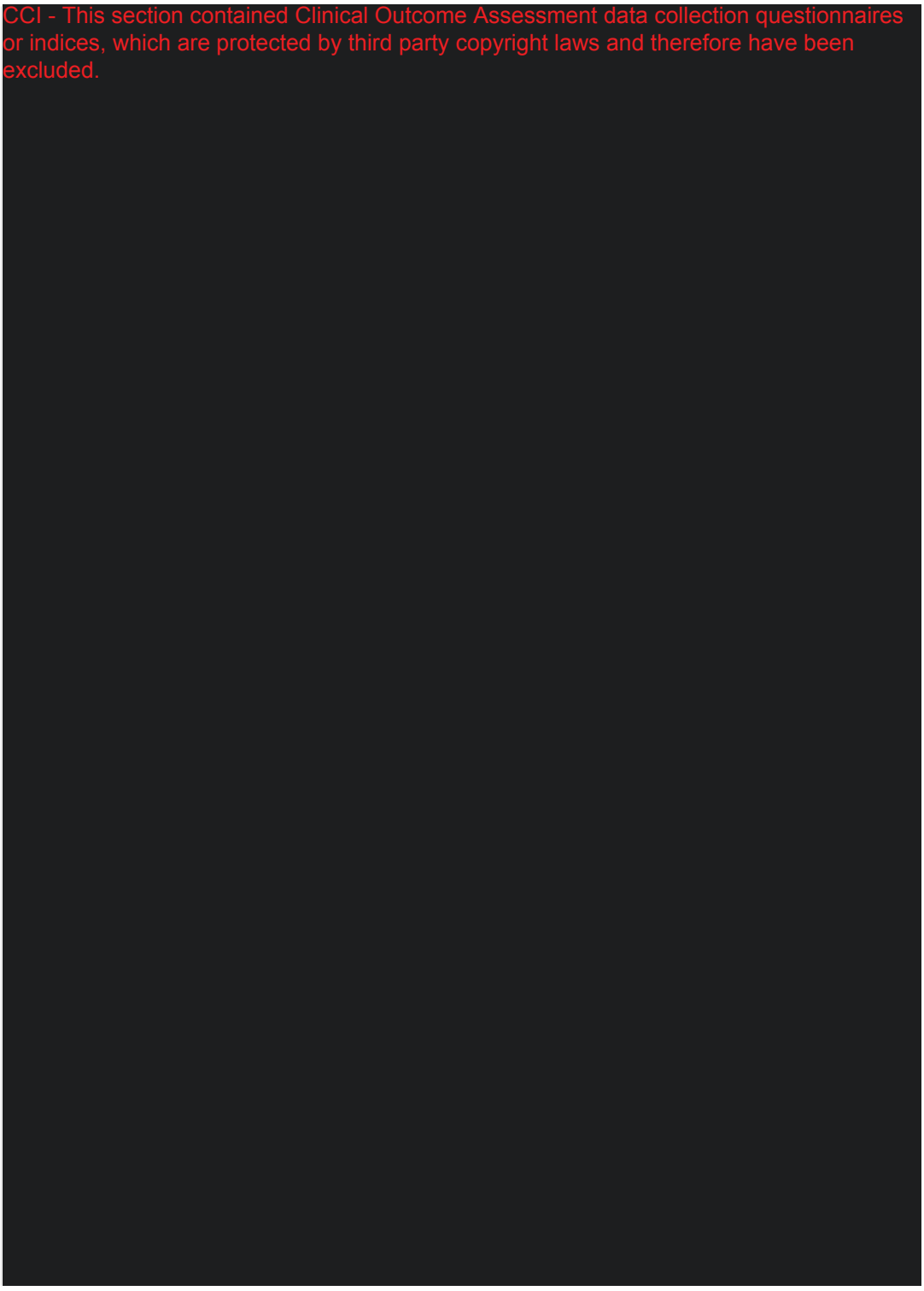
APPENDIX 5. SAMPLE FUNCTIONAL ASSESSMENT OF CANCER THERAPY – OVARIAN SYMPTOM INDEX (FOSI)

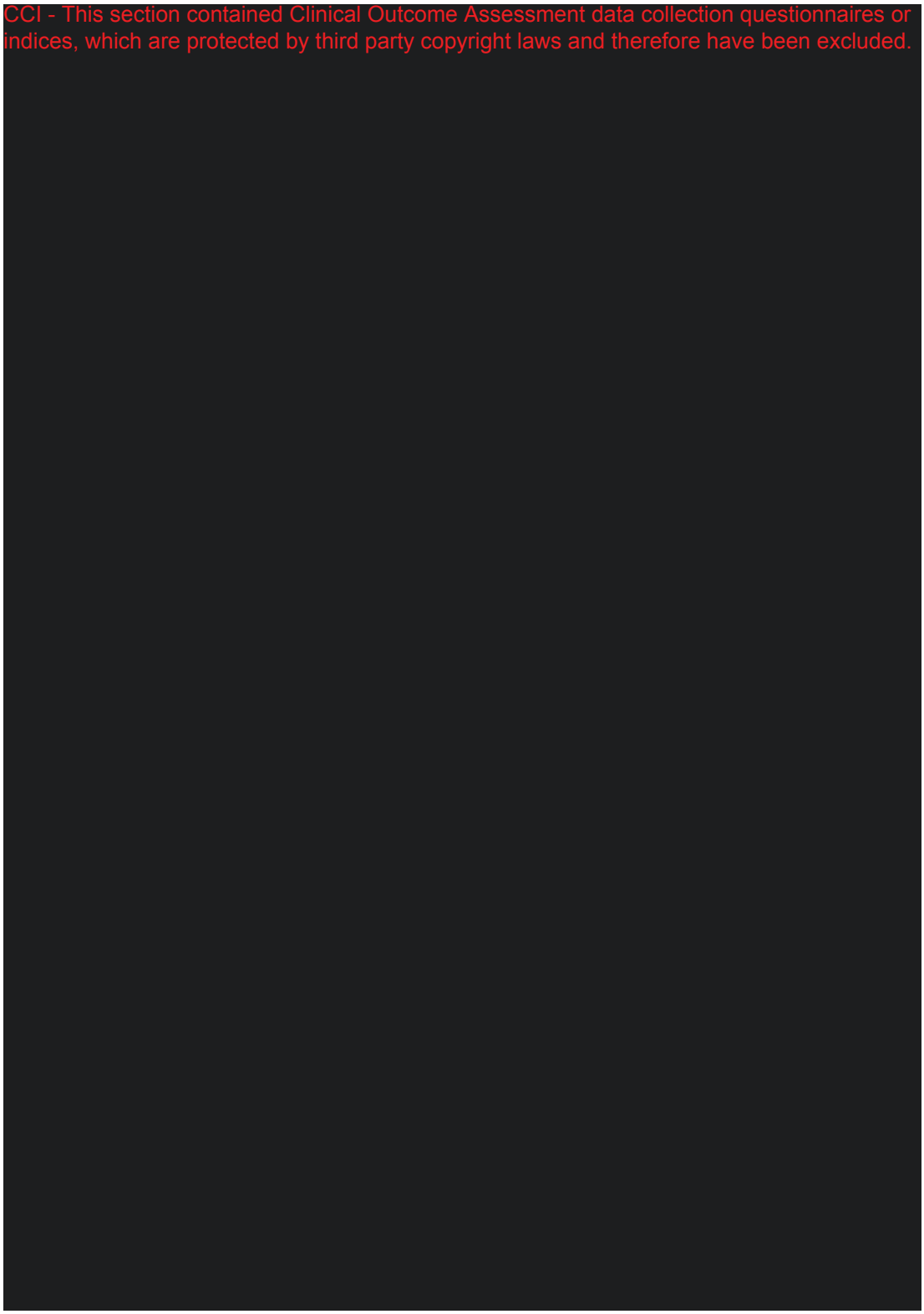
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

APPENDIX 6. SAMPLE EUROPEAN QUALITY OF LIFE SCALE, 5-DIMENSIONS (EQ-5D-5L)

Health Questionnaire

English version for the USA


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


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

APPENDIX 7. NEUROPATHY QUESTIONNAIRE

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

APPENDIX 8. DRUGS ASSOCIATED WITH QT PROLONGATION AND TORSADES DE POINTES

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others (including Selected Antiemetics)
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Doxepin	Droperidol	Sumatriptan
Quinidine	Gatifloxacin		Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin		Thioridazine	Arsenic
Dofetilide	Clarithromycin		Ziprasidone	Dolasetron
Ibutilide	Erythromycin			Methadone
	Ketoconazole*			
	Itraconazole			

*Topical use only allowed for ketoconazole

Sources: [24,25]