# A Phase 2, Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Niraparib in Patients with Advanced, Relapsed, High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Have Received Three or Four Previous Chemotherapy Regimens

| | | |
|---|---|---|
| Sponsor: | TESARO, Inc.<br>1000 Winter Street<br>Suite 3300<br>Waltham, MA 02451<br>PPD | TESARO UK, Limited<br>21 Holborn Viaduct<br>London<br>EC1A2DY United Kingdom<br>PPD |
| Medical Monitor | PPD MD<br>Senior Medical Director<br>PPD | |
| Clinical Research Organization: | PAREXEL International, LLC<br>195 West Street<br>Waltham, MA 02451 | |
| Sponsor Protocol No.: | PR-30-5020-C | |
| IND No.: | 100,996 | |
| EudraCT No.: | 2014-005478-12 | |
| Study Drug Name: | Niraparib capsules | |
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| Date of Amendment 3.1: | 7 September 2016 | |
| Date of Amendment 3.2: | 14 September 2016 | |
| Date of Amendment 4: | 7 April 2017 | |
| Date of Amendment 5: | 21 December 2017 | |
| 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.*

**Confidentiality Statement**

# SPONSOR SIGNATURE PAGE

**Declaration of Sponsor or Responsible Medical Officer**

**Title:** A Phase 2, Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Niraparib in Patients with Advanced, Relapsed, High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Have Received Three or Four Previous Chemotherapy Regimens

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 general ethical, and scientific principles governing clinical research as [illegible]i and the guidelines on Good Clinical Practice.

PPD

12/21/2017

PPD MD
Date

Senior Medical Director
TESARO, Inc.

# INVESTIGATOR SIGNATURE PAGE

**Declaration of the Principal Investigator**

**Title:** A Phase 2, Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Niraparib in Patients with Advanced, Relapsed, High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Have Received Three or Four Previous Chemotherapy Regimens

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

**Principal Investigator**

_____ _____

**Name:** **Date**
**Title:**
**Institution:**

# SYNOPSIS

| | |
|---|---|
| **Name of Sponsor/Company:** TESARO, Inc. | |
| **Name of Investigational Product:** Niraparib | |
| **Name of Active Ingredient:** Niraparib | |
| **Title of Study:** A Phase 2, Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Niraparib in Patients with Advanced, Relapsed, High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Have Received Three or Four Previous Chemotherapy Regimens | |
| **Study Center(s):** Approximately 60 sites | |
| **Studied Period (years):**<br>Estimated date first patient enrolled: March 2015<br>Estimated date last patient enrolled: December 2017 | **Phase of Development:** 2 |

**Objectives:**

Primary Objective:

To evaluate the Objective Response Rate (ORR) of niraparib in HRD-positive patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy.

Key Secondary Objectives:

- To evaluate the ORR of niraparib in all patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy.
- To evaluate the ORR of niraparib in all patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive or platinum-resistant to the last platinum-based therapy.
- To evaluate the ORR of niraparib in all patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Other Secondary Objectives:

- To evaluate the efficacy (ORR, DOR, DCR, PFS, TFST and OS) of niraparib in patients who have received 3 or 4 prior lines of anti-cancer therapy
- To evaluate the efficacy (ORR, DOR, DCR, PFS, TFST and OS) of niraparib in all patients regardless of prior lines of anti-cancer therapy.
- To evaluate the safety and tolerability of niraparib

Exploratory Objectives:

- To evaluate the efficacy and safety of niraparib in all patients who are platinum-refractory to the last platinum-based therapy.

- To evaluate the efficacy and safety of niraparib in all patients with prior PARP treatment.
- To evaluate QTc in a subset of niraparib-treated ovarian cancer patients
- To assess population pharmacokinetics (PK) and estimate PK parameters for niraparib and its major metabolite
- To explore potential biomarkers related to ovarian cancer and poly(ADP-ribose) polymerase (PARP) inhibition (e.g. DNA repair pathways)

**Methodology:**

This study is a multicenter (United States and Canada), open-label, single-arm, Phase 2 study evaluating the safety and efficacy of niraparib in patients with advanced, relapsed, HRD-positive (as identified with a centralized HRD test), high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were previously treated with chemotherapy and experienced a response lasting at least 6 months to first-line platinum-based therapy. Patients must have received 3 or 4 previous chemotherapy regimens.

In order to determine eligibility, a tumor sample will be sent to a centralized laboratory for t*BRCA*$^{mut}$ and HRD testing. Archival or fresh tissue is required in order to enroll in the study. The sample may be sent for testing in advance of the protocol-defined screening period in order to facilitate the screening and enrollment process. Patients must wait for the results from the on-study centralized HRD testing prior to receiving first dose. If g*BRCA*$^{mut}$ is previously detected, then it is not required to wait for tumor HRD test results prior to enrollment; however, archival tumor samples still need to be collected for central HRD testing and exploratory biomarker analyses. Patients may be eligible for enrollment if they have an HRD-positive tumor.

Blood samples also will be collected for all patients during screening for determination of g*BRCA*$^{mut}$ status. If HRD status is known, then it is not necessary to wait for g*BRCA*$^{mut}$ testing results for enrollment into the study. However, a blood sample still needs to be collected for central g*BRCA*$^{mut}$ testing.

In order to evaluate exploratory tumor biomarker changes, an optional fresh biopsy may be done at screening and at the end of treatment (EOT) visit.

Niraparib 300 mg will be administered orally once daily continuously beginning on Day 1 and every cycle (28 days) thereafter until the patient discontinues study treatment. Three capsules of 100-mg strength will be taken at each dose administration. Dose interruption (no longer than 28 days) and 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). Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions. Patients will continue on study medication until disease progression as long as in the investigator's opinion they are benefiting from treatment and do not meet any other discontinuation criteria.

As of 9 February 2016, the PK QTc sub-study had reached the enrollment target of 12 patients and is now closed to enrollment.

Blood samples will be collected for all patients during screening for the exploratory evaluation of circulating biomarkers.

Clinic visits will be weekly during Cycle 1 and then every 4 weeks (±3 days) for subsequent cycles. Response Evaluation Criteria in Solid Tumors (RECIST; v.1.1) tumor assessment via computed tomography or magnetic resonance imaging of the abdomen/pelvis and clinically indicated areas is required every 8 weeks (±7 days) from Cycle 1/Day 1 for 6 months and then every 12 weeks (±7 days) until progression. Copies of scans will be collected for future central evaluation if needed. 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. All adverse events (AEs) and serious adverse events (SAEs) will be collected and recorded for each patient from the day of signing the informed consent form until the EOT visit. New SAEs (including deaths) will be collected for 30 days after the last dose of study treatment. AESI and SAEs assessed as related to study treatment will be reported through the study and post-treatment assessments. 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.

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

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

**Number of Patients (Planned):** Approximately 500 patients will be enrolled in the study.

**Main Criteria for Inclusion:**

To be considered eligible to participate in the study, the patient must meet the following main inclusion criteria and all other inclusion criteria:

- Patients must agree to undergo tumor HRD testing and blood g*BRCA*$^{mut}$ status testing.
    a. This test result must show that patients have an HRD-positive tumor (see Appendix F), defined by the presence of a deleterious or suspected deleterious breast cancer gene (*BRCA*) mutation or be positive for genomic instability.

    Note: The study HRD test result must be received prior to study enrollment. The tumor sample may be submitted for HRD testing prior to the screening period if it appears the patient is likely to meet other eligibility requirements. To facilitate early testing, a separate informed consent form (ICF) specific for HRD testing will be available to be signed prior to testing.

    b. If historic blood g*BRCA*$^{mut}$ is detected by a central g*BRCA*$^{mut}$ testing, then tumor HRD sample test results are not required prior to enrollment; however, HRD testing still needs to be performed.

    Note: If g*BRCA*$^{mut}$ status is known by a local test, then a fresh sample must be submitted for centralized g*BRCA*$^{mut}$ testing. Local g*BRCA*$^{mut}$ results are not acceptable for enrollment. Only patients with centralized g*BRCA*$^{mut}$ and/or HRD-positive samples can be enrolled in this study.
- Patients must have completed 3 or 4 previous chemotherapy regimens (eg, gemcitabine, doxorubicin, topotecan, carboplatin, oxaliplatin, cisplatin, bevacizumab, or PARP inhibitors as single agents or in combination per standard of care).

a. Patients must have completed their last chemotherapy regimen > 4 weeks prior to treatment initiation.

- Patients must have measurable disease according to RECIST (v.1.1).

**Main Criteria for Exclusion:**

To be considered eligible to participate in the study, the patient must not meet any of the following main exclusion criteria or any other exclusion criteria:

- Patients must not have any known, persistent (> 4 weeks), ≥Grade 3 hematologic toxicity during the last cancer therapy.
- Patients must not have any known, persistent (>4 weeks), ≥Grade 3 fatigue during the last cancer therapy.
- Patients must not have received pelvic radiotherapy as treatment for primary or recurrent disease within 1 year of the first dose of study treatment.
- Patients must not have symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [eg, radiation or surgery at least 1 month prior to study entry]. The patient must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids [as long as these were started at least 4 weeks prior to enrollment] 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 demonstrate evidence of clinically stable disease for 28 days.
- Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, small bowel obstruction or other serious gastrointestinal disorder, or any psychiatric disorder that prohibits obtaining informed consent.
- Patients must not have received a transfusion (platelets or red blood cells) within 4 weeks of the first dose of study treatment.
- Patients must not have known history or current diagnosis of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or second primary malignancy other than MDS or AML.

**Investigational Product, Dosage, and Mode of Administration:**

Niraparib 300 mg (3 x 100-mg niraparib capsules) will be administered orally once daily continuously. 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 and food is permissible. The first dose will be administered at the site.

**Duration of Treatment:** Approximately 24 weeks. Patients who are benefitting from treatment will have access to study treatment as long as considered acceptable by their treating physician or until they are discontinued from study treatment or from the study.

**Criteria for Evaluation:**

Primary Endpoint:

- Investigator-assessed confirmed ORR per RECIST v1.1 in the HRD-positive patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy. Patients with prior PARP inhibitor treatment are excluded.

Key Secondary Endpoints:

- Investigator-assessed confirmed ORR per RECIST v1.1 in all patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy, regardless of HRD status. Patients with prior PARP treatment are excluded.
- Investigator-assessed confirmed ORR per RECIST v1.1 in all patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive or platinum-resistant to the last platinum-based therapy, regardless of HRD status. Patients with prior PARP treatment are excluded.
- Investigator-assessed confirmed ORR per RECIST v1.1 in all patients treated in the study.

The primary and key secondary efficacy endpoints will be tested sequentially to control the overall Type I error rate at 1-sided 0.025 level.

Other Secondary Endpoints:

- DOR, DCR, PFS, TFST and OS in patient groups included in the primary and key secondary endpoints.
- ORR, DOR, DCR, PFS, TFST and OS in patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-resistant to the last platinum-based therapy, by HRD status. Patients with prior PARP treatment are excluded.
- ORR, DOR, DCR, PFS, TFST and OS in all patients regardless of prior lines of anti-cancer therapy, including HRD subgroup analysis and platinum-sensitivity (sensitive vs. resistant) subgroup analysis. Patients with prior PARP treatment are excluded.

Safety:

- Safety of niraparib will be evaluated throughout the trial, including assessment of treatment-emergent AEs, clinical laboratory evaluations (hematology, chemistry), vital signs, physical examination, and use of concomitant medications

A subset of approximately 12 patients will undergo intensive, triplicate ECG monitoring to coincide with PK evaluation on Cycle1/Day 1

Pharmacokinetics:

- Evaluation of the PK of niraparib and its major metabolite; parameters of interest include area under the curve (AUC), minimum observed plasma concentration ($C_{min}$), maximum observed plasma concentration ($C_{max}$), time to maximum concentration ($t_{max}$), and/or AUC at steady-state ($AUC_{ss}$), $C_{min,ss}$, $C_{max,ss}$, and, if the data allow, oral clearance (CL/F) and oral volume of distribution (Vz/F)

Exploratory Analysis:

- To evaluate potential biomarkers related to ovarian cancer and of poly(ADP-ribose) polymerase (PARP) inhibitor inhibition (e.g. DNA repair pathways)
- Efficacy and safety of niraparib in patients who are platinum-refractory to the last platinum therapy

- Efficacy and safety of niraparib in patients with prior PARP treatment.

**Statistical Methods:**

General Analysis Considerations:

Efficacy analysis will be performed on the following populations:

- Intent-to-Treat (ITT) Population, defined as all dosed patients with measurable disease at baseline
- Response-Evaluable Population, all ITT patients with at least one evaluable post-baseline tumor scan
- PP population, consisting of all patients in the ITT Population enrolled in the study who do not have protocol deviations that may significantly impact the interpretation of efficacy results.

Safety analysis will be performed on the Safety Population, defined as all patients who received at least 1 dose of study drug.

All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methods. The 2-sided 95% CIs will be provided as appropriate. Exploratory biomarkers may be evaluated with efficacy and safety variables.

All AEs will be listed and tabulated. Physical examination findings, vital signs, and clinical laboratory results will be listed and summarized using descriptive statistics; shift tables will be presented as appropriate.

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

Descriptive statistics and categorical analyses of ECG variables will be provided for the subset of patients (approximately 12) with intensive ECG collection. A population PK analysis plan will be written to describe the analyses of ECG variables and PK parameters.

Sample Size:

The study protocol initially allowed enrollment of all patients with at least 3 prior lines of anti-cancer therapy. In the subsequent protocol amendments, the study enrollment was adjusted to allow only HRD-positive patients with 3 or 4 prior lines of anti-cancer therapy. This adjustment was made in consideration of the evolving role of PARP inhibitors in ovarian cancer treatment based on external data. Overall, approximately 500 patients are expected in the study. The study enrollment is also expected to include a minimum number of t*BRCA*$^{mut}$ patients (≥50) and HRD-positive patients (≥150).

For the primary efficacy endpoint of ORR in HRD-positive patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy, an alternative hypothesis of ORR ≥30% is considered against a null hypothesis of ORR ≤10%.

For the key secondary efficacy endpoints of ORR tested in broader subgroups to include platinum-resistant patients and/or HRD-negative/unknown patients, an alternative hypothesis of ORR ≥25% is considered against a null hypothesis of ORR ≤10%.

The rationale of choosing the null and alternative hypothesis for the primary and the key secondary efficacy endpoints is based on data external from this study. These clinical trials of PARP inhibitors

(e.g. niraparib, olaparib, and rucaparib) suggest that platinum-sensitivity and/or HRD-positivity (including *BRCA* mutant) play a role in how patients with ovarian cancer respond to treatment. There is limited data for the overall HRD-positive population in ovarian cancer treatment. In a rucaparib study that included patients who are LOH-positive (another assay evaluating tumor homologous recombination deficiency), ORR in the non-t*BRCA*/LOH-positive patients with at least 2 prior lines of therapy was 17%.[1] A recent publication of platinum-sensitive patients with at least 1 prior line of therapy presented an ORR of 29% in the non-t*BRCA*/LOH-positive group.[2] Therefore, choice of the hypotheses of Ho: ORR ≤10% vs. Ha: ORR ≥30% for the primary efficacy and Ho: ORR ≤10% vs. Ha: ORR ≥25% for the key secondary analyses would be appropriate for testing the efficacy of niraparib treatment in the specified populations.

It is estimated that 45 patients would provide 90% power for testing the primary efficacy analyses. Statistical power for various sample sizes are presented below to provide guidance for the key secondary hypotheses when tested individually (regardless of sequential testing). The power is calculated by assuming the exact binomial distribution using East® software Version 6.4.

| n | Statistical Power* |
|---|---|
| 45 | 72% |
| 60 | 85% |
| 75 | 92% |
| 90 | 96% |

* Ho: ORR≤10% vs Ha: ORR≥25%

As of August 2017, approximately 450 patients were dosed in the study. Approximately 320 patients had 3 or 4 prior lines of anti-cancer therapy (~150 HRD positive). Based on a preliminary calculation of the platinum-sensitivity to the last platinum-based therapy, the number of enrolled patients for the primary endpoint and the key secondary efficacy endpoints are considered adequate to ensure sufficient power for the planned analysis.

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## TABLES IN TEXT



## FIGURES IN TEXT

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ADL | activities of daily living |
| AE | adverse event |
| alt | Alternative |
| AML | acute myeloid leukemia |
| AUC | area under the curve |
| $AUC_{ss}$ | area under the curve at steady-state |
| BER | base excision repair |
| *BRCA* | breast cancer gene |
| CA-125 | cancer antigen 125 |
| CBC | complete blood count |
| CI | confidence interval |
| CL/F | oral clearance |
| $C_{max}$ | maximum observed plasma concentration |
| $C_{max,ss}$ | maximum observed plasma concentration at steady-state |
| $C_{min}$ | minimum observed plasma concentration |
| $C_{min,ss}$ | minimum observed plasma concentration at steady-state |
| CN | copy number |
| CNS | central nervous system |
| CR | complete response |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DCR | disease control rate |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EOT | end of treatment |
| g*BRCA*$^{mut}$ | germline *BRCA* mutation |
| t*BRCA*$^{mut}$ | tumor *BRCA* mutation |
| GCP | Good Clinical Practice |
| HRD | homologous recombination deficiency |
| ICF | informed consent form |

| | |
|---|---|
| ICH | International Council on Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| ITT | intent to treat |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| LOH | loss of heterozygosity |
| LST | large-scale state transitions |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Application |
| MRI | magnetic resonance imaging |
| NHEJ | nonhomologous end-joining |
| ORR | objective response rate |
| PARP | poly(ADP-ribose) polymerase |
| PD | progressive disease |
| PDy<br>PFS | pharmacodynamic<br>progression-free survival |
| P-gp | P-glycoprotein |
| PK | Pharmacokinetic |
| PP | per protocol |
| PR | partial response |
| QD | once daily |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| TAI | tumor telomeric allelic imbalance |
| TEAE | treatment-emergent adverse event |
| TFST | time to first subsequent treatment |
| $t_{max}$ | time to maximum concentration |
| ULN | upper limit of normal |
| Vz/F | oral volume of distribution |

# 1. INTRODUCTION

## 1.1. Background: Poly(ADP-ribose) Polymerase and Homologous Recombination Deficiency

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

Normal cells repair up to 10,000 DNA defects daily, and single-strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the homologous recombination or BER pathways, are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. They enter the S (DNA replication) phase of the cell cycle with unrepaired single- and double-strand breaks. Pre-existing single-strand breaks are converted to double-strand breaks as the replication machinery passes. Accumulated double-strand breaks present during S phase are repaired by homologous recombination. Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells unable to perform DNA repair via homologous recombination (eg, due to inactivation of genes required for homologous recombination, such as breast cancer gene [*BRCA*] 1 or *BRCA*2) are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S phase and are more likely to use the error-prone nonhomologous end-joining (NHEJ) or alternative (alt)-NHEJ pathways to repair double-strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to mutations that promote the development of cancer. Over time, the buildup of excessive DNA errors in combination with the inability to complete S phase (because of stalled replication forks) contributes to cell death.

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline *BRCA* mutation (g*BRCA*$^{mut}$) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on NHEJ, alt-NHEJ, and BER for maintenance of genomic integrity. PARP inhibitors block alt-NHEJ and BER, forcing tumors with *BRCA* deficiencies to use the error-prone NHEJ to fix double-strand breaks. Non-*BRCA* deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors. The rationale for anticancer activity in a subset of non-g*BRCA*$^{mut}$ tumors is that they share distinctive DNA repair defects with g*BRCA*$^{mut}$ carriers, a phenomenon broadly described as "*BRCA*ness."[3] DNA repair defects can be caused by germline or somatic alterations to the homologous recombination DNA repair pathway. In a recent analysis of approximately 500 high-grade serous ovarian adenocarcinoma tumors, approximately 50% contained homologous recombination defects.[4] A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib.

Defects in the homologous recombination pathway might result in specific structural changes in DNA. Previously, chromosomal copy number (CN) changes have been reported to be associated with *BRCA*1 and *BRCA*2 mutations.[5,6] Recent evidence, however, indicates that evaluation of the patterns of loss of heterozygosity (LOH) and homologous recombination deficiency (HRD) may be more robust than CN changes alone. LOH results in the irreversible loss of one of the parental alleles. In contrast, CN gains are not necessarily permanent. Therefore, if HRD leaves a footprint of genomic alterations, LOH and CN variants may provide a more stable record of those changes compared with CN variants alone. In a recent study, the patterns of genome-wide LOH were analyzed in 3 different epithelial ovarian cancer data sets extensively characterized for *BRCA*1 and *BRCA*2 defects by evaluating HRD status.[7] The HRD analysis is a DNA-based assay that is capable of detecting HRD independent of its etiology based on genome-wide single nucleotide polymorphism data. An HRD-(LOH) score was developed, which is strongly associated with functional defects in *BRCA*1 and *BRCA*2. This score also strongly correlated with promoter methylation of RAD51C, a gene implicated in the homologous recombination pathway. Additional DNA-based algorithms of HRD have been developed based on whole genome tumor telomeric allelic imbalance, HRD-(TAI),[8] and large-scale state transitions, HRD-(LST).[9] In a recent study, all 3 HRD algorithms were independently associated with *BRCA*1/2 deficiency and response to cisplatin treatment in triple-negative breast cancer.[10] The arithmetic mean of the 3 HRD algorithms was significantly associated with *BRCA*1/2 status in a breast all-comers cohort and with cisplatin response in a second independent triple-negative breast cancer cohort. The final clinical HRD score results from the sum of HRD-LOH, HRD-TAI, and HRD-LST scores and is a single value along a continuous scale from 0 to 100. Analysis of more than 1,000 breast and ovarian cancer tumor samples has identified 2 distinct HRD populations, HRD-negative and HRD-positive, with 95% of all g*BRCA*$^{mut}$ tumors with concomitant LOH at the *BRCA* gene in the sample classified as HRD-positive.

Clinical studies have shown that PARP inhibitors are active for recurrent ovarian cancer.[11-17] Clinical anticancer activity has been observed in patients with and without g*BRCA*$^{mut}$ and in patients who are platinum-sensitive and platinum-resistant. PARP inhibition appears to be most active in patients with g*BRCA*$^{mut}$ platinum-sensitive disease.[11,13,15] Additionally, maintenance therapy in patients with relapsed, platinum-sensitive ovarian cancer appears promising.[16] Of patients with a *BRCA* mutation, median progression-free survival (PFS) was significantly longer in the PARP inhibitor group than in the placebo group (11.2 months vs. 4.3 months; hazard ratio: 0.18; $p < 0.0001$). Similar findings were noted for patients with wild-type *BRCA*, although the difference between groups was smaller (7.4 months vs. 5.5 months; hazard ratio: 0.54; $p = 0.007$). Patient-reported outcomes, including Functional Assessment of Cancer Therapy – Ovarian Symptom Index, did not show a significant difference between the placebo and treatment groups, suggesting that maintenance treatment did not decrease functioning or quality of life in these patients. Patient-reported outcome data beyond progression was not captured, and therefore quality of life effects related to subsequent chemotherapy treatments (likely to occur sooner in the placebo group) could not be used to assess the benefit of extending PFS on patient-reported outcomes for patients treated with a PARP inhibitor vs. placebo.

## 1.2. Niraparib Background

Niraparib is a potent, orally active PARP-1 and -2 inhibitor being developed as an agent for tumors with defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors.

Nonclinical data on niraparib in ovarian cancer are discussed in detail in the Investigator's Brochure and described briefly in Section 1.2.1.

Niraparib clinical data are discussed in detail in the niraparib Investigator's Brochure and described briefly in Section 1.2.2.

### 1.2.1. Nonclinical Experience

In preclinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with homologous recombination defects. In a *BRCA*1-mutant xenograft study, niraparib dosed orally caused tumor regression, which was mirrored by >90% reduction in tumor weight compared with the control; in a *BRCA*2-mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Utilizing patient-derived ovarian xenografts (PDX), niraparib previously demonstrated response in both *BRCA* mutation and *BRCA* wild-type tumors.[18] To better illustrate the anti-tumor effects of niraparib in ovarian PDX models, samples from a collection of high-grade ovarian tumors were subjected to HRD analysis to determine the frequency of *BRCA* mutation and *BRCA* hypermethylation. Single nucleotide polymorphism data were analyzed using all 3 algorithms (loss of heterozygosity [LOH], tumor telomeric allelic imbalance [TAI], and large-scale state transitions [LST]). The final HRD score was the sum of the LOH+TAI+LST scores with numerical outputs ranging from 0 to 100. Collectively, there was 25% *BRCA* deficiency in this primary tumor collection, consistent with previous studies in high-grade ovarian cancer.[4] Using a threshold of 50% tumor growth inhibition as a guide, in vivo response to niraparib monotherapy was observed in 46% of ovarian cancer PDX modes . The response rate to niraparib in *BRCA* wild type, HRD negative models was 36%. The response rate in HRD positive models was 52%. The response rate to niraparib in $BRCA^{mut}$ models was 80%. These findings are consistent with the NOVA clinical study where a PFS benefit was observed in all patient subgroups.

### 1.2.2. Clinical Experience

Clinical safety data are available for a total of 144 patients who received niraparib as part of 5 Phase 1 studies conducted to date.

The common expected drug-related adverse events (AEs) for niraparib have been reported as: fatigue, nausea, anemia, thrombocytopenia, decreased appetite, neutropenia, vomiting, constipation, leukopenia, diarrhea, insomnia, dyspnea, electrocardiogram (ECG) QT prolonged, headache, stomatitis, hyponatremia, and alopecia. The majority of these events were effectively managed by dose interruption and/or reduction. AEs resulted in treatment discontinuation in approximately 15% of patients.

Myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and second primary malignancies other than MDS/AML have been observed in patients receiving treatment with olaparib, rucaparib, and niraparib; given the common mechanism of action among these PARP

inhibitors, MDS, AML, and second primary malignancies other than MDS/AML therefore represent a potential risk to patients receiving niraparib. Guidance on monitoring patients for new events of MDS/AML, and second primary malignancies other than MDS/AML and the follow-up of patients with these suspected events is provided in Section 6.2.6 and Section 7.

Currently, there are 5 ongoing Phase 3 niraparib studies. A short description of the relevant monotherapy studies (Study PR-30-5010-C [BRAVO] and Study PR-30-5011-C [NOVA]) is provided below.

Study PR-30-5010-C (BRAVO) is a 2:1 randomized, open-label, multicenter, controlled clinical study in patients with previously treated human epidermal growth factor receptor 2-negative g*BRCA*$^{mut}$ breast cancer. In this study, patients received treatment with niraparib 300 mg once daily (QD) or physician's choice single-agent chemotherapy (eribulin, vinorelbine, gemcitabine, or capecitabine). Evaluation of computed tomography (CT) scans and magnetic resonance imaging (MRI), including determination of response to treatment and date of progression based on Response Evaluation Criteria in Solid Tumors (RECIST; v.1.1), was conducted by a central blinded review committee comprised of 2 radiologists, with an arbiter as necessary. The results of the central blinded assessment are used in determination of the primary efficacy endpoint of PFS and the study investigators also assess response to treatment and date of progression based on RECIST (v.1.1). BRAVO was initiated (first patient consented) on 25 February 2014. Following a recent interim analysis of data by the independent data monitoring committee (IDMC), the study was closed to further enrollment. A large number of patients in the chemotherapy control arm (physician's choice) did not continue in the trial long enough to receive their first radiological scan, resulting in an unusually high rate of censoring in the control arm. It is believed that this is likely associated with the desire of patients who carry germline *BRCA* mutations to be treated with a PARP inhibitor rather than chemotherapy and the increased availability of PARP inhibitors. No safety concerns have been noted by the IDMC with respect to niraparib. Following closure of enrollment, data analysis and review by the Sponsor is ongoing.

Study PR-30-5011-C (NOVA) is a double-blind, 2:1 randomized, placebo-controlled study of maintenance with niraparib compared with placebo in patients with platinum-sensitive ovarian cancer who have received at least 2 platinum-based regimens, had a response to their last regimen, and have no measurable disease >2 cm and normal cancer antigen 125 (CA-125) (or >90% decrease) following their last treatment. In this study, there are 2 independent patient cohorts comprising patients who have deleterious g*BRCA*$^{mut}$ versus those who have a tumor with high-grade serous histology but without g*BRCA*$^{mut}$ (non-g*BRCA*$^{mut}$). The study assesses the effect of treatment with niraparib 300 mg QD on PFS. Progression is assessed by RECIST (v.1.1) and clinical criteria using blinded central review by 2 independent radiologists and an arbiter, if necessary, as well as per blinded central clinician review. Results of the blinded central reviews are used in determination of the primary efficacy endpoint of PFS. NOVA was initiated (first patient consented) on 10 July 2013. Data from the final primary analysis of the Phase 3 main study, as well as the QTc substudy, recently became available. The results of the PFS primary endpoint for each of the 3 primary efficacy populations in platinum-sensitive patients (ie, g*BRCA*$^{mut}$ cohort, HRDpos cohort, and overall non-g*BRCA*$^{mut}$ cohort) is shown in Table 1. Additionally, the 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). 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.

**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) | |

[a] Progression-free survival is defined as the time in months from the date of randomization to progression or death.

## 1.3. Rationale for Current Trial

Treatment options are limited for patients whose ovarian cancer has progressed following multiple lines of prior therapy. At the time that this study was initiated, the absence of an approved treatment or standard of care in the recurrent setting represented an unmet need. National Comprehensive Cancer Network guidelines recommended treatment with single-agent topotecan, doxorubicin, or gemcitabine, however the optimal combination and sequence of these agentsis unclear and the exact population who would derive the most benefit from these treatments is not well defined.

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, g*BRCA*$^{mut}$ subgroup.

In a Phase 2 study of maintenance therapy in 265 patients with relapsed, platinum-sensitive ovarian cancer, daily therapy with PARP inhibitor olaparib, compared with placebo, was associated with a PFS benefit (hazard ratio: 0.35) and prolongation of the median PFS from 4.8 months to 8.4 months.[15]

In a Phase 1/2 study with niraparib (PN001), 104 patients with advanced solid tumors who had received a median of 5 prior therapies were enrolled, of which 49 were ovarian cancer patients (13 platinum-sensitive, 35 platinum-resistant, and 1 platinum-refractory). Of the 49 patients, 22 had confirmed *BRCA*1 or *BRCA*2 mutation, of whom 20 were radiologically assessable. Eight (40%) of these 20 patients achieved a confirmed partial response (PR) by RECIST and CA-125 Gynecologic Cancer Intergroup criteria at doses ranging from 80 to 400 mg per day. Median response duration was 387 days (range: 159 to 518 days). Three (33%) of 9 patients with platinum-resistant *BRCA*-mutant ovarian cancer had PR by RECIST and CA-125 criteria. Additionally, a 50% response rate (5 of 10 evaluable patients) was observed at daily doses

ranging from 290 to 300 mg among patients with *BRCA*-mutant ovarian cancer who had received more than 3 lines of prior chemotherapy.

Thus, niraparib has demonstrated potential for fulfilling an unmet medical need for the treatment of patients with relapsed ovarian cancer who have received multiple lines of prior therapy.

The present study is designed to determine the efficacy and safety of niraparib in these patients with a high unmet medical need. Furthermore, the present study will assess if the HRD test can be utilized to identify patients with a higher probability of clinical benefit.

# 2. STUDY OBJECTIVES

## 2.1. Primary Objective

The primary objective of the study is to evaluate the Objective Response Rate (ORR) of niraparib in HRD-positive patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy.

## 2.2. Secondary Objectives

The key secondary objectives of the study are as follows:

- To evaluate the ORR of niraparib in all patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy.
- To evaluate the ORR of niraparib in all patients with advanced, relapsed, high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive or platinum-resistant to the last platinum-based therapy.
- To evaluate the ORR of niraparib in all patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The other secondary objectives of the study are as follows:

- To evaluate the efficacy (ORR, DOR, DCR, PFS, TFST and OS) of niraparib in patients who have received 3 or 4 prior lines of anti-cancer therapy To evaluate the efficacy (ORR, DOR, DCR, PFS, TFST and OS) of niraparib in all patients regardless of prior lines of anti-cancer therapy.
- To evaluate the safety and tolerability of niraparib

## 2.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- To evaluate the efficacy and safety of niraparib in all patients who are platinum-refractory to the last platinum-based therapy.
- To evaluate the efficacy and safety of niraparib in all patients with prior PARP treatment.
- To evaluate QTc in a subset of niraparib-treated ovarian cancer patients (This sub-study has been closed for enrollment since 9 February 2016)
- To assess population pharmacokinetics (PK) and estimate PK parameters for niraparib and its major metabolite
- To explore potential biomarkers related to ovarian cancer and poly(ADP-ribose) polymerase (PARP) inhibition (e.g. DNA repair pathways)

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design and Plan

This study is a multicenter, open-label, single-arm, Phase 2 study evaluating the safety and efficacy of niraparib in patients with advanced, relapsed, homologous recombination deficiency (HRD)-positive, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with recurrent disease who were previously treated with chemotherapy and experienced a response lasting at least 6 months to first-line platinum-based therapy. Patients must have received 3 or 4 previous chemotherapy regimens (including, but not limited to, gemcitabine, doxorubicin, topotecan, carboplatin, oxaliplatin, cisplatin, bevacizumab, or PARP inhibitors as single agents or in combination per standard of care). The study will assess by ORR whether treatment with niraparib will benefit HRD positive patients who received 3 or 4 prior anti-cancer therapies and are platinum-sensitive to the last platinum-based therapy. As secondary objectives, niraparib efficacy (ORR, DOR, DCR, PFS, TFST, and OS) will be assessed in patients who have received 3 or 4 prior lines of anti-cancer therapy by platinum-sensitivity to the last platinum-based therapy; and in all treated patients regardless of prior lines of anti-cancer therapy.

In order to determine eligibility, a tumor sample will be sent to a centralized laboratory for immediate HRD testing. Archival or fresh tissue is required in order to enroll in the study. The sample may be sent in advance of the protocol-defined screening period in order to facilitate the screening and enrollment process. Patients must wait for the results from the on-study centralized HRD testing prior to enrollment, unless they have previously detected g*BRCA* mutation. Blood samples also will be collected for all patients during screening for determination of g*BRCA*$^{mut}$ status. If HRD status is known, then it is not necessary to wait for HRD testing results for enrollment into the study, however confirmatory HRD testing still needs to be performed.

In order to evaluate tumor markers, an optional fresh biopsy may be done at screening and at the end of treatment (EOT) visit.

Niraparib 300 mg will be administered orally QD continuously beginning on Day 1 and every cycle (28 days) thereafter until the patient discontinues study treatment. Three capsules of 100-mg strength will be taken at each dose administration. Dose interruption (no longer than 28 days) and 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). Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions. Patients will continue on study medication until disease progression as long as in the investigator's opinion they are benefiting from treatment and do not meet any other discontinuation criteria.

Blood samples for measurements of plasma levels of niraparib and its major metabolite will be obtained on Cycle 1/Day 1 predose and 2 hours postdose, Cycle 2/Day 1 predose and 2 hours postdose, Cycle 4/ Day 1 predose, and Cycle 8/ Day 1 predose. At selected sites, a subset of approximately 12 patients will undergo intensive, triplicate ECG monitoring to coincide with PK evaluation on Cycle1/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 have triplicate ECGs and PK samples taken predose and at 1, 2, 4, 6, and 8 hours postdose. Patients will be

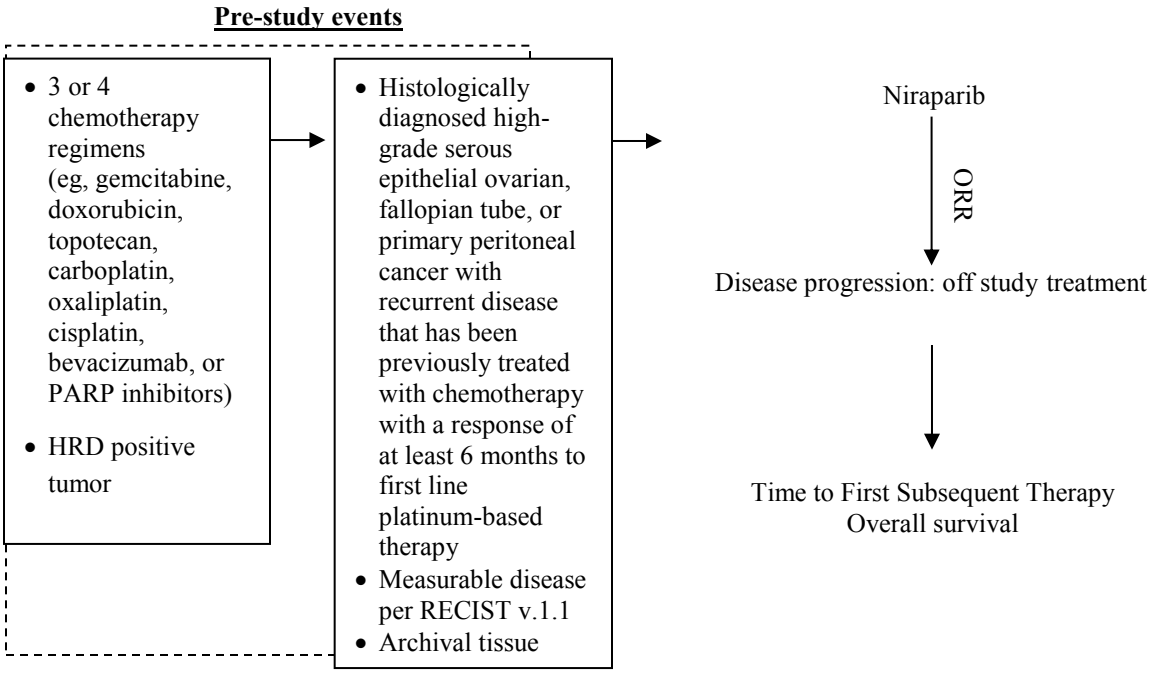
supine and rested for approximately 2 minutes before ECGs are recorded. The average of the triplicate measures will be used for analysis. This subset of patients will undergo all other assessments in the study. As of 9 February 2016, the PK QTc sub-study had reached the enrollment target of 12 patients and is now closed to enrollment.

Blood samples will be collected for all patients at screening for the exploratory evaluation of circulating biomarkers.

Clinic visits will be weekly during Cycle 1 and then every 4 weeks (±3 days) for subsequent cycles. Response Evaluation Criteria in Solid Tumors (RECIST; v.1.1) tumor assessment via CT or MRI of the abdomen/pelvis and clinically indicated areas is required every 8 weeks (±7 days) from Cycle 1/Day 1 for 6 months and then every 12 weeks until progression. Copies of scans will be collected for future central evaluation if needed. 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. All AEs and serious adverse events (SAEs) will be collected and recorded for each patient from the day of signing the screening informed consent form (ICF) until the EOT visit. New SAEs (including deaths) will be collected for 30 days after the last dose of study treatment. 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. The Adverse Events of Special Interest (AESIs) for this study are MDS, AML, secondary cancers (new primary malignancies other than MDS/AML), pneumonitis, and embryo-fetal toxicity. AESIs must be reported to the Sponsor as soon as the Investigator becomes aware of them (Section 6.2.5.3).

Approximately 500 patients will be enrolled in the study at approximately 60 sites. The study will be conducted in conformance with Good Clinical Practice (GCP).

**Figure 1: Study Design**




Abbreviations: ORR = objective response rate; PARP = poly(ADP-ribose) polymerase; RECIST = Response Evaluation Criteria in Solid Tumors

# 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. Patients must be female and at least 18 years of age.
2. Patients must provide written informed consent.
3. Patients must agree to undergo tumor HRD testing and blood g*BRCA*$^{mut}$ status testing.
    a. This test result must show that patients have an HRD-positive tumor, defined by the presence of a deleterious or suspected deleterious breast cancer gene (*BRCA*) mutation or be positive for genomic instability (Please see HRD results sample form in Appendix F).

Note: The study HRD test result must be received prior to enrollment. The tumor sample may be submitted for HRD testing prior to the screening period if it appears the patient is likely to meet other eligibility requirements. To facilitate early testing, a separate informed consent form (ICF) specific for HRD testing will be required to be signed prior to testing.

    b. If historic blood g*BRCA*$^{mut}$ is detected by a central g*BRCA*$^{mut}$ testing, then tumor HRD sample test results are not required prior to enrollment; however, HRD testing still needs to be performed.

Note: If g*BRCA*$^{mut}$ status is known by a local test, then a fresh sample must be submitted for centralized g*BRCA*$^{mut}$ testing. Local g*BRCA*$^{mut}$ results are not acceptable for enrollment. Only patients with centralized g*BRCA*$^{mut}$ and/or HRD-positive samples can be enrolled in this study.

4. Patients must have histologically diagnosed high-grade (Grade 2 or 3) serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with recurrent disease and must have been previously treated with chemotherapy and experienced a response lasting at least 6 months to first-line platinum-based therapy.
5. Patients must have completed 3 or 4 previous chemotherapy regimens (eg, gemcitabine, doxorubicin, topotecan, carboplatin, oxaliplatin, cisplatin, bevacizumab, or PARP inhibitors as single agents or in combination per standard of care).
    a. Patients must have completed their last chemotherapy regimen > 4 weeks prior to treatment initiation.
6. Patients must have measurable disease according to RECIST (v.1.1).
7. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix C).
8. Patients must have adequate organ function, defined as follows:
    a. Absolute neutrophil count ≥ 1,500/µL
    b. Platelets ≥ 150,000/µL
    c. Hemoglobin ≥ 10 g/dL

d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault equation
e. Total bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ 1 x ULN
f. Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN

9. Patients must have formalin-fixed, paraffin-embedded tumor samples available from the primary or recurrent cancer or agree to undergo fresh biopsy prior to study treatment initiation.
10. Patients must be able to take oral medications.
11. Patients of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin; hCG) within 72 hours prior to receiving the first dose of study treatment.
12. Patients must be either postmenopausal, free from menses for > 12 months, surgically sterilized, or willing to use adequate contraception to prevent pregnancy or must agree to abstain from heterosexual activity throughout the study, starting with enrollment through 90 days after the last dose of study treatment (see Appendix E for contraception guidelines).
13. Patients must agree to blood samples during screening and at the end of treatment for potential cytogenetic analysis.

## 4.2. Exclusion Criteria

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

1. Patients must not have had palliative radiotherapy encompassing > 20% of the bone marrow within 1 week of the first dose of study treatment.
2. Patients must not have any known, persistent (> 4 weeks), ≥ Grade 3 hematologic toxicity during the last cancer therapy.
3. Patients must not have any known, persistent (>4 weeks), ≥ Grade 3 fatigue during the last cancer therapy
4. Patients must not have received pelvic radiotherapy as treatment for primary or recurrent disease within 1 year of the first dose of study treatment.
5. Patients must not have symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [eg, radiation or surgery at least 1 month prior to study entry]. The patient must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids [as long as these were started at least 4 weeks prior to enrollment] 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 demonstrate evidence of clinically stable disease for 28 days.
6. Patients must not have known hypersensitivity to the components of niraparib.

7. Patients must not have had major surgery per Investigator judgment within 3 weeks of starting the study and patient must have recovered from any effects of any major surgery.
8. Patients must not have had diagnosis, detection, or treatment of invasive cancer other than ovarian cancer ≤ 24 months prior to enrollment (except basal or squamous cell carcinoma of the skin that has been definitively treated).
9. Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, small bowel obstruction or other serious gastrointestinal disorder, or any psychiatric disorder that prohibits obtaining informed consent.
10. Patients must not have received a transfusion (platelets or red blood cells) within 4 weeks of the first dose of study treatment.
11. Patients must not have current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study or interfere with the patient's participation for the full duration of the study treatment or that makes it not in the best interest of the patient to participate.
12. Patients must not be pregnant or breastfeeding, or expecting to conceive children, within the projected duration of the study treatment.
13. Patients must not be immunocompromised (patients with splenectomy are allowed).
14. Patients must not have known, active hepatic disease (ie, hepatitis B or C).
15. Patients must not have a corrected QT interval (QTcF) prolongation > 470 msec at screening or history of drug induced ventricular tachycardia or fibrillation.
    a. Note: If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (ie, the patient otherwise has no cardiac abnormalities), then the patient may be eligible to participate in the study following discussion with the Medical Monitor.
16. [INTENTIONALLY LEFT BLANK TO RETAIN NUMBERING OF THE ELIGIBILITY CRITERION FROM THE ORIGINAL PROTOCOL]
17. Patients must not have known history or current diagnosis of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or second primary malignancy other than MDS/AML.

## 4.3. Patient Withdrawal and Replacement

Patients who are benefitting from treatment will have access to study treatment as long as considered acceptable by their treating physician or until they are discontinued for one of the reasons noted below (Section 4.3.1 and Section 4.3.2).

### 4.3.1. Discontinuation from Treatment

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

- Any treatment-related National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; v.4.03) Grade 3 or 4 events (see separate guidelines for platelets below) that have not reverted to CTCAE Grade 1 or better within 28 days of dose interruption.
  - At the Investigator's discretion, following dose interruption (no longer than 28 days), patients may be considered for dose reductions (to a maximum of 2 dose reductions [ie, a minimum dose of 100 mg once daily (QD)]). If upon rechallenge with study treatment at the lowest allowable dose any CTCAE Grade 3 or 4 AEs recur, the patient must be discontinued.
- In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose or 1 dose level lower when the platelet count has resolved to ≥100,000/μL. Subsequent occurrences should trigger dose reduction upon resumption of therapy. If the platelet count has not reverted within 28 days of interruption to ≥ 100,000/μL on first or subsequent occurrence, the patient should be discontinued.
- Disease progression according to RECIST (v.1.1) or clinical criteria by Investigator
- Risk to patients as judged by the Investigator and/or Sponsor
- Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor
- Patient request
- Patient becomes pregnant
- Sponsor decision to terminate study

Patients who discontinue from treatment will continue to receive post-treatment assessments as part of the study unless they are discontinued from the study (Section 4.3.2).

### 4.3.2. Discontinuation from the Study

Patients may be discontinued from the study for any of the following reasons:

- 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
- End of the study (when responder or discontinuation status for all patients is known)

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

## 4.4. Patient Identification

All patients who enter into the screening period of the study (defined as the point at which the patient signs the main study ICF) or agree to pre-screening HRD testing (defined as the point at which the patient signs the screening 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.

# 5. STUDY MEDICATION

## 5.1. Identity

Niraparib ([3S]-3-[4-phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate.

## 5.2. Administration

Niraparib 300 mg (3 x 100-mg niraparib capsules) will be administered orally QD continuously. 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 and food is permissible.

Study treatment will be dispensed to patients on Cycle 1/Day 1 and on Day 1 of every cycle (28 days) thereafter until the patient discontinues study treatment. The first dose will be administered at the site.

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

## 5.3. Dose Modification

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

Treatment must be interrupted for any nonhematologic CTCAE (v.4.03) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or Grade 1 or less within 28 days of interruption, the patient may restart treatment with niraparib but with a dose level reduction according to Table 2 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 (ie, to a minimum dose of 100 mg QD).

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

**Table 2: Dose Reductions for Nonhematologic Toxicities**

| Event | Dose[a] |
|---|---|
| Initial dose | 300 mg QD |
| 1st dose reduction for CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible; or any grade toxicity considered intolerable by the patient | 200 mg QD |
| 2nd dose reduction for CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible; or any grade toxicity considered intolerable by the patient | 100 mg QD |
| Continued CTCAE Grade 3 or 4 treatment-related SAE/AE ≥ 28 days | Discontinue study treatment |

Abbreviations: AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, QD = once daily, SAE = serious adverse event.

[a] Dose not to be decreased below 100 mg QD.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts and are outlined in Table 3.

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.

In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose or 1 dose level lower when the platelet count has resolved to ≥100,000/µL. Subsequent occurrences should trigger dose reduction upon resumption of therapy. If the platelet count has not reverted within 28 days of interruption to ≥ 100,000/µL on first or subsequent occurrence, the patient should be discontinued.

If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will be also required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.

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

It is strongly recommended that the patient 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.

**Table 3: Dose Modification/Reduction for Hematologic Toxicities**

| | |
|---|---|
| Platelet count 75,000-99,999/µL[a] | Study treatment must be interrupted until platelet counts are ≥ 100,000/µL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at same dose or reduced dose based on clinical judgment. |
| 2nd occurrence of platelet count 75,000-99,999/µL[a] | Study treatment must be interrupted until platelet counts are ≥ 100,000/µL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at a reduced dose. |
| Platelet count < 75,000/µL[a b] | Study treatment must be interrupted until platelet counts are ≥ 100,000/µL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at a reduced dose. |

**Table 3: Dose Modification/Reduction for Hematologic Toxicities (Continued)**

| | |
|---|---|
| Neutrophil < 1,000/μL | Study treatment must be interrupted until neutrophil counts are ≥ 1,500/μL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at a reduced dose. |
| Hemoglobin ≤ 8 g/dL | Study treatment must be interrupted until hemoglobin is ≥ 9 g/dL, with weekly blood counts for CBC monitored until recovery. Study treatment may then be resumed at a reduced dose. |

Abbreviations: CBC = complete blood count

[a] If the platelet count has not reverted within 28 days of interruption to ≥ 100,000/μL on first or subsequent occurrence, the patient should be discontinued.

[b] For patients with platelet count ≤ 10,000/μL, prophylactic platelet transfusion per guidelines may be considered17,18 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.

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

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

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

## 5.4. Packaging, Labeling, and Storage

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

The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-patient-specific.

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. Study Treatment Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatment throughout the clinical study. The study treatment accountability log includes information including the enrollment number, amount and date dispensed, and amount and date 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 study treatment accountability log. The pharmacist will dispense study treatment for each patient according to the protocol and Pharmacy Manual, if applicable.

## 5.6. Previous and Concomitant Medications

Any medication the patient takes other than the study treatment, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: trade name or generic name if trade name is not available, route of administration, start date, stop date, frequency, 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 or have taken since the previous visit.

Niraparib has been associated with QT prolongation when co-administered with medications known to cause QTc prolongation. Therefore, Investigator should be advised to use caution with drugs listed in Appendix D. Additionally, niraparib has potential to induce cytochrome P450 (CYP)1A2 and is a substrate for P-glycoprotein (P-gp); therefore, Investigator should be advised to use caution with drugs metabolized by CYP1A2 (see Appendix A) or drugs that are inhibitors or substrates of P-gp. The niraparib safety profile includes risk for thrombocytopenia; therefore, Investigator should be advised to use caution with anticoagulation and antiplatelet drugs.

### 5.6.1. Prohibited Medications and Other Study Restrictions

An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown; therefore, live virus and bacterial vaccines should not be administered to patients 4 weeks before or during the study (defined by the time of first dose).

No other anticancer therapy is permitted during the course of the study treatment for any patient. Temporary steroid use will be permitted for treatment of AEs or for prophylaxis. Of note, topical steroids are permitted without limitation. 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, 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. Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment) is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

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

Patients who are blood donors should not donate blood during the study and for 90 days after the last dose of study treatment.

# 6. VARIABLES AND METHODS OF ASSESSMENT

## 6.1. Efficacy Variables

### 6.1.1. Primary Efficacy: Objective Response Rate

The ORR is defined as the proportion of patients achieving complete response (CR) or partial response (PR) as assessed by the Investigator per RECIST (v.1.1) (Appendix B).

### 6.1.2. Secondary Efficacy

#### 6.1.2.1. Duration of Response

Duration of response is defined as the time from first documentation of CR or PR until the time of first documentation of disease progression (PD) as assessed by the Investigator per RECIST (v.1.1) or clinical criteria (Appendix B).

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 may also be determined if at least 1 of the following criteria is met:

1. 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 criteria
2. Definitive clinical signs and symptoms of PD unrelated to nonmalignant or iatrogenic causes ([a] intractable cancer-related pain; [b] malignant bowel obstruction/worsening dysfunction; or [c] unequivocal symptomatic worsening of ascites or pleural effusion) AND CA-125 progression according to Gynecologic Cancer Intergroup criteria.

Abnormal CA-125 levels on-study do not represent disease progression; however, they may prompt imaging if clinically indicated. 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. If CT/MRI shows existing (baseline) lesions that only equivocally suggest PD and additional diagnostic tests are required to determine unequivocal PD, the official date of PD will be the date PD was unequivocally determined. Alternatively, with new lesions (except ascites and effusions) that are initially equivocal that are later unequivocally determined, the date of progression will be the date the lesion was initially identified.

#### 6.1.2.2. Disease Control Rate

Disease control rate is defined as the proportion of patients achieving CR, PR, or stable disease (SD) as assessed by the Investigator per RECIST (v.1.1) (Appendix B).

#### 6.1.2.3. Progression-Free Survival

Progression-free survival is defined as the time from the date of first dose to the earlier date of assessment of progression or death by any cause in the absence of progression as assessed by the Investigator per RECIST (v.1.1) or clinical criteria (Appendix B). PFS evaluation will be performed as described by the SAP.

#### 6.1.2.4. Overall Survival

OS is defined as the time from the date of the first dose 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.

As part of OS assessment, information will be collected on subsequent anticancer therapies following study treatment. Using source documentation (including clinic notes), the following information will be collected:

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

#### 6.1.2.5. Time to First Subsequent Therapy (TFST)

Time to first subsequent therapy (TFST) is defined as the time from the date of first dose to the date of first subsequent therapy or death, whichever occurs first. Using source documentation (including clinic notes) the same information will be collected as described in Overall Survival (Section 6.1.2.4).

## 6.2. Safety Variables

Safety parameters evaluated during the conduct of the study include: treatment-emergent AEs (TEAEs), clinical laboratory (hematology and chemistry), vital signs, physical examination, and use of concomitant medications.

### 6.2.1. Definitions

**Adverse event:** An *adverse event* 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.

Adverse events 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.

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

**Serious adverse event:** A *serious adverse event* is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - Note: This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Any AE that prolongs hospitalization will be considered an SAE.
  - Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, disease progression, etc.) will not be considered an SAE; however, the reason for the planned hospitalization should be captured in medical history.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s)
  - An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 6.2.2. Assessment of Adverse Events

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

#### 6.2.2.1. Intensity

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

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

A distinction should be made between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above in Section 6.2.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

#### 6.2.2.2. Causality

The Investigator will assess the causality/relationship between the study treatment 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).

### 6.2.3. Collecting and Recording Adverse Events

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

All AEs and SAEs will be collected and recorded in the eCRF for each patient from the day of signing the screening ICF until the EOT visit (see Table 4 for schedule of events). New SAEs (including deaths) will be collected for an additional 30 days after the last dose of study treatment. 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 normal levels, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

If an Investigator becomes aware of an SAE after the 30-day follow-up period post treatment discontinuation and considers the SAE related to investigational product, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in this section.

Adverse events may be volunteered spontaneously by the study 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?" The Investigator will document the nature of the AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study treatment as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study treatment and/or study procedure.

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

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

### 6.2.4. 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 6.2.3 and Section 6.2.5.

### 6.2.5. Reporting Serious Adverse Events

The Investigator must report all SAEs within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE.

For all SAEs, an SAE report form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE report must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. Also, any additional SAE documentation must be a clear photocopy

with the patient's personal identifiers removed. The Investigator must sign and date all SAE forms.

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

- Name of person sending the report (ie, name, address of Investigator)
- Patient identification (screening number, initials [if permitted by local data privacy regulations], NOT patient name)
- Protocol number
- Description of SAE
- Causality assessment

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

**SAE REPORTING CONTACT INFORMATION**

Email: PPD

Fax: PPD

#### 6.2.5.1. Submission and Distribution of Adverse Events/Serious Adverse Events

Per regulatory requirements, if an SAE is required to be submitted to a Regulatory Authority a copy of this report (CIOMS or MedWatch 3500A) will be distributed to the Investigators/site. The Investigator/site will submit a copy the report to their respective institutional review board (IRB) or independent ethics committee (IEC) per local requirements.

#### 6.2.5.2. Pregnancy

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

Pregnancy alone is not regarded as an AE unless there is a possibility that the study treatment may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

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

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

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs (see Section 6.2.5).

#### 6.2.5.3. Adverse Events of Special Interest

MDS, AML, secondary cancers (new malignancies other than MDS/AML), pneumonitis, and embryo-fetal toxicity are Adverse of Special Interest (AESIs). AESIs must be reported to the Sponsor and recorded as such on the eCRF and on an SAE form; the SAE form must be submitted within 24 hours of the Investigator becoming aware as noted for SAEs in Section 6.2.5. AESI monitoring must occur during the study, during long-term follow-up and after study discontinuation.

### 6.2.6. Clinical Laboratory Assessment

The following laboratory variables will be determined in accordance with Table 4 (schedule of events):

- Complete blood count:
  - Hemoglobin
  - Platelets
  - Mean platelet volume (optional*)
  - Mean corpuscular volume
  - White blood cell count
  - Differential white cell count
- Serum chemistry assessments for safety include:
  - Sodium
  - Potassium
  - Calcium
  - Magnesium
  - Chloride
  - Glucose
  - Creatinine
  - Total bilirubin
  - Gamma glutamyltransferase

  - Alkaline phosphatase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Urea or blood urea nitrogen
  - Total protein
  - Albumin
  - Lactate dehydrogenase
  - Amylase
- Serum CA-125
- Serum pregnancy testing

These tests will be performed by the local laboratory at the clinical site.

Any laboratory values assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the SAE reporting process (see Section 6.2.5).

Hematological testing may occur more frequently than is specified in Table 4 when additional testing is medically indicated per Investigator judgment. Additional tests may be performed at a laboratory facility other than the study site, but test results must be reported to the study site, the study site must keep a copy of test results with the patient's study file, and the results must be entered into the electronic data capture system.

For any suspected case of MDS/AML or second primary malignancies other than MDS/AMLreported 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,[19] and other sample testing reports related to MDS/AML or secondary cancer (new malignancies other than 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.

* Note: Although mean platelet volume collection is optional, it is highly encouraged, especially for patients with high-grade thrombocytopenia.

### 6.2.7. Physical Examination and Vital Signs

Physical examinations, including height (screening only), weight, and vital signs (blood pressure [BP], pulse, and temperature), will be performed in accordance with the schedule of events (Table 4).

Any physical examination or vital sign findings assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the SAE reporting process (see Section 6.2.5).

#### 6.2.8. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (see Appendix C) in accordance with the schedule of events (Table 4). The same observer should assess performance status each time.

#### 6.2.9. Additional Safety Assessments

All patients will undergo a single ECG assessment at the screening visit (Table 4). The ECG assessment should be performed prior to any blood draws for PK or other laboratory evaluations. Patients will be supine and rested for approximately 2 minutes before ECGs are recorded. ECGs may be archived for future central evaluation if needed.

A subset of approximately 12 patients will undergo intensive, triplicate ECG monitoring to coincide with PK evaluation on Cycle1/Day 1 (see Section 6.4 for time points). This subset of patients will undergo all other assessments in the study.

Any ECG findings assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the SAE should be recorded and reported according to the SAE reporting process (see Section 6.2.5).

### 6.3. Demographics and Baseline Characteristics

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

#### 6.3.1. Patient Eligibility

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

#### 6.3.2. Patient Demography

Patient demography consists of:

- Age at screening
- Race
- Ethnicity
- Sex

#### 6.3.3. 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 and toxicities (including hematologic events) for each prior treatment
- Date of recurrence for each treatment
- ECOG performance status
- Collection of hematologic events during prior therapy

### 6.3.4. Medical and Surgical History

Major medical and surgical history (including medication history), including history of prior thrombocytopenia, neutropenia, leukopenia, or anemia within 1 year prior to signing the main study ICF, will be collected. Details of any prior invasive malignancy will be collected. Medical and surgical history will be obtained by interviewing the patient or by reviewing his/her medical records.

### 6.3.5. Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.6. Medications will be coded using World Health Organization Anatomical Therapeutic Chemical classification.

## 6.4. Pharmacokinetics

Plasma samples for population PK assessment will be analyzed for concentrations of niraparib and its major metabolite. A population PK modeling approach will be used to describe plasma concentrations of niraparib and its major metabolite in patients. In the analysis, a number of covariates will be evaluated to determine if they contribute to differences in the PK estimates among individuals. Parameters of interest include area under the curve (AUC), minimum observed plasma concentration ($C_{min}$), maximum observed plasma concentration ($C_{max}$), and/or AUC at steady-state ($AUC_{ss}$), $C_{min,ss}$, $C_{max,ss}$, and, if the data allow, oral clearance (CL/F) and oral volume of distribution (Vz/F).

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

For all patients, blood samples for measurements of plasma levels of niraparib will be obtained on Cycle 1/Day 1 predose (within 30 minutes) and 2 hours postdose (±15 minutes), Cycle 2/Day 1 predose (within 30 minutes) and 2 hours postdose (±15 minutes), Cycle 4/Day 1 predose (within 30 minutes), and Cycle 8/Day 1 predose (within 30 minutes). If niraparib is not

administered, collection of predose blood sample is required, however postdose sample collection is not required.

At selected sites, a subset of approximately 12 patients will undergo intensive, triplicate ECG monitoring to coincide with PK evaluation on Cycle1/Day 1. These patients will have triplicate ECGs taken prior to the PK blood draw predose and at 1, 2, 4, 6, and 8 hours postdose.

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

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

## 6.5. Blood and Tissue Samples

Blood samples will be collected for all patients during screening for determination of g*BRCA*$^{mut}$ status.

Blood samples will be collected for all patients during screening for the exploratory evaluation of circulating markers.

Tumor samples, archival and/or fresh biopsy, for all patients will be collected prior to study treatment initiation for the evaluation of tumor markers of niraparib sensitivity or resistance, such as those related to DNA repair deficiency, including centralized HRD and t*BRCA*$^{mut}$ status testing. Centralized HRD testing must be completed prior to enrollment. If historic blood g*BRCA*$^{mut}$ is detected by a central g*BRCA*$^{mut}$ testing as part of screening, then tumor HRD sample test results are not required prior to enrollment, however the test should be performed for all enrolled patients. Sites are encouraged to send tumor samples for HRD testing as soon as a patient is considered for enrollment in this study.

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

DNA from the blood and tumor samples will be stored and may be used at a later time for biomarker testing including potential to bridging to candidate companion diagnostic assays.

The testing of markers related to tumor immunology may be conducted from tissue or blood.

# 7. STUDY CONDUCT

## 7.1. Schedule of Procedures

A schedule of events is provided in Table 4.

**Table 4: Schedule of Events**

| **Cycle**[a] | **Screening**[b] | **1** | | | | **Subsequent Cycles**[a] | **EOT** | **Post-Treatment Assessments** |
|---|---|---|---|---|---|---|---|---|
| **Day** | **-28 to -1** | **1** | **8** | **15** | **22** | **Cycle n, Day 1** | **(within 7 days of last dose)** | |
| Informed consent[b c] | X | | | | | | | |
| Demographics | X | | | | | | | |
| Medical, surgical, cancer, and medication history | X | | | | | | | |
| Sample collection (tumor) for centralized t*BRCA*$^{mut}$/HRD testing[c] | X[c] | | | | | | | |
| Sample collection (whole blood) for g*BRCA*$^{mut}$ testing | X | | | | | | | |
| Tumor sample *(optional)*[d] | X | | | | | | X | |
| Blood sample for exploratory biomarker analyses[e] | X | | | | | | | |
| Blood sample for PK[f] | | X | | | | X | | |
| Tumor assessment (RECIST)[g] | X | | | | | X[g] | X | X[g] |
| Chest CT/MRI[h] | X | | | | | | | |
| Pregnancy test[i] | X | | | | | X | | |
| Serum chemistry | X | X[j] | | X | | X | X | |
| CBC[k] | X | X[j] | X[l] | X | X[l] | X | X | |
| Serum CA-125[j] | X | X[g] | | | | X[g] | X | X |
| ECG[m] | X[m] | | | | | | | |
| Physical examination | X | | | | | | | |
| Symptom-directed physical examination | | X | | X | | X[n] | X | |
| Vital signs, height, weight[o] | X | X | | X | | X | X | |

| **Cycle**[a] | **Screening**[b] | **1** | | | | **Subsequent Cycles**[a] | **EOT** | **Post-Treatment Assessments** |
|---|---|---|---|---|---|---|---|---|
| **Day** | **-28 to -1** | **1** | **8** | **15** | **22** | **Cycle n, Day 1** | **(within 7 days of last dose)** | |
| ECOG performance status | X | | | | | X[n] | X | |
| Bone marrow aspirate and biopsy [p] | | X[p] | | | | | | |
| Concomitant medications | X | X | | X | | X | X | |
| Adverse event monitoring | X | X | | X | | X | X[q] | X |
| Study treatment dispensed/collected | | X | | | | X | X | |
| Survival assessment[r] | | | | | | | | X |

Abbreviations: CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; g*BRCA*$^{mut}$ = germline breast cancer gene mutation; t*BRCA*$^{mut}$ = tumor breast cancer mutation; HRD = homologous recombination deficiency; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Treatment cycles are 28 days long, with visits on Day 1 of each cycle unless otherwise specified. Visits (other than Cycle 1) continue every 28 days until study treatment discontinuation. All visits have a window of ± 3 days (calculated in reference to Cycle 1/Day 1).

[b] Screening tests that could be considered standard of care (ie, CT/MRI, physical examination, vital signs, height, weight, and assessment of serum chemistry, CBC, pregnancy testing, and serum CA-125) that were performed within the protocol-required timelines (ie, within the 28-day screening window; within 72 hours prior to first dose [ie, Cycle 1/Day 1] where required) but prior to informed consent being obtained may be used as part of the patient's screening assessment.

[c] For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation. Centralized HRD testing of tumor sample must be completed with results reported prior to enrollment. The sample may be sent in advance of the protocol-defined screening period in order to facilitate the screening and enrollment process. A separate ICF may be signed prior to the screening period for HRD testing in order to facilitate early testing. Depending on local site requirements, patients may sign a screening study ICF prior to the screening period to facilitate early HRD testing only. All other study tests and procedures must be done in the screening window (Day -28 to Day -1). For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained.

[d] Formalin-fixed, paraffin-embedded tumor sample consisting of a total of 100-micron thickness of sections (≥ 80-micron minimum) or unsectioned paraffin block.

[e] Blood samples will be collected for all patients during screening for the exploratory evaluation of circulating biomarkers. The sponsor may discontinue the blood collection when samples have been collected from an adequate number of patients.

[f] Blood samples for PK may be collected on Cycle 1/Day 1 predose (within 30 minutes) and 2 hours (± 15 minutes) postdose, on Cycle 2/ Day 1 predose (within 30 minutes) and 2 hours (± 15 minutes) postdose, on Cycle 4/Day 1 predose (within 30 minutes), and on Cycle 8/Day 1 predose (within 30 minutes). At selected sites, a subset of patients (approximately 12) will undergo triplicate ECG monitoring to coincide with PK evaluation on Cycle 1/Day 1 predose and at 1, 2, 4, 6, and 8 hours postdose. 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 or other laboratory evaluations.

[g] RECIST tumor assessment via CT or MRI of abdomen/pelvis and clinically indicated areas required at screening, every 8 weeks (± 7 days) from Cycle 1/Day 1 (ie, Cycle 3, Cycle 5, Cycle 7) for 6 months, and then every 12 weeks (ie, Cycle 10, Cycle 13, Cycle 16, etc.) until progression.Positron emission tomography/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 a reason other than disease progression as defined in the protocol or death, withdrawal of consent, or loss to follow-up, then scans and CA-125 testing should continue at the specified intervals (until the start of subsequent anticancer treatment). 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.

[h] 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.

[i] Negative serum pregnancy test required within 72 hours prior to first dose of study treatment (ie, Cycle 1/Day 1) for females of childbearing potential; repeated every 3 months for duration of study treatment (ie, Cycle 4, Cycle 7, etc).

[j] If screening laboratory testing (serum chemistry, CBC, CA-125) performed within 72 hours of Day 1, repeat testing is not required.

[k] If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will be also required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume.

[l] Collection of blood for the Cycle 1/Day 8 and Day 22 CBC may be done at the study center's local laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an adequate laboratory. The laboratory must have the capability to provide results to the Principal Investigator electronically or by fax within 24 hours of blood collection.

[m] Patients will undergo a single ECG monitoring assessment at screening, prior to laboratory evaluations. At selected sites, a subset of patients (approximately 12) will undergo triplicate ECG monitoring to coincide with PK evaluation on Cycle 1/Day 1 predose and at 1, 2, 4, 6, and 8 hours postdose. Triplicate ECGs should be performed between 2 and 5 minutes apart and should be performed prior to blood draws for PK or other laboratory evaluations.

[n] Symptom-directed physical examination is to be conducted at every visit and ECOG assessed every 12 weeks (± 7 days) until EOT.

[o] Vital signs include BP, pulse, and temperature. Height obtained at screening only.

[p] For any suspected case of MDS/AML or secondary cancer (new malignancies other than MDS/AML) reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization criteria[19] and other sample testing results related to MDS/AML or secondary cancer (new malignancies other than MDS/AML).

[q] New SAEs recorded up to 30 days after last dose of study treatment administration.

[r] Every 90 (± 7) days after treatment discontinuation. In addition to survival, this assessment also includes outcomes for subsequent anticancer therapies including any new malignancy information.

## 7.2. Procedures by Visit

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
  - A main study ICF will be signed before any study procedures are performed. Patients may sign a separate HRD screening ICF prior to the screening period to facilitate early HRD testing only.
  - Note: Screening tests that could be considered standard of care (ie, CT/MRI, physical examination, vital signs, height, weight, and assessment of serum pregnancy, serum chemistry, CBC, and serum CA-125) that were performed within the protocol-required timelines (ie, within the 28-day screening window; within 72 hours of first dose [ie, Cycle 1/Day 1] where required) but prior to informed consent being obtained may be used as part of the patient's screening assessment. 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.
- Demographics
- Archival or fresh tumor sample for centralized tumor *BRCA*$^{mut}$/HRD testing
  - For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation
  - Centralized HRD testing of tumor sample must be completed with results reported prior to enrollment. The sample may be sent after the screening ICF has been signed but in advance of the protocol-defined screening period in order to facilitate the screening and enrollment process. If historic blood g*BRCA*$^{mut}$ is detected by a central g*BRCA*$^{mut}$ testing as part of screening, then tumor HRD sample test results are not required prior to enrollment.
- Medical/surgical/cancer/medication history, including history of prior thrombocytopenia, neutropenia, leukopenia, or anemia within 1 year prior to signing the main ICF
- Fresh biopsy tumor sample (optional)
- Blood sample for centralized g*BRCA*$^{mut}$ testing (whole blood)
- Blood sample for exploratory biomarker analyses (whole blood)
- Serum pregnancy test (within 72 hours prior to first dose [ie, Cycle 1/Day 1]) (for females of childbearing potential only)
- Physical examination

- Vital signs (BP, pulse, and temperature) and weight
- Height
- ECOG performance status
- CBC
- Serum chemistry
- Serum CA-125
- Single ECG assessment (prior to any laboratory assessments)
- 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)
- AE monitoring
- Concomitant medications

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

### 7.2.2. Cycle 1, Day 1

- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- CBC (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
- Blood sample for PK determination predose (within 30 minutes) and 2 hours (± 15 minutes) postdose; the exact time of the blood draw is to be recorded
- At selected sites, a subset of patients (approximately 12) will undergo triplicate ECG monitoring to coincide with PK evaluation predose and at 1, 2, 4, 6, and 8 hours postdose; triplicate ECGs should be performed between 2 and 5 minutes apart and should be performed prior to blood draws for PK or other laboratory evaluations
- Study treatment capsules dispensed; first dose administered at the site
- AE monitoring
- Concomitant medications

### 7.2.3. Cycle 1, Day 8

- CBC
  - Collection of blood for the Cycle 1/Day 8 CBC may be done at the study center's local laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an adequate laboratory. The laboratory must have the capability to provide results to the Principal Investigator electronically or by fax within 24 hours of blood collection.

### 7.2.4. Cycle 1, Day 15

- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- CBC
- Serum chemistry
- AE monitoring
- Concomitant medications

### 7.2.5. Cycle 1, Day 22

- CBC
  - Collection of blood for the Cycle 1/Day 22 CBC may be done at the study center's local laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an adequate laboratory. The laboratory must have the capability to provide results to the Principal Investigator electronically or by fax within 24 hours of blood collection.

### 7.2.6. Day 1, Subsequent Cycles

- Symptom-directed physical examination at every visit until EOT
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status every 12 weeks (± 7 days) from Cycle 1/Day 1 (ie, Cycle 4, Cycle 7, Cycle 10, etc) until EOT
- CBC
- Serum chemistry
- Serum CA-125
- Serum pregnancy test at 3-month intervals from screening (Cycles 4, 7, etc)
- Blood sample for PK determination on Cycle 2/Day 1 predose (within 30 minutes) and 2 hours (± 15 minutes) postdose, on Cycle 4/Day 1 predose (within 30 minutes), and on Cycle 8/Day 1 predose (within 30 minutes). If niraparib is not administered, collection of predose blood sample is required, however postdose sample collection is not required.

- RECIST (v.1.1) tumor assessment of the abdomen/pelvis and other areas (if clinically indicated) every 8 weeks (± 7 days) from Cycle 1/Day 1 for 6 months (ie, Cycle 3, Cycle 5, Cycle 7), and then every 12 weeks (ie, Cycle 10, Cycle 13, Cycle 16, etc.) until progression
- Study treatment capsules dispensed/collected, as appropriate
- AEs
- Concomitant medications

### 7.2.7. End of Treatment (within 7 days of last dose)

- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- CBC
- Serum chemistry
- Serum CA-125
  - If a patient discontinues treatment for a reason other than disease progression as defined in the protocol or death, withdrawal of consent, or loss to follow-up, then scans and CA-125 testing should continue at the specified intervals (every 12 weeks until the start of subsequent anticancer treatment).
- Fresh biopsy tumor sample (optional)
- RECIST (v.1.1) tumor assessment of the abdomen/pelvis and other areas (if clinically indicated)
  - If a patient discontinues treatment for a reason other than disease progression as defined in the protocol or death, withdrawal of consent, or loss to follow-up, then scans and CA-125 testing should continue at the specified intervals (every 12 weeks until the start of subsequent anticancer treatment).
- Study treatment capsules collected
- AEs (SAEs recorded up to 30 days after treatment discontinuation), SAEs assessed as study drug related throughout study and post-treatment assessments and AESI
- Concomitant medications

### 7.2.8. Post-Treatment Assessments (Study Visit Not Always Required)

- Serum CA-125
  - If a patient discontinues treatment for a reason other than disease progression as defined in the protocol or death, withdrawal of consent, or loss to follow-up, then scans and CA-125 testing should continue at the specified intervals (every 12 weeks until the start of subsequent anticancer treatment).

- RECIST (v.1.1) tumor assessment of the abdomen/pelvis and other areas (if clinically indicated)
  - If a patient discontinues treatment for a reason other than disease progression as defined in the protocol or death, withdrawal of consent, or loss to follow-up, then scans and CA-125 testing should continue at the specified intervals (every 12 weeks until the start of subsequent anticancer treatment).
- AE monitoring
  - New SAEs recorded up to 30 days after last study treatment administration
  - SAEs assessed as related to the study treatment
  - Any AEs will be monitored until it has resolved, any abnormal laboratory values have returned to baseline or normalized, there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient has died
  - AESI
- Survival assessment every 90 days including assessment of outcomes of subsequent anticancer therapies following study treatment
  - For patients only being followed for survival, survival assessment may be conducted via telephone
- Anticancer therapies assessment
  - Name (and/or class)
  - Start date
  - Dose-limiting toxicities
  - Best response (CR, PR, SD, PD)
  - Progression date

### 7.2.9. Unscheduled Assessments

For any suspected case of MDS, AML or secondary cancer (new malignancies other than MDS/AML)reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy to be conducted. See Section 6.2.6 for details.

# 8. STATISTICAL METHODS

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

## 8.1. Analysis Populations

Efficacy analysis will be performed on the following populations:

- Intent-to-Treat (ITT) Population, defined as all dosed patients with measurable disease at baseline.
- Response-Evaluable Population, defined as all ITT patients with at least one evaluable post-baseline tumor scan.
- Per-protocol (PP) population, consisting of all patients in the ITT Population 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.

Safety analysis will be performed on the Safety Population, defined as all patients who received at least 1 dose of study drug.

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

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

## 8.3. Efficacy Analyses

### 8.3.1. Primary Efficacy Parameter

The primary efficacy endpoint is the investigator-assessed confirmed ORR per RECIST v1.1 in the HRD-positive patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy. Patients with prior PARP inhibitor treatment are excluded. The alternative hypothesis of ORR ≥30% will be tested against a null hypothesis of ORR ≤10%. The rationale of the hypothesis and the power calculation are detailed in section 8.8. The response rate and 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided.

### 8.3.2. Secondary Efficacy Parameters

The following key secondary efficacy endpoints are defined:

- Investigator-assessed confirmed ORR per RECIST v1.1 in all patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last

platinum-based therapy, regardless of HRD status. Patients with prior PARP treatment are excluded.

- Investigator-assessed confirmed ORR per RECIST v1.1 in all patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive or platinum-resistant to the last platinum-based therapy, regardless of HRD status. Patients with prior PARP treatment are excluded.
- Investigator-assessed confirmed ORR per RECIST v1.1 in all patients treated in the study.

The alternative hypothesis of ORR ≥25% will be tested against a null hypothesis of ORR ≤10%. The response rate and 95% CI along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for each key secondary endpoint. The primary and key secondary efficacy endpoints will be tested sequentially to control the overall Type I error rate at 1-sided 0.025 level.

Other secondary efficacy endpoints will be analyzed descriptively including:

- DOR, DCR, PFS, TFST and OS in patient groups included in the primary and key secondary endpoints.
- ORR, DOR, DCR, PFS, TFST and OS in patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-resistant to the last platinum-based therapy, by HRD status. Patients with prior PARP treatment are excluded.
- ORR, DOR, DCR, PFS, TFST and OS in all patients regardless of prior lines of anti-cancer therapy, including HRD subgroup analysis and platinum-sensitivity (sensitive vs. resistant) subgroup analysis. Patients with prior PARP treatment are excluded.

Other exploratory analyses will include:

- ORR, DOR, DCR, PFS, TFST and OS in patients with prior PARP treatment, including HRD subgroup analysis
- ORR, DOR, DCR, PFS, TFST and OS in patients who are platinum-refractory to the last platinum-based therapy, including HRD subgroup analysis

Response rate and 95% CI based on the binomial distribution will be provided.

Time-to-event analysis will be performed using Kaplan-Meier method to provide median estimates and 95% CI.

## 8.4. Safety Analyses

Adverse event terms will be coded using the Medical Dictionary for Regulatory Activities and will be summarized for all treated patients. Incidence of AEs occurring during the study will be summarized by system organ class and preferred term. Adverse events will also be summarized by causality and grade. Serious adverse events will be listed separately. Descriptive summary statistics will be used to summarize changes over time in laboratory values, vital signs and physical examination findings Laboratory parameter changes will be described using shift tables according to CTCAE (v.4.03). Administrative interim safety data will be examined on an ongoing basis to ensure patient safety.

## 8.5. Pharmacokinetic Analyses

For all patients, as appropriate, blood samples for measurements of plasma levels of niraparib and its major metabolite 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 will be obtained on Cycle 4/Day 1 and Cycle 8/Day 1 predose (within 30 minutes) only.

Pharmacokinetic parameters including AUC, $C_{min}$, $t_{max}$, $C_{max}$, $AUC_{ss}$, $C_{minss}$, $C_{maxss}$, and, if the data allow, CL/F and Vz/F, will be determined.

In addition, the PK/pharmacodynamic relationship between concentrations of niraparib and its major metabolite with efficacy and safety measures will be investigated, and exposure (AUC, and/or $C_{max}$) determined for niraparib and its major metabolite will be correlated with safety (selected AEs) and efficacy variables.

Descriptive statistics and categorical analyses of ECG variables will be provided for the subset of patients (approximately 12) with intensive ECG collection. A separate population PK analysis plan will be written to describe the analyses of ECG variables and PK parameters.

## 8.6. Biomarker Analyses

Efficacy in the biomarker subgroups, such as t*BRCA* and HRD or HRR gene mutations, will be explored and analyzed descriptively.

## 8.7. Post-Treatment Analyses

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

## 8.8. Determination of Sample Size

The study protocol initially allowed enrollment of patients with at least 3 prior lines of anti-cancer therapy. With subsequent protocol amendments, the study enrollment was adjusted to allow only HRD-positive patients with 3 or 4 prior lines of anti-cancer therapy. This adjustment was made in consideration of the evolving role of PARP inhibitors in ovarian cancer treatment based on external data. Overall, approximately 500 patients are expected in the study. The study enrollment is also expected to include a minimum number of t$BRCA^{mut}$ patients (≥50) and HRD-positive patients (≥150).

For the primary efficacy endpoint of ORR in HRD-positive patients who have received 3 or 4 prior lines of anti-cancer therapy and are platinum-sensitive to the last platinum-based therapy, an alternative hypothesis of ORR ≥30% is considered against a null hypothesis of ORR ≤10%.

For the key secondary efficacy endpoints of ORR tested in broader subgroups to include platinum-resistant patients and/or HRD-negative/unknown patients, an alternative hypothesis of ORR ≥25% is considered against a null hypothesis of ORR ≤10%.

The rationale of choosing the null and alternative hypothesis for the primary and the key secondary efficacy endpoints are based on data external from this study; these clinical trials of PARP inhibitors (e.g. niraparib, olaparib, and rucaparib) which suggests that platinum-sensitivity and/or HRD positivity (including *BRCA* mutant) play a role in how patients with ovarian cancer

respond to treatment. There is limited data for the overall HRD-positive population in ovarian cancer treatment. In a rucaparib study that included patients who are LOH-positive (another assay evaluating tumor homologous recombination deficiency), ORR in the non-t*BRCA*/LOH-positive patients with at least 2 prior lines of therapy was 17%.[1] A recent publication of platinum-sensitive patients with at least 1 prior line of therapy presented an ORR of 29% in the non-t*BRCA*/LOH-positive group.[2] Therefore, choice of the hypotheses of Ho: ORR ≤10% vs. Ha: ORR ≥30% for the primary efficacy and Ho: ORR ≤10% vs. Ha: ORR ≥25% for the key secondary analyses would be appropriate for testing the efficacy of niraparib treatment in the specified populations.

It is estimated that 45 patients would provide 90% power for testing the primary efficacy analyses. Statistical power for various sample sizes are presented below to provide guidance for the key secondary hypotheses when tested individually (regardless of sequential testing). The power is calculated by assuming the exact binomial distribution using East® software Version 6.4.

| N | Statistical Power* |
|---|---|
| 45 | 72% |
| 60 | 85% |
| 75 | 92% |
| 90 | 96% |

* Ho: ORR≤10% vs Ha: ORR≥25%

As of August 2017, approximately 450 patients were dosed in the study. Approximately 320 patients had 3 or 4 prior lines of anti-cancer therapy (~150 HRD positive). Based on a preliminary calculation of the platinum-sensitivity to the last platinum-based therapy, the number of enrolled patients for the primary endpoint and the key secondary efficacy endpoints are considered adequate to ensure sufficient power for the planned analysis.

# 9. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

## 9.1. Data Quality Assurance

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

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

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

## 9.2. Access to Source Data/Documents

An 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 compliant with Code of Federal Regulations 21 Part 11.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. 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, 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 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 Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

## 9.4. Good Clinical Practice

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

## 9.5. Informed Consent

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

The ICF must be signed and dated; one copy will be given to the patient and the Investigator will retain a 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.

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

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 IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

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

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

The anonymity of participating patients must be maintained. Patients will be specified on study documents by their enrollment number or birth date, not by name. Documents that identify the patient (eg, the signed informed consent document) must be maintained in confidence by the Investigator.

## 9.8. Study Monitoring

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

The study will be monitored by the Sponsor (or designee). Monitoring will be done by personal visits from a representative of the sponsor (site monitor) who will review the eCRFs 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

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

## 9.10. Ethical Considerations

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

## 9.11. Publication Policy

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

# 10. REFERENCE LIST

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# APPENDIX A. DRUGS KNOWN TO INHIBIT OR INDUCE CYP1A2

| **Inhibitors of CYP1A2** | | |
|---|---|---|
| **Strong**<br>≥ 5-fold increase in AUC or >80% decrease in CL | **Moderate**<br>≥ 2 but < 5-fold increase in AUC or 50%-80% decrease in CL | **Weak**<br>≥ 1.25 but < 2-fold increase in AUC or 20**%**-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**<br>80% decrease in AUC | **Moderate**<br>50%-80% decrease in AUC | **Weak**<br>20%-50% decrease in AUC |
| | Montelukast, phenytoin, smokers versus non-smokers | Moricizine, omeprazole, phenobarbital |
| **Substrates of CYP1A2** | | |
| **Sensitive substrates**[a] | | **Substrates with narrow therapeutic range**[b] |
| Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine | | Theophylline, tizanidine, Warfarin |

AUC = area under the curve; CL = clearance.
Source: CDER, 2012.[20]

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

[b] 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).

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

**Response Criteria by RECIST v.1.1**

**Evaluation of Target Lesions**

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

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

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

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

**Evaluation of Non-Target Lesions**

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

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

Non-CR/Non-PD: Persistence of 1 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 5: 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 6: 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 stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

# APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

Source:[21]

# APPENDIX D. SELECT 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:[22,23]

# APPENDIX E. CONTRACEPTION GUIDELINES

Patients of childbearing 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 informed consent form through the study treatment washout period, which is at least 90 days) must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 90 days after last dose of study treatment(s):

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence, if this is the preferred and usual lifestyle of the subject

# APPENDIX F. SAMPLE MYRIAD MYCHOICE® HRD CDX TEST RESULT FORM


CONFIDENTIAL

MYRIAD myChoice HRD CDx

## Myriad myChoice® HRD CDx Test Result

**RECEIVING HEALTHCARE PROVIDER**
**Physician Name, MD**
Myriad Oncology Partners
320 Wakara Way
Salt Lake City, UT 84108

**ORDERING PHYSICIAN**
**Physician Name, MD**

**SPECIMEN**

| | |
|---|---|
| Specimen Type: | FFPE Tissue |
| Tissue: | Breast |
| Surgery/Biopsy Date: | Date |
| Sample Received: | Apr 8, 2015 |
| Report Date: | Apr 9, 2015 |
| Final Report Date: | Apr 30, 2015 |

**PATIENT**

| | |
|---|---|
| Name: | Patient Name |
| Date of Birth: | PPD 1950 |
| Patient ID: | |
| Gender: | Female |
| Accession #: | PPD |
| Requisition #: | 000000 |

**Block(s) Analyzed:** 19238157

**Myriad myChoice® HRD CDx Status: POSITIVE**

**RESULT DESCRIPTION**

**Myriad myChoice® HRD CDx** classifies a tumor sample as Homologous Recombination Deficient (HRD Positive), or Homologous Recombination Non-Deficient (HRD Negative). Next generation sequencing is used to measure a molecular signature for genomic instability, and to assess mutation status of the *BRCA1* and *BRCA2* genes in tumor DNA. Tumors with deleterious or suspected deleterious mutations in *BRCA1* or *BRCA2* are classified as HRD positive, regardless of the molecular signature result.

**INTENDED USE:** Myriad myChoice® HRD CDx is a next generation sequencing-based in vitro diagnostic test, which assesses tumor genomic instability in ovarian or breast tumors and simultaneously detects and classifies variants in the *BRCA1* and *BRCA2* genes, including sequence variants and large rearrangements using DNA obtained from formalin-fixed paraffin-embedded (FFPE) tumor tissue. The results from this assay may be used as an aid in treatment decision-making for investigational studies using Poly-ADP Ribose Polymerase (PARP) inhibitors for patients with breast and/or ovarian cancer. This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, Inc., a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108.

CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use.

**Genomic Instability Status: POSITIVE**

The genomic instability status is a measurement of three biomarkers (loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions) associated with homologous recombination deficiency.

**Tumor *BRCA1*/*BRCA2* Mutation Status: POSITIVE**

| GENE | CLINICALLY SIGNIFICANT MUTATION(S) | INTERPRETATION |
|---|---|---|
| *BRCA1* | c.2311T>C (p.Leu771Leu) | DELETERIOUS MUTATION |
| *BRCA1* | c.4308T>C (p.Ser1436Ser) | DELETERIOUS MUTATION |
| *BRCA2* | None Detected | NO DELETERIOUS MUTATIONS |

**NOTE: This result may or may not reflect the germline *BRCA1* and *BRCA2* status of this individual. Follow-up germline testing may be appropriate.**

This Authorized Signature pertains to this laboratory report:

PPD PhD
Diplomate ABMG
Laboratory Director

PPD PhD
Diplomate ABMG
Laboratory Director

PPD MD
Diplomate ABP, ABMG
Laboratory Director
Anatomic Pathology

PPD MD, PhD
Chief Medical Officer
Myriad Genetic Laboratories

myriad

Myriad Genetic Laboratories, Inc. | 320 Wakara Way, Salt Lake City, Utah 84108 | PH: PPD FX: PPD



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