Title: A Phase 2, Multicenter, Open-label, Single-arm Study to Evaluate the Safety and Efficacy of Niraparib in Japanese Patients With Advanced, Relapsed, High-grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Have Received 3 or 4 Previous Chemotherapy Regimens

NCT Number: NCT03759600

Statistical analysis plan Approve Date: 08-AUG-2019

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Niraparib-2002

A Phase 2, Multicenter, Open-label, Single-arm Study to Evaluate the Safety and Efficacy of Niraparib in Japanese Patients With Advanced, Relapsed, High-grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Have Received 3 or 4 Previous Chemotherapy Regimens

PHASE 2

Version: 1.0

Date: 08 August 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 2

Protocol Date: 18 January 2019

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BRCA	breast cancer (gene)
CI	confidence interval
CNS	central nervous system
CR	complete response
ECGs	electrocardiograms
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FUACT	follow-up anti-cancer treatment
GGT	γ-glutamyl transferase
INR	international normalized ratio
LDH	lactate dehydrogenase
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Inevaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression-free survival
PR	partial response
PT	preferred term
PTE	pretremtent event
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TFST	time to first subsequent therapy
WHO Drug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

To evaluate the efficacy of niraparib in HRD-positive Japanese 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.

4.2 Secondary Objectives

To evaluate the safety of niraparib in HRD-positive Japanese 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.

4.3 Additional Objectives

To evaluate the pharmacokinetics of niraparib in HRD-positive Japanese 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.

4.4 Study Design

This study is a phase 2, multicenter, 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 3 or 4 previous chemotherapy regimens.

Patients must have received 3 or 4 previous chemotherapy regimens. 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. The safety of niraparib will also be assessed in Japanese patients who received 3 or 4 prior anti-cancer therapies and are platinum-sensitive to the last platinum- based therapy.

In order to determine eligibility, a tumor sample will be tested for HRD testing. Archival or fresh tissue is required in order to enroll in the study. The sample may be tested in advance of the protocol-defined screening period (ie, within 40 days before Cycle 1 Day 1) if the consent has been obtained, in order to facilitate the screening and enrollment process. Patients must wait for the results from the on-study HRD testing provided by the central laboratory prior to enrollment, unless they have previously detected g*BRCA* mutation. If g*BRCA*mut is detected by a prior g*BRCA*mut testing, 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.

Eligible subjects will receive 300 mg/day of the study drug orally QD continuously (in 28-day cycles) and the treatment will continue until the patient meet a discontinuation criteria specified in the study protocol.

Dose interruption (no longer than 28 days) and dose reductions (maximum reduction to 100 mg/day) 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.

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) version 1.1 will be used for tumor assessment via a computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas, which is required at the end of every 2 cycles (8 weeks with a window of ±7 days from date of visit) through 6 months (ie, Cycle 6), then at the end of every 3 cycles (12 weeks with a window of ±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 AEs will be collected and recorded for each patient from the day of signing the informed consent form (ICF) until 30 days after last dose of study treatment administration, or beginning of subsequent anticancer therapy, whichever comes first. 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.

Blood samples for measurements of plasma levels of niraparib will be obtained on Cycle 1 Day 1 predose and 2 hours postdose, Cycle 2 Day 1 predose and 2 hours postdose, and Cycle 4 Day 1 predose.

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoint

- Objective response rate (ORR).

5.1.2 Secondary Endpoints

- Duration of response (DOR).
- Disease control rate (DCR).
- Safety of niraparib, including.
  - The subject incidence of TEAEs after study drug administration.
  - The subject incidence of Grade 3 or higher TEAEs.
  - The subject incidence of serious TEAEs
  - The subject incidence of TEAEs leading to drug discontinuation.
  - The subject incidence of TEAEs leading to dose interruption because of TEAEs.
  - The subject incidence of TEAEs leading to dose reduction because of TEAEs.
- Progression free survival (PFS).
- Overall survival (OS).

5.1.3 Safety Endpoints

- Laboratory values.
- Vital signs.
- ECOG performance status.
- Electrocardiograms (ECGs).

5.1.4 Additional Endpoints

- Plasma concentrations of niraparib for population pharmacokinetics.

6.0 DETERMINATION OF SAMPLE SIZE

A study with 14 subjects will provide at least 80% power of binomial test to detect an ORR ≥29% when testing a null hypothesis of ORR ≤5% at 1-sided significance level of 5%. Sixteen patients will be enrolled in this study considering that a few of them may be non-evaluable.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after the start of study drug and within 30 days after the date of last dose.
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who were enrolled in a study but prior to administration of study drug.
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Dose Level: 300 mg, 200 mg, 100 mg.
- Total Study Duration (days): Last visit date or date of death - Enrollment date + 1.
- Overall Treatment Exposure (days): Date of last dose - date of first dose + 1
- Dose intensity (mg/day): Sum of the total daily doses ingested divided by Overall Treatment Exposure.
- Relative Dose Intensity (%): Dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose intensity is 300 (mg/day).
- Dose reduction regardless of causality: Dose consumed is less than prescribed for any reason.
- Dose interruptions regardless of causality: Dose consumed is 0 mg for any reason (includes missed doses).
- Dose interruptions due to AE: Dose consumed is 0 mg due to AE.
- Initial dose level for each cycle: Dose level on the first date when dose is not 0 mg for each cycle.
- DCR: The proportion of patients achieving best overall response of CR, PR, or stable disease (SD) as assessed by the Investigator per RECIST (v1.1).
- DOR: The time from the earliest date of initial response date of confirmed CR or PR until the earlier date of radiological progressive disease (PD) or death by any cause. The DOR (months) will be calculated as: (Earliest date of radiological PD or Death – Earliest of (Date of confirmed CR or PR) + 1) / 30.4375.

  General censoring rules for the analysis of DOR will be as follows:

  – Patients known to be alive and known not to have started new (non-protocol) anti-cancer treatment, who are progression-free, and who have a baseline and at least 1 post-dosing

radiological assessment, are censored at the date of the last radiological assessment that verified lack of PD.

– Patients starting new anti-cancer treatment prior to or on progression or death are censored at the date of last radiological assessment documenting no progression prior to the new anti-cancer treatment.

- PFS: The time from the date of first dose of study treatment to the earlier date of assessment of radiological progression or death by any cause. Progression-free survival (months) will be calculated as: (Earlier of (Date of radiological PD or Death) - First dose date + 1) / 30.4375.

  General censoring rules for the analysis of PFS will be as follows:

  – No adequate post-baseline radiological assessments and no death; therefore PFS is censored at the date of the first dose unless death occurred.

  – Patients known to be alive and known not to have started new (non-protocol) anti-cancer treatment, who are progression-free, and who have a baseline and at least 1 post-dosing radiological assessment, are censored at the date of the last radiological assessment that verified lack of PD.

  – Patients starting new anti-cancer treatment prior to progression or death are censored at the date of last radiological assessment documenting no progression prior to the new anti-cancer treatment.

- OS: The time from the date of first dose of study treatment to the date of death by any cause. Patients known to be alive will be censored at the last known survival follow-up date. The OS (months) will be calculated as: (Death date - First dose date + 1) / 30.4375.
- TFST: The date of first dose of study treatment in the current study to the earlier date of first dose of first new anti-cancer treatment or death. Patients who are alive without a new anti-cancer treatment will be censored on the last contact date. TFST (months) will be calculated as: (Earlier of (First dose of first new anti-cancer treatment or death – First dose date + 1) / 30.4375.
- For waterfall plot of best percent change in target lesion size (section 7.9.3.1) and subgroup analysis (section 7.9.4.7), tumor BRCA1/BRCA2 mutation status will be dichotomized as "Positive" or "Negative" ("Negative" or "Unknown"); "Unknown" is combined with "Negative".
- TEAE leading to study drug modification: Any TEAE leading to dose reduction, dose interruption or dose discontinuation.

7.1.2 Definition of Study Days

The following definitions and calculation formulas will be used.

- Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. If the date of the observation is

on the same date or after the day of the first dose, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.

- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1. Follow-up Day will be calculated relative to Day 1.

7.1.3 Definition of Study Visit Windows

When calculating Study Day relative to a reference date (ie, date of first dose [Day 1]), if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

When calculating Follow-up Day relative to a reference date (ie, date of last dose [Follow-up Day 0]), it will be calculated as: date of observation - reference date. Hence, reference day is always Follow-up Day 0.

All evaluable data (ie, non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the earlier observation will be used.

If multiple observations exist on the same date, the observation whose Hemoglobin value is lower (the value before transfusion) will be used for analysis.

Table 7.a Visit Window of Hematology

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 - 1	
Cycle 1, Day 8	Study Day: 8	5 - 11	
Cycle 1, Day 15	Study Day: 15	12 - 18	
Cycle 1, Day 22	Study Day: 22	19 - 25	
Cycle (n) (Cycle 2 and thereafter), Day 1	Study Day: 28(n - 1) + 1	28(n - 1) - 2 to 28 (n - 1) + 4	<38

Table 7.b Visit Window of Serum Chemistry, Coagulation

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 - 1	
Cycle 1, Day 15	Study Day: 15	12 - 18	
Cycle (n) (Cycle 2 and thereafter), Day 1	Study Day: 28(n - 1) + 1	28(n - 1) - 2 to 28 (n - 1) + 4	<38

Table 7.c Visit Window of Serum CA-125 and ECOG Performance Status

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 - 1	
Cycle (n) (Cycle 2 and thereafter), Day 1	Study Day: 28(n - 1) + 1	28(n - 1) - 2 to 28 (n - 1) + 4	<38

Table 7.d Visit Window of Vital Signs and Weight

Visit	Scheduled Study Day (days)		Time Interval (days)	
			Study Day	Follow-up Day
Baseline	Study Day:	1	-28 - 1	
Cycle 1, Day 15	Study Day:	15	12 - 18	
Cycle (n) (Cycle 2 and thereafter), Day 1	Study Day:	28(n - 1) + 1	28(n - 1) - 2 to 28(n - 1) + 4	<38

7.1.4 Significance Level and Confidence Coefficient

- Significance level: 5% (one-sided test).
- Confidence coefficient:
  - Analysis for ORR: 90% (two-sided).
  - Analysis for other endpoints: ORR 95% (two-sided).

7.1.5 Conventions for Missing Dates

When calculating the "Duration between the End Date of the Last Chemotherapy Regimen and the First Dose of Study Treatment (months)", missing the day or day and month of the end date of last chemotherapy will be set as follows. If the day is missing, the day will be assumed to be the first date of the month when the last chemotherapy was used. If the imputed date of the end of the last chemotherapy is earlier than the end date of the previous chemotherapy, the imputed date is set to the next day of the end date of the previous chemotherapy. If the day and month are both missing, the day and month will be assumed to be January 1. If the imputed date of the end of the last chemotherapy is earlier than the end date of the previous chemotherapy, the imputed date is set to the next day of the end date of the previous chemotherapy.

When calculating the "Time from First Diagnosis to First Dose (years)", missing the day or day and month of the date of the first diagnosis will be set as follows. If the day is missing, the day will be assumed to be the first date of the month when the subject was first diagnosed. If the day and month are both missing, the day and month will be assumed to be January 1.

7.2 Analysis Sets

- Full Analysis Set:
  All subjects who receive at least 1 dose of study drug and have measurable disease at baseline.
- Safety Analysis Set:
  All subjects who received at least 1 dose of study drug.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Were Enrolled

Analysis Variables:

Date First Subject Signed Informed Consent Form

Date of Data Cutoff

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Not applicable.

7.3.3 Subject Eligibility

Not applicable.

7.3.4 Number of Subjects Who Were Enrolled by Site

Analysis Set:

All Subjects Who Were Enrolled

Analysis Variables:

Status of Enrollment

[Enrolled]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Were Enrolled by Site

Frequency distribution will be provided for each stratum.

7.3.5 Disposition of Subjects

Analysis Set:

All Subjects Who Were Enrolled

Analysis Variables:

Study Drug Administration Status

[Enrolled but Not Treated]

Reason for Not Being Treated

[Death, Adverse Event, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Lost to Follow-up, Screen Failure, Other]

Study Drug Completion Status

[Ongoing, Discontinued Study Drug]

Reason for Discontinuation of Study Drug

[Death, Adverse Event, Protocol Deviation, Progressive Disease, Pregnancy, Study Terminated by Sponsor, Withdrawal by Subject, Lost to Follow-up, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

7.3.6 Protocol Deviations and Analysis Sets

7.3.6.1 Protocol Deviations

Analysis Set:

All Subjects Who Were Enrolled

Analysis Variables:

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Methods:

(1) Protocol Deviations

Frequency distribution will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.6.2 Analysis Sets

Analysis Set:

All Subjects Who Were Enrolled

Analysis Variables:

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Full Analysis Set [Included]

Safety Analysis Set [Included]

Analytical Methods:

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:

Safety Analysis Set

Full Analysis Set

Analysis Variables:

Age (years) [18<= - <65, 65<= - <=Max]

[18<= - <65, 65<= - <75, 75<= - <=Max]

Gender [Male, Female]

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]

Time from First Diagnosis to First Dose (years)

Primary Tumor Site [Ovarian, Primary Peritoneal, Fallopian Tube]

Cancer Stage (FIGO) at time of Initial Diagnosis [I, IA, IB, IC, II, IIA, IIB, IIC, III, IIIA, IIIB, IIIC, IV, Unknown, Other]

Height (cm)

Weight (kg) [Min<= - <58, 58<= - <77, 77<= - <=Max]

BMI (kg/m^2)

ECOG Performance Status [0, 1, 2, 3, 4]

Number of Prior Lines of Chemotherapy [3, 4, 5<= - <=Max]

Prior Taxane [Yes, No]

Prior bevacizumab [Yes, No]

Prior doxorubicin [Yes, No]

Prior liposomal doxorubicin [Yes, No]

Prior gemcitabine [Yes, No]

Duration between the End Date of the Last Chemotherapy Regimen and the First Dose of Study Treatment (months)

Duration between the End Date of the Last Platinum-based Therapy and the First Dose of Study Treatment (months)

Prior Surgery/Procedure for Study Indication [Yes, No]

Number of Prior Surgery/Procedure for Study Indication [0, 1, 2, 3<= - <=Max]

Prior Radiation Therapy Related to the Study Indication [Yes, No]

Response to Last Platinum-based Therapy [CR, PR, SD, PD, NE, Unknown]

Time to Progression after the Last Platinum Therapy [6-12 Month, More Than 12 Month, Other, Unknown]

Ovarian Cancer Pathology

Histological

Histologic Subtype [Serous, Endometrioid, Mucinous, Other]

Tumor Grade [Low Grade, Grade 1, Grade 2, Grade 3, High Grade, Not Assessable]

Germline BRCA1 Mutant [Yes, No, Unknown]

Germline BRCA2 Mutant [Yes, No, Unknown]

HRD CDx Test Result [Negative, Positive, Unknown]

Genomic Instability Status [Negative, Positive, Unknown]

Tumor BRCA1/BRCA2 Mutation Status [Negative, Positive, Unknown]

Analytical Methods:

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medication History (not Included Ovarian Cancer Treatment)

Prior Ovarian Cancer Treatment

Concomitant Medications

Analytical Methods:

(1) Medication History (not Included Ovarian Cancer Treatment) by Preferred Medication Name

(2) Prior Ovarian Cancer Treatment by Preferred Medication Name

(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Number of Cycles Started [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 <= - <= Max]

Total Study Duration (days)

Overall Treatment Exposure (days)

Dose Intensity (mg/days)

Relative Dose Intensity (%)

Initial Dose Level for Each Cycle

Analytical Methods:

(1) Study Drug Exposure and Compliance

For initial dose level for each cycle, frequency distributions will be provided by dose level and overall by visit for each cycle for the first year. Composite bar chart will be plotted by visit for each cycle for the first year.

For other than initial dose level for each cycle, frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.8 Study Drug Modification

Analysis Set:

Safety Analysis Set

Analysis Variables:

Dose Reductions

Dose Reduction for Any Reason

Dose Interruptions

Dose Interruption for Any Reason

Dose Interruption Due to AE

Analytical Methods:

(1) Study Drug Modification

Frequency distributions will be provided by 4 weeks for the first 48 weeks, and by 24 weeks thereafter and overall.

7.9 Efficacy Analysis

7.9.1 Primary Efficacy Endpoint(s)

7.9.1.1 Overall Response Rate

Analysis Set:

Full Analysis Set

Analysis Variables:

ORR

Overall Response [CR, PR, SD, PD, NE]

Analytical Methods:

(1) ORR

For ORR, point estimate and the 2-sided 90% exact CI will be provided.

(2) Summary of Overall Response

For overall response, frequency distributions will be provided.

7.9.2 Secondary Efficacy Endpoint(s)

7.9.2.1 Disease Control Rate

Analysis Set:

Full Analysis Set

Analysis Variables:

DCR

Analytical Methods:

(1) DCR

For DCR, point estimate and the 2-sided 95% exact CI will be provided.

7.9.2.2 Duration of Response

Analysis Set:

Full Analysis Set

Analysis Variables:

DOR

Analytical Methods:

(1) DOR

For DOR, breakdown of the number of subjects who were censored and who experienced an event will be summarized. Quartiles of DOR and the two-sided 95% confidence intervals will be estimated using the Kaplan-Meier method. Kaplan-Meier estimate of DOR proportion at specified points will also be provided. The Kaplan-Meier plot of DOR will be presented. The definition of DOR refers to section 7.1.1. DOR will be conducted using the population who respond to niraparib in the FAS.

7.9.2.3 Progression Free Survival

Analysis Set:

Full Analysis Set

Analysis Variables:

PFS

Analytical Methods:

(1) PFS

For PFS, the same analyses as those for DOR will be conducted using the FAS. The definition of PFS refer to section 7.1.1.

7.9.2.4 Overall Survival

Analysis Set:

Full Analysis Set

Analysis Variables:

OS

Analytical Methods:

(1) OS

For OS, the same analyses as those for DOR will be conducted using the FAS. The definition of OS refer to section 7.1.1.

7.9.3 Additional Efficacy Endpoint(s)

7.9.3.1 Best Percent Change in Target Lesion Size

Analysis Set:

Full Analysis Set

Analysis Variables:

Best Percent Change in Target Lesion Size

Analytical Methods:

(1) Waterfall plot

A waterfall plot of best percent change in target lesion size will be presented.

7.9.3.2 Time to First Subsequent Therapy

Analysis Set:

Full Analysis Set

Analysis Variables:

TFST

Analytical Methods:

(1) TFST

For TFST, the same analyses as those for DOR will be conducted using the FAS. The definition of TFST refers to section 7.1.1.

7.9.4 Statistical/Analytical Issues

7.9.4.1 Adjustments for Covariates

Not applicable.

7.9.4.2 Handling of Dropouts or Missing Data

Missing test results will not be used for hypothesis testing and estimations.

Values less than or equal to the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values greater than or equal to the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.9.4.3 Multicenter Studies

Not applicable.

7.9.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.9.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

7.9.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.9.4.7 Examination of Subgroups

Analysis Set:

Full Analysis Set

Analysis Variables:

ORR

Subgroups:

Age (years)	[18<= - <65, 65<= - <=Max]
Primary Tumor Site	[Ovarian, Primary Peritoneal, Fallopian Tube]
Tumor BRCA1/BRCA2 Mutation Status	[Negative, Positive]

Analytical Methods:

(1) Subgroup Analysis for ORR

For ORR, point estimate and the 2-sided 90% exact CI will be provided for the above each subgroup.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis

Not applicable.

7.10.2 Pharmacodynamic Analysis

Not applicable.

7.11 Other Outcomes

Not applicable.

7.12 Safety Analysis

7.12.1 Adverse Events

7.12.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Relationship to Study Drug	[Related, Not Related]
Toxicity Grade	[Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Methods:

The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)

3) Grade 3 or higher Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Grade 3 or higher Drug-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
5) Toxicity Grade of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
7) Treatment-Emergent Adverse Events leading to study drug reduction (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events leading to study drug interruption (number of events, number and percentage of subjects)
9) Treatment-Emergent Adverse Events leading to study drug modification (number of events, number and percentage of subjects)
10) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
11) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
12) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
13) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 11)

  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.

- Summary for 5)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum toxicity grade.

- Summaries other than 2), 5), and 11)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

7.12.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Toxicity Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Methods:

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Grade 3 or higher Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Toxicity Grade of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(8) Toxicity Grade of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(9) Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by System Organ Class and Preferred Term

(10) Treatment-Emergent Adverse Events Leading to Study Drug Interruption by System Organ Class and Preferred Term

(11) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(12) Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term

(13) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(14) Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term

(15) Grade 3 or higher Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term

(16) Serious Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term

(17) Drug-Related Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (7) and (8)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (7) and (8)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum toxicity grade. Percentages will be based on the number of subjects in the safety analysis set.

7.12.1.3 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Were Enrolled

Analysis Variables:

PTE

Analytical Methods:

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.12.1.4 The Subject Incidence of Grade 3 or 4 Thrombocytopenia Occurring within 30 Days after Initial Administration of Niraparib.

Analysis Set:

Safety Analysis Set

Analysis Variables:

Grade 3 or 4 Thrombocytopenia Occurring within 30 days after Initial Administration of Niraparib

Analytical Methods:

The number and percentage of Subjects with Thrombocytopenia will be provided using frequency distribution.

7.12.1.5 The Subject Incidence of Toxicity Grade of Thrombocytopenia Occurring within 30 Days after Initial Administration of Niraparib.

Analysis Set:

Safety Analysis Set

Analysis Variables:

Thrombocytopenia Occurring within 30 days after Initial Administration of Niraparib

Categories:

Toxicity Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Methods:

The number and percentage of Subjects with Thrombocytopenia will be provided using frequency distribution. A subject with multiple occurrences of Thrombocytopenia will be counted once for the Thrombocytopenia with the maximum toxicity grade.

7.12.2 Clinical Laboratory Evaluations

7.12.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Erythrocytes, Hematocrit, Hemoglobin, Leukocytes, ANC/ Leukocytes, Basophils /Leukocytes, Eosinophils/Leukocytes, Lymphocytes/Leukocytes, Monocytes/Leukocytes, Platelets count, MCV, MPV

Serum Chemistry

Albumin, ALP, ALT, Amylase, AST, Total bilirubin, Direct bilirubin, Blood Urea Nitrogen, Calcium, Creatinine, Chloride, Gamma Glutamyl Transferase (GGT), Glucose, LDH, Magnesium, Phosphorus, Potassium, Sodium, Protein

Coagulation

INR, aPTT

Serum CA-125

Serum CA-125

Visit:

Hematology

Cycle 1: Baseline, Day 8, Day 15, Day 22

Cycle 2 and Thereafter: Day 1

Serum Chemistry, Coagulation

Cycle 1: Baseline, Day 15

Cycle 2 and Thereafter: Day 1

Serum CA-125

Cycle 1: Baseline

Cycle 2 and Thereafter: Day 1

Analytical Methods:

For each variable, summaries (1) to (3) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Baseline) will be provided for each visit.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade for laboratory abnormalities will be provided.

7.12.2.2 Urinalysis

Not applicable.

7.12.3 Vital Signs and Weight

Analysis Set:

Safety Analysis Set

Analysis Variables:

Systolic Blood Pressure

Diastolic Blood Pressure

Pulse Rate

Weight

Temperature

Visit:

Cycle 1: Baseline, Day 15

Cycle 2 and Thereafter: Day 1

Analytical Methods:

For each variable, summaries (1) and (2) will be provided.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Baseline) will be provided for each visit.

(2) Case Plots

Plots over time for each subject will be presented.

7.12.4 12-Lead ECGs

Not applicable.

7.12.5 Other Observations Related to Safety

7.12.5.1 ECOG Performance Status

Analysis Set:

Safety Analysis Set

Analysis Variables:

ECOG Performance Status

Analytical Methods:

(1) Summary of Shift of ECOG Performance Status

Shift table showing the number of subjects in each category at baseline and the worst post-baseline result will be provided.

7.13 Interim Analysis

Not applicable.

7.14 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

8.0 REFERENCES

Not applicable.

9.0 APPENDIX

Not applicable.