Title: A Phase 2, Multicenter, Open-label, Single-arm Study to Evaluate the Safety of Niraparib in Japanese Patients With Platinum-sensitive, Relapsed Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Achieved CR or PR in the Last Chemotherapy Containing Platinum-based Anticancer Agents

NCT Number: NCT03759587

Statistical analysis plan Approve Date: 03-JUN-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-2001

A Phase 2, Multicenter, Open-label, Single-arm Study to Evaluate the Safety of Niraparib in Japanese Patients With Platinum-sensitive, Relapsed Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Achieved CR or PR in the Last Chemotherapy Containing Platinum-based Anticancer Agents

PHASE 2

Version: 2nd

Date: 03 June 2019

Prepared by:

PPD

PPD

Based on:

Protocol Version: Amendment 2

Protocol Date: 18 January 2019

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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 safety of niraparib in Japanese patients with platinum-sensitive, relapsed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, who achieved CR or PR in the last chemotherapy containing platinum-based anticancer agents.

4.2 Secondary Objectives

To evaluate the efficacy of niraparib in Japanese patients with platinum-sensitive, relapsed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, who achieved CR or PR in the last chemotherapy containing platinum- based anticancer agents.

4.3 Additional Objectives

To evaluate the pharmacokinetics of niraparib in Japanese patients with platinum-sensitive, relapsed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, who achieved CR or PR in the last chemotherapy containing platinum-based anticancer agents.

4.4 Study Design

The study is a phase 2, multicenter, open-label, single-arm study to evaluate the safety of niraparib in Japanese patients with platinum-sensitive, relapsed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, who achieved CR or PR in the last chemotherapy containing platinum-based anticancer agents.

The eligible patients must have received at least 2 platinum-based regimens with the last regimen prior to study enrollment; had a response assessed by a physician of CR or PR to their last regimen; must not have any measurable lesion >2 cm, and must have normal cancer antigen (CA)-125 equal to or less than the upper limit of the normal range, or >90% decrease following their last treatment and which was stable for at least 7 days. The study will evaluate the safety of niraparib as a maintenance therapy based on a primary endpoint of the incidence of Grade 3 or 4 thrombocytopenia occurring within 30 days after initial administration of niraparib in this population.

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.

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.

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 Cycle 14, then at the end of every 3 cycles (12 weeks with a window of ±7 days) until progression. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals in the protocol until progression is confirmed or until the start of subsequent anticancer treatment.

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

- The subject incidence of Grade 3 or 4 thrombocytopenia occurring within 30 days after initial administration of niraparib.

5.1.2 Secondary Endpoints

- The safety of niraparib, including
  - The subject incidence of TEAEs.
  - 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.
- Overall response rate.

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

The incidence of thrombocytopenia in non-Japanese patients was estimated to be 35% based on an overseas clinical study, and the incidence of thrombocytopenia in subject population in this study was estimated to be 46% (the rationale for each incidence is shown below). The sample size in this study is set to be 15, because the probability that the point estimate of the incidence of thrombocytopenia will be ≥35% is 76%, with which a certain level of evaluation is expected to be achievable.

Rationale for Threshold of 35% for the Incidence of Thrombocytopenia

In the analysis of clinical data versus baseline body weight and platelet count in the NOVA study, the incidence of Grade 3 or 4 thrombocytopenia during the first 30 days after the initial dose of niraparib was higher in patients with baseline body weight of <77 kg or baseline platelet count of <150,000/μL (34.6%, 97/280 subjects) than in those with body weight of ≥77 kg and platelet count of ≥150,000/μL (11.8%, 10/85 subjects). Therefore, the threshold for the incidence of thrombocytopenia is considered as 35%.

Rationale for Threshold of 46% for the Expected Incidence of Thrombocytopenia

According to the results of minimum platelet count by baseline body weight during the first 30 days after the initial dose of niraparib in the NOVA study, the incidence of platelet count decreased to 50,000/μL, which is almost equal to or more than Grade 3 thrombocytopenia, was 46% in patients with baseline body weight of <58 kg.

According to the body weight distribution in ovarian cancer patients in Japan, based on the research by Ipsos Healthcare using prescription information as data source, ≥77% patients had body weight of ≤59 kg. Therefore, the expectation of the incidence of thrombocytopenia in subject population in this study was considered as 46%.

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.
- Duration of exposure to study drug (days): Date of last dose - date of first dose minus any skipped or interrupted + 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 reduction due to AE: Dose consumed is less than prescribed due to AE.
- 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.
- PFS: The time from the date of enrollment to the earlier date of progression assessed by the Investigator per RECIST (v.1.1) or clinical criteria, or death by any cause. Progression-free survival (months) will be calculated as: (PD/Death date - enrollment date + 1) / 30.4375
  General censoring rules for the analysis of PFS will be as follows:
  - No adequate post-baseline radiological assessments; therefore PFS is censored at the date of enrollment unless death occurred within 17 weeks of enrollment (in which case the death is an event) or clinical PD is determined.

  - 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 treatment.
  - Documentation of progression or death after an unacceptably long interval (>17 weeks, ie, 2 consecutive missed or indeterminate overall response assessments) since the last radiological assessment will be censored at the date of last radiological assessment documenting no progression.

- OS: The time from the date of enrollment 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 - enrollment date + 1) / 30.4375.
- TFST: The date of enrollment to the earlier of the start date of first follow-up anti-cancer treatment (FUACT) or death. Patients alive and not starting a first FUACT will be censored at the date last known to be alive. TFST (months) will be calculated as: (Start date of first FUACT – enrollment date + 1) / 30.4375.
- 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.

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

- Confidence coefficient: 95% (two-sided).

7.1.5 Conventions for Missing Adverse Event Dates

Not applicable.

7.1.6 Conventions for Missing Concomitant Medication Dates

Not applicable.

7.2 Analysis Sets

- Safety Analysis Set:
  All subjects who received at least one dose of study drug.
- Full Analysis Set:
  All subjects who received at least one dose of study drug.
- Response-evaluable Analysis Set:
  Response-evaluable analysis set is defined as patients who receive at least 1 dose of study drug and have at least one measurable disease at baseline.

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 discontinued the study drug 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]

Response-evaluable 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

Analysis Variables:

Age (years) [18<= - <=64, 65<= - <=74, 75<= - <=Max]

Gender [Male, Female]

Height (cm)

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

BMI (kg/m^2)

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

BRCA1 Mutant [Yes, No, Unknown]

BRCA2 Mutant [Yes, No, Unknown]

Time to Progression after the Penultimate (Next to Last) Platinum Therapy

[6-12 Month, More Than 12 Month, Other, Unknown]

Best Response during the Last Platinum Regimen [CR, PR]

Time from Last Platinum Therapy to Start of Study Drug (days)

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

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

Duration since Initial Diagnosis of Primary Cancer (years)

Cancer Stage at time of Initial Diagnosis

[I, IA, IB, IC, II, IIA, IIB, IIC, III, IIIA, IIIB, IIIC, IV, Unknown, Other]

Sites of Metastatic Disease

[Ascites or pleural effusion, CNS, Liver, Lung, Gastrointestinal, Genitourinary, Peritoneum, Lymph nodes, Bone or muscle, Other]

Number of Metastatic Sites [Min<= - <3, 3<= - <=Max]

Prior Radiation Therapy [Yes, No]

Prior Surgery/Procedure [Yes, No]

Prior Chemotherapy [Yes, No]

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

Prior History of Myelosuppression [Yes, No, Unknown]

Any Prior Myelosuppression

Prior Thrombocytopenia

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

Prior Leukopenia

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

Prior Anemia

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

Prior Neutropenia

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

Baseline Platelet Count (10^9/L)

Ovarian Cancer Pathology

Histological

Histologic Subtype [Serous, Endometrioid, Mucinous, Other]

Tumor Grade

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

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)

Duration of Exposure to Study Drug (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. Composite bar chart will be plotted by visit for each cycle.

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 Reduction due to AE

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.

7.9 Efficacy Analysis

7.9.1 Primary Efficacy Endpoint(s)

Not applicable. In this study, safety will be evaluated as the primary endpoint.

7.9.2 Secondary Efficacy Endpoint(s)

7.9.2.1 Progression Free Survival

Analysis Set:

Full Analysis Set

Analysis Variables:

PFS

Analytical Methods:

(1) PFS.

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

7.9.2.2 Overall Survival

Analysis Set:

Full Analysis Set

Analysis Variables:

OS

Analytical Methods:

(1) OS.

For OS, the same analyses as those for PFS in the section 7.9.2.1 will be conducted using the FAS. The definition of OS refer to section 7.1.1.

7.9.2.3 Overall Response Rate

Analysis Set:

Response-Evaluable Analysis Set

Analysis Variables:

ORR

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

Analytical Methods:

(1) ORR.

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

(2) Summary of Overall Response.

For overall response, frequency distributions will be provided.

7.9.3 Additional Efficacy Endpoint(s)

7.9.3.1 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 PFS 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

Not applicable.

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 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.

7.12.1.2 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.

7.12.1.3 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.

7.12.1.4 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.

7.12.1.5 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.

7.12.2 Clinical Laboratory Evaluations

7.12.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Erythrocytes, Hematocrit, Hemoglobin, Leukocytes, ANC, Basophils, Eosinophils, 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

From the SAP version 1.0, the following parts were updated. In section 7.1.1, the definition of the dose intensity was modified and units for some analysis variables were added for clarity as below.

Before the change

Section 7.1.1 Study Definitions

Total Study Duration: Last visit date or date of death - Enrollment date + 1.

Duration of exposure to study drug: Date of last dose - date of first dose minus any skipped or interrupted + 1.

Dose intensity (mg/day): Sum of the total daily doses ingested divided by Duration of exposure to study drug.

After the change

Section 7.1.1 Study Definitions

Total Study Duration (days): Last visit date or date of death - Enrollment date + 1.

Duration of exposure to study drug (days): Date of last dose - date of first dose minus any skipped or interrupted + 1.

Dose intensity (mg/day): Sum of the total daily doses ingested divided by Overall treatment exposure.

Reason for the change

The definition of the dose intensity was modified to be consistent with that of NOVA study.

Before the change

Section 7.4 Demographic and Other Baseline Characteristics

Analysis Variables:

Time from Last Platinum Therapy to Start of Study Drug

After the change

Section 7.4 Demographic and Other Baseline Characteristics

Analysis Variables:

Time from Last Platinum Therapy to Start of Study Drug (days)

Reason for the change

Text was added for clarity

Before the change

Section 7.7 Study Drug Exposure and Compliance

Analysis Variables:

Total Study Duration

Relative Dose Intensity

After the change

Section 7.7 Study Drug Exposure and Compliance

Analysis Variables:

Total Study Duration (days)

Relative Dose Intensity (%)

Reason for the change

Text was added for clarity.

8.0 REFERENCES

Not applicable.

9.0 APPENDIX

Not applicable.