Clinical Study Protocol

NCT Number: NCT03759587

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

Study Number: Niraparib-2001

Document Version and Date: Amendment 3 / 09-Nov-2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

Note; This document was translated into English as the language on original version was Japanese.

PROTOCOL

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

Japan Phase 2 Study of Niraparib (Maintenance Therapy) in Patients With Relapsed Ovarian Cancer

Sponsor: Takeda Pharmaceutical Company Limited.
4-1-1 Doshomachi, Chuo-ku, Osaka 540-8645

Study Number: Niraparib-2001

EudraCT Number: Not Applicable

Compound: Niraparib (MK-4827)

Date: 09 November 2021 **Amendment Number:** 03
(English translation:
09 November 2021)

Amendment History:

Date	Amendment Number	Region
05 October 2018 (English translation: 16 November 2018)	Initial version	All sites
14 November 2018 (English translation: 22 January 2019)	Amendment 01	All sites
18 January 2019 (English translation: 12 March 2019)	Amendment 02	All sites
09 November 2021 (English translation: 09 November 2021)	Amendment 03	All sites

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	See Section 10.0.
Medical Monitor (medical advice on protocol and compound)	See Protocol Annex

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted] Date

[redacted] Date

1.3 Protocol Amendment 03 Summary of Changes

The primary purpose of this amendment is to change a frequency of imaging for tumor assessment due to consideration for effect of long-term radiation on subject.

Other minor text changes related to imaging were added for clarification.

Full details on changes are given in Appendix H.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Pharmaceutical Company, Ltd.	**Compound:** Niraparib (MK-4827)
Title of Protocol: 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	**EudraCT No.:** Not Applicable
Study Number: Niraparib-2001	**Phase:** 2

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 complete response (CR) or partial response (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 Cycle 38, and at the end of every 6 cycles (24 weeks with a window of ±7 days) until progression. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for 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.

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.

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.

Subject Population: Japanese adult 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

Number of Subjects: 15 subjects	**Number of Sites:** Approximately 30 sites in Japan
Dose Level(s): The study drug will be administered at 300 mg QD, orally, continuously, in 28-day cycles, and the treatment will continue until the patient meet a discontinuation criteria specified in the study protocol.	**Route of Administration:** Oral
Duration of Treatment: Subjects may receive study drug until they experience objective PD, experience unacceptable toxicity, withdrawal of consent or until study discontinuation due to any other reasons specified in the study protocol.	**Period of Evaluation:** The estimated time frame for study completion (screening, study drug administration and follow-up period) is approximately 28 months.

Main Criteria for Inclusion:

1. Japanese female patients aged 20 years or older on the day of signing informed consent.
2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Patient must have a histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.
4. Patient must have a high-grade (or Grade 3) serous or high-grade predominantly serous histology or known to have g*BRCA*mut.
5. Patients must have completed at least 2 previous lines of platinum-containing therapy:

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

   a For the penultimate platinum-based chemotherapy prior to study enrollment, patients must have had platinum-sensitive disease after this treatment, defined as achieving a response (CR or PR) and disease progression (PD) >6 months after completion of her last dose of platinum therapy (documented 6 to 12 months or >12 months). Source documentation was required.

   b For the last line of platinum-based chemotherapy prior to study enrollment:

      i. Patients must have received a platinum-containing regimen for a minimum of 4 cycles.

      ii. Patients must have achieved a partial or complete tumor response.

      iii. Following the last regimen, patients must have had either:

1. CA-125 equal to or less than the upper limit of the normal range.
2. CA-125 decrease by more than 90% during the last platinum regimen, and which was stable for at least 7 days (ie, no increase >15%).

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

c Patients must have been enrolled within 8 weeks after completion of their final dose of the platinum-containing regimen.

6. Patients must have performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale.
7. Patients must have adequate organ function as indicated by the following laboratory values:
   a Absolute neutrophil count (ANC) ≥1,500/μL.
   b Platelet count ≥100,000/μL.
   c Hemoglobin ≥9 g/dL.
   d Serum creatinine ≤1.5× institutional upper limit of normal (ULN) OR calculated creatinine clearance ≥50 mL/minute, using the Cockcroft-Gault equation.
   e Total bilirubin ≤1.5×ULN OR direct bilirubin ≤1×ULN.
   f Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN unless liver metastases were present, in which case they had to be ≤5×ULN.
8. Patients must be able to take oral medications.
9. Female patients of childbearing potential must be negative for pregnancy test (β-hCG) within 7 days prior to receiving the first dose of study treatment.
10. Female patients who:
    a Are postmenopausal for at least 1 year before the screening visit, OR
    b Are surgically sterile, OR
    c If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, OR
    d Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Main Criteria for Exclusion:

1. Patients who have had drainage of ascites during last 2 cycles of last chemotherapy.
2. Patients who have had palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment.
3. Patients who have persistent Grade ≥3 toxicity from last cancer therapy.
4. Patients who have symptomatic, uncontrolled brain or leptomeningeal metastases. To be considered "controlled," central nervous system (CNS) disease must have undergone treatment (eg, radiation or chemotherapy) at least 1 month prior to study enrollment. The patient must not have had any new or progressive signs or symptoms related to the CNS disease and must have been taking a stable dose of steroids or no 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 at baseline was not required. Patients with spinal cord compression might have been considered if they had received definitive treatment for this and evidence of clinically stable disease for 28 days.
5. Patients who have known hypersensitivity to the components of niraparib.
6. Patients who have had prior treatment with a known PARP inhibitor.
7. Patient who have had treatment with any investigational products within 28 days or 5 half-lives (whichever was longer) before the first dose.
8. Patients who have had major surgery per investigator judgment within 3 weeks of the first dose. Patient must have recovered from any effects of any major surgery.
9. Patients who have diagnosis, detection, or treatment of invasive second primary malignancy other than ovarian cancer ≤24 months prior to study enrollment (except basal or squamous cell carcinoma of the skin that was definitively treated). Note: Patients must not have any known history or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), irrespective of the time for disease history.
10. Patients who are considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the first dose) 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.
11. Patients who have received a transfusion (platelets or red blood cells) within 4 weeks of the first dose of study treatment.
12. Patients who have received a live virus and bacterial vaccines within 4 weeks of the first dose of study treatment.
13. Patients who have a history or current evidence of any condition, therapy, or lab abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study, interfere with the patient's participation throughout the study period, or study participation is not in the best interest of the patient
14. Patients who are regular user (including "recreational use") of any illicit drugs at the time of signing informed consent or have a recent history (within the past year) of drug or alcohol abuse.
15. Patients who are pregnant or breast-feeding, or expecting to conceive within the planned duration of the study. NOTE: If a breast-feeding woman discontinue breast-feeding, she may be enrolled in the study.
16. Patients who are immunocompromised (patients with splenectomy are allowed).
17. Patients who have known HIV positive.
18. Patients who have known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection.

    NOTE: Patients who are positive for hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) must have an undetectable HCV viral load.

Main Criteria for Evaluation and Analyses:

Primary:

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

Secondary:

- 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 because of TEAEs.
  - 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).
- Overall response rate (ORR).

Statistical Considerations:

In this study, patients who receive at least 1 dose of study drug will be defined as safety analysis set. The subject incidence of Grade 3 or 4 thrombocytopenia within 30 days after the initial dose of niraparib is calculated as a primary endpoint using safety analysis set.

In addition, the following adverse events are coded by MedDRA and the subject incidence is calculated by SOC and PT using safety analysis set: TEAE, Grade 3 or above TEAE, serious TEAE, TEAE leading to treatment discontinuation, TEAE leading to dose interruption and TEAE leading to dose reduction.

In this study, patients who receive at least 1 dose of study drug will be defined as full analysis set (FAS). PFS and OS will be analyzed using Kaplan-Meier method to provide quartiles and progression/survival rate at specified points with 95% CI using FAS. The Kaplan-Meier plot for PFS and OS will also be provided.

ORR and its two-sided 95% confidence interval (CI) based on binominal distribution will be provided using the FAS. The two-sided 95% CI will be calculated based on binominal distribution.

Sample Size Justification:

To evaluate safety of niraparib in Japanese patients, the incidence of Grade 3 or 4 thrombocytopenia within 30 days after the initial dose of niraparib will be compared between Japanese and non-Japanese patients to make a certain level of evaluation that the incidence in Japanese patients is not obviously higher than that in non-Japanese patients. Fifteen patients can be evaluable sample size for the rationale.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloblastic leukemia
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
β-hCG	beta human chorionic gonadotropin
BRCA	breast cancer (gene)
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EU	European Union
eCRF	electronic case report form
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FPI	first patient in
FSH	follicle stimulating hormone
g*BRCA*	germline breast cancer gene
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HRD	homologous recombination deficiency/deficient
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IRB	institutional review board
LPLV	last patient last visit
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PBMC	peripheral blood mononuclear cells
PD	progressive disease (disease progression)
PFS	progression-free survival
P-gp	P-glycoproetein
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PR	partial response
PT	preferred term
QTc	QT interval corrected for heart rate
QTcF	Fridericia's corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

4.0 INTRODUCTION

4.1 Background

Niraparib is an orally available, potent, and highly selective PARP1 and PARP2 inhibitor. Niraparib was originated by [redacted] and developed by [redacted] for the treatment of a variety of cancer types.

DNA repair is accomplished by serval mechanisms in healthy cells including, but not limited to, homologous recombination, base excision repair, and nonhomologous end-joining. Some cells are incapable of homologous recombination due to the inactivation of genes such as *BRCA*1, *BRCA*2, ataxia telangiectasia mutated (ATM), and others. In the absence of homologous recombination, these cells must rely on alternative DNA repair mechanisms.

A complete loss of function or inactivation of both *BRCA* alleles occurs commonly in women who are carriers of a g*BRCA*mut. A loss of *BRCA* function compromises the repair of double-strand DNA breaks via the homologous recombination pathway resulting in the use of an alternative DNA repair pathway such as NHEJ. Reliance on mechanisms such as NHEJ contributes significantly to the accumulation of mutations in ovarian cells and may ultimately promote the development of ovarian tumors.[1][2]

PARP1 and PARP2 are zinc-finger DNA-binding proteins that detect damaged DNA and promote DNA repair by several mechanisms. After detecting DNA damage, PARP activates the BER pathway via an intracellular signaling mechanism. Conversely, PARP inhibitors block DNA repair by the BER pathway. In cells incapable of DNA repair via homologous recombination (eg, *BRCA*1 and *BRCA*2 mutations), PARP inhibition leads to irreparable DSB, collapsed replication forks, and an increased use of the NHEJ pathway. These disruptions result in genomic instability and ultimately cell death. The synergy between cellular defect and drug-induced effect is referred to as synthetic lethality.[3] Treatment with PARP inhibitors represents an opportunity to selectively kill cancer cells with deficiencies in homologous recombination and other DNA repair mechanisms. Recently, it has been reported that, breast cancer gene (*BRCA*) mutation-negative, wild-type tumors, can result in a *BRCA*1/2 mutation-like state as a result of deficiency in repair of DNA double-strand breaks by homologous recombination due to other factors. It is anticipated that PARP inhibitors may induce synthetic lethality against such tumor.[4] In ovarian cancer, the homologous recombination deficiency (HRD) score has been found useful as an indicator of HRD, including such genomic instability.[5]

Based on the results of a [redacted] sponsored overseas phase 3 pivotal study (NOVA study), niraparib has been approved in the in March 2017 and in Europe in November 2017, as a maintenance therapy for adult patients with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who achieved complete response (CR) or partial response (PR) to a chemotherapy containing platinum-based anticancer agents.

Nonclinical and clinical study result summaries are shown below. For further details, refer to the current Investigator's Brochure and package inserts in regions/countries where niraparib is approved.

4.1.1 Nonclinical Studies

In animal models, maximal in vivo efficacy was achieved in mutant breast cancer susceptibility gene (*BRCA*) 1 (*BRCA*1mut) ovarian tumor models with once daily (QD) oral administration of niraparib at a dose sufficient to suppress approximately 90% of the PARP-enzymatic activity in the tumor at 8 hours postdose. The same dose translated to a >50% inhibition of PARP activity in peripheral blood mononuclear cells (PBMCs) at 8 hours postdose.

Data from nonclinical experiments demonstrate that tumors containing *BRCA* mutations or that are otherwise positive by commercially available homologous recombination deficiency (HRD) tests regressed in response to niraparib treatment. Moreover, tumor growth inhibition was observed in a subset of HRD-negative (HRDneg) models, suggesting that there is a gradient of response to niraparib that is observed on a population basis by use of different biomarkers.

4.1.2 Clinical Studies

Niraparib clinical studies have been conducted in Japan and overseas countries, and the safety and tolerability of niraparib has been evaluated in over 1214 patients with advanced cancer who have received at least 1 dose of niraparib. The highest dose studied in the overseas Phase 1 trials was 400 mg QD, and the dose-limiting toxicity at this dose was thrombocytopenia. The recommended phase 2 dose for niraparib monotherapy was 300 mg QD, and this dose was subsequently approved for the treatment of ovarian cancer (OC) in the United States (US) and European Union (EU), based on the result of overseas phase 3 study.

4.1.2.1 Study PR-30-5011-C (NOVA main) (Overseas Phase 3)

The main study of PR-30-5011-C is a double-blind, 2:1 randomized, placebo-controlled study in platinum-sensitive ovarian cancer patients who have either g*BRCA*mut or a tumor with high-grade serous histology, but without a g*BRCA* mutation (non-g*BRCA*mut) who were in response to their last platinum-based therapy. Enrollment into the cohorts was determined prospectively by the results of [redacted] testing.

A total of 203 patients were enrolled in the g*BRCA*mut cohort and 350 patients were enrolled in the non-g*BRCA*mut cohort. Overall, 553 patients were randomized, 372 patients to niraparib and 181 patients to placebo. Preliminary efficacy data (as of the data cut date of 30 May 2016) are available for the 553 patients who comprised the intent-to-treat (ITT) population and the 546 patients who comprised the safety population. 266 patients remain on-treatment.

In NOVA study, niraparib 300 mg was administered to patients with platinum-sensitive, relapsed ovarian cancer who responded to the last chemotherapy containing platinum-based anticancer agents once daily in a double-blind manner to compare with the placebo group. Consequently, niraparib met the primary endpoint of prolonging PFS versus placebo in all 3 prospectively defined primary patient populations (g*BRCA*mut cohort, HRDpos group of the non-g*BRCA*mut cohort, and the overall non g*BRCA*mut cohort) (Table 4.a).

Table 4.a Progression-Free Survival in the Primary Efficacy Cohorts (ITT Population, N = 553)

Treatment	Median PFS (a) (95% CI) (Months)	Hazard Ratio (b) (95% CI) p-value (c)	% of Patients without Progression or Death at (d):		
			6 Months	12 Months	18 Months
g*BRCA*mut Cohort					
Niraparib (n = 138)	21.0 (12.9, NE)	0.27 (0.173, 0.410) p<0.0001	80%	62%	50%
Placebo (n = 65)	5.5 (3.8, 7.2)		43%	16%	16%
HRDpos Group					
Niraparib (n = 106)	12.9 (8.1, 15.9)	0.38 (0.243, 0.586) p<0.0001	69%	51%	37%
Placebo (n = 56)	3.8 (3.5, 5.7)		35%	13%	9%
Non-g*BRCA*mut Cohort					
Niraparib (n = 234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607) p<0.0001	61%	41%	30%
Placebo (n = 116)	3.9 (3.7, 5.5)		36%	14%	12%

Source: PR-30-5011-C (NOVA main) CSR
g*BRCA*: breast cancer susceptibility gene; CI: confidence interval; g*BRCA*mut: germline *BRCA* mutation; HRDpos: homologous recombination deficiency positive; ITT: intent-to-treat; NE: not estimated; non-g*BRCA*mut: without a germline *BRCA* mutation; PFS: progression-free survival.
(a) Progression-free survival is defined as the time in months from the date of randomization to progression or death.
(b) Niraparib: Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.
(c) Based on stratified log-rank test using randomization stratification factors.
(d) Estimates from product-limit method. Confidence intervals constructed using log-log transformation.

In NOVA study, niraparib 300 mg was tolerable. The most commonly observed TEAEs (all grades) of niraparib were nausea (niraparib: 73.6%, placebo: 35.2%), anaemia (48.5%, 6.7%), thrombocytopenia (46.0%, 3.4%), fatigue (45.8%, 32.4%) and constipation (39.8%, 20.1%). Of these, Grade 3 or 4 TEAEs were thrombocytopenia (28.3%, 0.6%), anaemia (24.8%, 0%) and neutropenia (11.2%, 0.6%).

The most common Grade 3 or 4 adverse events that were reported in the niraparib group were thrombocytopenia (28.3%), anemia (24.8%), and neutropenia (11.2%), which were managed with dose modifications (Table 4.b). Most patients achieved their individual MTD by the third month. The average dose of niraparib during the study was 206 mg. Only 14.7% patients had dose discontinued due to adverse events.

Table 4.b Grade 3/4 Treatment Emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Arm (Safety Population, N = 546)

MedDRA Preferred Term	Niraparib (N = 367) n (%)	Placebo (N = 179) n (%)
Any CTCAE Grade 3/4 TEAE	**272 (74.1)**	**41 (22.9)**
Thrombocytopenia	104 (28.3)	1 (0.6)
Anaemia	91 (24.8)	0
Neutropenia	41 (11.2)	1 (0.6)
Neutrophil count decreased	32 (8.7)	2 (1.1)
Hypertension	30 (8.2)	4 (2.2)
Platelet count decreased	27 (7.4)	0
Fatigue	21 (5.7)	0

Source: PR-30-5011-C (NOVA Main Study) Clinical Study Report
NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; MedDRA, Medical Dictionary for Regulatory Activities

4.1.2.2 Study Niraparib-1001 (Japanese Phase 1 Study)

Study Niraparib-1001 is a phase 1, open-label, non-randomized, cohort-based, dose-escalation study to establish the safety and tolerability of niraparib in Japanese patients with advanced solid tumors. In this study, dose-escalation will proceed according to a 3+3 design. A total of 6 patients were treated with 200 mg QD (Cohort 1) or 300 mg QD (Cohort 2) of niraparib. Niraparib was administered QD, continuously for 21-day in cycle. The starting dose was not to be adjusted depending on the baseline body weight or platelet count.

The enrollment was completed and the total of 9 patients were enrolled to Cohort 1 or Cohort 2 of the study. In Cycle 1 of Cohort 1(niraparib 200 mg QD), no dose limiting toxicity (DLT) was observed. In Cycle 1 of Cohort 2 (niraparib 300 mg QD), DLT was observed in 1 of 6 subjects, and niraparib 300 mg was deemed tolerable in Japanese patients with advanced solid tumors.

The observed DLT was Grade 4 thrombocytopenia. According to the preliminary data of the TEAEs reported as of 31 October 2018, the TEAEs reported in more than 1 subject were vomiting and thrombocytopenia/platelet count decreased (4 subjects each), nausea and anorexia (3 subjects each), and diarrhoea, alkaline phosphatase increased, creatinine increased, leukopenia/white blood cell count decreased, neutrophil count decreased/febrile neutropenia and fatigue/malaise (2 subjects each).

As of 14 November 2018, the study drug administration is ongoing in 4 subjects.

4.1.2.3 Identification of Factors for Thrombocytopenia

A further review of the results of clinical studies indicated that the patient body weight and platelet count at baseline effect on the occurrence of thrombocytopenia. In NOVA study, the incidence of Grade 3 or 4 thrombocytopenia in 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). In addition, the incidence of Grade 3 or 4 treatment-related 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 (49.6%, 139/280 subjects; 45.7%, 128/280 subjects) than in those with body weight of ≥77 kg and platelet count of ≥150,000/μL (31.8%, 27/85 subjects; 27.1%, 23/85 subjects) as well. In addition, dose reductions did not lead to a decrement in efficacy for the patients who are dose reduced to achieve their individual maximum tolerated dose in NOVA study.

4.1.3 Benefit-Risk of Niraparib

The NOVA trial demonstrated that niraparib maintenance therapy results in a statistically significant and clinically meaningful delay in time to cancer progression or death in patients with platinum-sensitive recurrent OC regardless of *BRCA* mutation or HRD tumor status. Patient reported outcome data from validated survey tools indicate that niraparib-treated subjects reported no significant difference from placebo in measures associated with symptom-specific and general quality of life. Niraparib treatment did not reduce the effectiveness of subsequent therapies and continued to show beneficial treatment effect in the secondary efficacy measure of PFS.

The most common adverse drug reactions occurring in approximately 20% of the subjects in clinical trials were as follows: nausea, fatigue, anemia, vomiting, constipation, thrombocytopenia, decreased appetite, headache, insomnia, and abdominal pain. The occurrence of these events is consistent with niraparib's mechanism of action and readily manageable with dose modifications. No additional safety information has been received from clinical trials with regard to other safety issues such as pregnancy, overdose, and lack of efficacy.

There have been no reports of risks associated with the investigational or diagnostic procedures included in the clinical trials, no reports of risks that might be associated with insufficient quality of the IMP, and no significant reports of lack of efficacy with niraparib.

4.2 Rationale for the Proposed Study

This Japan phase 2 study is designed to assess a primary endpoint of the incidence of Grade 3 or 4 thrombocytopenia within 30 days after the initial dose of niraparib to evaluate safety of niraparib in Japanese patients comparable to the population in NOVA study.

In an overseas phase 3 study (NOVA study), niraparib 300 mg was administered to patients with platinum-sensitive, relapsed OC who responded to the last chemotherapy containing platinum-based anticancer agents once daily in a double-blind manner to compare with the placebo group. The results showed a significant reduction in the risk of progression or death (primary endpoint of PFS) in all three pre- specified primary analysis populations (g*BRCA*mut cohort, HRD-positive patients in the non-g*BRCA*mut cohort and the entire non-g*BRCA*mut cohort), supporting the efficacy and safety of niraparib as a maintenance therapy for patients with platinum-sensitive, relapsed OC. There is no clear difference in treatment system of OC between

Japan and overseas countries. No obvious differences were observed in the PK of niraparib among races. Therefore, it could be possible to extrapolate the results of NOVA study into Japanese patients.

Meanwhile, as mentioned above, a further review of the results of clinical studies indicated the patient body weight and platelet count at baseline effect on the occurrence of thrombocytopenia. In NOVA study, the incidence of Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the <77 kg cohort than in the ≥77 kg cohort.

In the Japan phase 1 study, the tolerability of niraparib at up to 300 mg was determined in Japanese patients with advanced solid tumors who were treated with niraparib 200 mg or 300 mg (dosed QD, orally, continuously in 21-day cycles). The observed DLT was Grade 4 thrombocytopenia.

In this situation, Takeda plan to evaluate the safety of niraparib in Japanese patients, using the subject incidence of Grade 3 or 4 thrombocytopenia occurring within 30 days after initial administration of niraparib (the valuable used for initial dose consideration in overseas studies) as a primary endpoint.

In this study, the initial dose of niraparib is determined as 300 mg, based on the maximum dose at which tolerability was observed in Japanese patients. Given the overseas clinical data that the patient body weight can affect the occurrence of study drug-related TEAEs, it is important to examine the safety of niraparib in Japanese patients because the body weight of Japanese patients is generally lower than that of patients in US or EU.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 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.

5.1.2 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.

5.1.3 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.

5.2 Endpoints

5.2.1 Primary Endpoints

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

5.2.2 Secondary Endpoints

- 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 (OS)
- Overall response rate (ORR)

5.2.3 Safety Endpoints

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

5.2.4 Additional Endpoints

- Plasma concentrations of niraparib for population pharmacokinetics

6.0 STUDY DESIGN

6.1 Overview of 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 Cycle 38, and at the end of every 6 cycles

(24 weeks with a window of ±7 days) until progression. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for 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.

6.2 Number of Patients

Approximately 15 patients will be enrolled in this study from approximately 30 study centers in Japan. Enrollment is defined as the time when the sponsor sends an enrollment sheet back to the investigational site (see Section 9.4.11).

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive study drug until they experience PD, unacceptable toxicity, withdrawal of consent, or for any of the other reasons outlined in Section 9.8. The OS follow-up should be performed until any of reason for withdrawal of patients from study (described in Section 9.9) including death occur.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

End of study is defined as a date that last patient complete post treatment assessments.

Primary Analysis

The final analyses (primary analysis) for the primary endpoint will be conducted 30 days or more after initial dose for last enrolled patient. The estimated time frame for primary analysis is approximately 6 to 8 months from first patient enrollment.

Other Planned Analyses

If follow-up assessment continues after the final analyses for the primary endpoint, a CSR safety addendum is planned for when all enrolled patients have had the opportunity to complete follow-up assessment.

Study Completion

The estimated time frame for study completion (screening, study drug administration and follow-up period) is approximately 28 months.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary: • The subject incidence of Grade 3 or 4 thrombocytopenia occurring within 30 days after initial administration of niraparib.	-	30 days after initial dose for last enrolled patient Approximately 6 to 8 months
Secondary: • Safety and tolerability	-	
− The number and percentage of subjects with TEAEs (a)	The number and percentage of subjects with TEAEs in the safety analysis set.	Approximately 28 months
− The number and percentage of subjects with Grade 3 or higher TEAEs (a)	The number and percentage of subjects with Grade 3 or higher TEAEs in the safety analysis set.	Approximately 28 months
− The number and percentage of subjects with serious TEAEs (a)	The number and percentage of subjects with serious TEAEs in the safety analysis set.	Approximately 28 months
− The number and percentage of subjects with TEAEs leading to drug discontinuation (a)	The number and percentage of subjects with TEAEs leading to drug discontinuation in the safety analysis set.	Approximately 28 months
− The number and percentage of subjects with TEAEs leading to dose interruption (a)	The number and percentage of subjects with TEAEs leading to dose interruption in the safety analysis set.	Approximately 28 months
− The number and percentage of subjects with TEAEs leading to dose reduction (a)	The number and percentage of subjects with TEAEs leading to dose reduction in the safety analysis set.	Approximately 28 months
• Progression-free survival	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.	Approximately 28 months
• Overall survival	The time from the date of enrollment to the date of death by any cause.	Approximately 28 months
• Overall response rate	The proportion of patients achieving CR or PR in the FAS.	Approximately 28 months

CR: complete response; FAS: full analysis set; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; TEAE: treatment-emergent adverse event.
(a) TEAEs are defined as AEs that occur after the first dose of study drug until 30 days after the last dose of study drug.

6.3.4 Total Study Duration

It is anticipated that patient enrollment will be completed approximately 2 months from the enrollment of the first patient into the study.

It is anticipated that this study will last for approximately 28 months.

6.3.5 Posttrial Access

The study will be continued until last patient complete post treatment assessments.

After a marketing approval of niraparib is obtained in Japan before the study completion/withdrawal, this study will be continued as a post-marketing clinical study in compliance with the GCP and the Good Post-marketing Study Practice.

7.0 STUDY POPULATION

The study will be conducted 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.

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Japanese female patients aged 20 years or older on the day of signing informed consent.
2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Patient must have a histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.
4. Patient must have a high-grade (or Grade 3) serous or high-grade predominantly serous histology or known to have g*BRCA*mut.
5. Patients must have completed at least 2 previous lines of platinum-containing therapy:

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

   a. For the penultimate platinum-based chemotherapy prior to study enrollment, patients must have had platinum-sensitive disease after this treatment, defined as achieving a response (CR or PR) and disease progression >6 months after completion of her last dose of platinum therapy (documented 6 to 12 months or >12 months). Source documentation was required.
   b. For the last line of platinum-based chemotherapy prior to study enrollment:
      i. Patients must have received a platinum-containing regimen for a minimum of 4 cycles.
      ii. Patients must have achieved a partial or complete tumor response.
      iii. Following the last regimen, patients must have had either.
         1. CA-125 equal to or less than the upper limit of the normal range.
         2. CA-125 decrease by more than 90% during the last platinum regimen, and which was stable for at least 7 days (ie, no increase >15%).
      iv. Following the last regimen, patients could not have had any measurable lesion >2 cm at the time of study enrollment.

c. Patients must have been enrolled within 8 weeks after completion of their final dose of the platinum- containing regimen.

6. Patients must have performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale.
7. Patients must have adequate organ function as indicated by the following laboratory values:
   a. Absolute neutrophil count (ANC) ≥1,500/μL.
   b. Platelet count ≥100,000/μL.
   c. Hemoglobin ≥9 g/dL.
   d. Serum creatinine ≤1.5× institutional upper limit of normal (ULN) OR calculated creatinine clearance ≥50 mL/minute, using the Cockcroft-Gault equation.
   e. Total bilirubin ≤1.5×ULN OR direct bilirubin ≤1×ULN.
   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN unless liver metastases were present, in which case they had to be ≤5×ULN.
8. Patients must be able to take oral medications.
9. Female patients of childbearing potential must be negative for pregnancy test (β-hCG) within 7 days prior to receiving the first dose of study treatment.
10. Female patients who:
    a. Are postmenopausal for at least 1 year before the screening visit, OR
    b. Are surgically sterile, OR
    c. If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, OR
    d. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Patients who have had drainage of ascites during last 2 cycles of last chemotherapy.
2. Patients who have had palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment.
3. Patients who have any persistent Grade ≥3 toxicity from last cancer therapy.

4. Patients who have symptomatic, uncontrolled brain or leptomeningeal metastases. To be considered "controlled," central nervous system (CNS) disease must have undergone treatment (eg, radiation or chemotherapy) at least 1 month prior to study enrollment. The patient must not have had any new or progressive signs or symptoms related to the CNS disease and must have been taking a stable dose of steroids or no 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 at baseline was not required. Patients with spinal cord compression might have been considered if they had received definitive treatment for this and evidence of clinically stable disease for 28 days.
5. Patients who have known hypersensitivity to the components of niraparib.
6. Patients who have had prior treatment with a known PARP inhibitor.
7. Patient who have had treatment with any investigational products within 28 days or 5 half-lives (whichever was longer) before the first dose.
8. Patients who have had major surgery per investigator judgment within 3 weeks of the first dose. Patient must have recovered from any effects of any major surgery.
9. Patients who have diagnosis, detection, or treatment of invasive second primary malignancy other than ovarian cancer ≤24 months prior to study enrollment (except basal or squamous cell carcinoma of the skin that was definitively treated). Note: Patients must not have any known history or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), irrespective of the time for disease history.
10. Patients who are considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the first dose) 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.
11. Patients who have received a transfusion (platelets or red blood cells) within 4 weeks of the first dose of study treatment.
12. Patients who have received a live virus and bacterial vaccines within 4 weeks of the first dose of study treatment.
13. Patients who have a history or current evidence of any condition, therapy, or lab abnormality (including active or uncontrolled myelosuppression [ie, anemia, leukopenia, neutropenia, thrombocytopenia]) that might confound the results of the study, interfere with the patient's participation throughout the study period, or study participation is not in the best interest of the patient
14. Patients who are regular user (including "recreational use") of any illicit drugs at the time of signing informed consent or have a recent history (within the past year) of drug or alcohol abuse.

15. Patients who are pregnant or breast-feeding, or expecting to conceive within the planned duration of the study. NOTE: If a breast-feeding woman discontinue breast-feeding, she may be enrolled in the study.
16. Patients who are immunocompromised (patients with splenectomy are allowed).
17. Patients who have known HIV positive.
18. Patients who have known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection.

    NOTE: Patients who are positive for hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) must have an undetectable HCV viral load.

8.0 STUDY DRUG

8.1 Study Drug Administration

The study drug will be administered at 300 mg QD, orally continuously, in 28-day cycles. Niraparib will be administered until subjects experience objective PD, experience unacceptable toxicity, withdrawal of consent or until study discontinuation due to any other reasons specified in the study protocol.

The study drug should be administered at approximately the same time every day. In the event of missed doses or vomited doses, the dose will not be re-administered. The study drug should not be chewed before swallowing. The study drug may be taken with water.

Patients will be provided dosing diary and instructed to record any dose of study drug and the time of administration in their dosing diary in study treatment period.

8.2 Dose Modification Guidelines

8.2.1 Criteria for Dose Reduction, Interruption, and Discontinuation

Dose interruption and/or reduction may be implemented at any time for any grade toxicity if the investigator or subinvestigator deems that the toxicity is intolerable by the patient.

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

(1) Dose Modifications for Non-Hematologic Toxicities

Treatment must be interrupted for any NCI CTCAE (v.4.03) Grade 3 or 4 non-hematologic toxicity which the investigator or subinvestigator considers to be related to administration of niraparib. If the Grade 3 or 4 non-hematologic toxicity is appropriately resolved to baseline or Grade 1 or less within 28 days following interruption, the patient may restart treatment with niraparib at the same dose level. However, if prophylaxis is not considered feasible, treatment with niraparib should be restarted with a dose level reduction according to Table 8.a. After the restart, if the event recurs at the same or worse grade, treatment should be interrupted again and, upon resolution, treatment with niraparib should be restarted with a dose level reduction according to Table 8.a.

Dose reductions to 200 mg/day and subsequently to 100 mg/day will be allowed. No further dose reduction will be allowed. If the toxicity requiring dose interruption has not resolved completely or to NCI CTCAE Grade 1 during the maximum 4-week (28-day) dose interruption period, and/or the patient has already undergone the maximum dose reductions, the patient must permanently discontinue study treatment.

Table 8.a Dose Reductions for Non-Hematologic Toxicities

Event	Dose(a)
Initial dose	300 mg QD
1st dose reduction for NCI CTCAE Grade 3 or 4 treatment-related SAEs/AEs where prophylaxis with medication is not considered feasible.	200 mg QD
2nd dose reduction for NCI CTCAE Grade 3 or 4 treatment-related SAEs/AEs where prophylaxis with medication is not considered feasible.	100 mg QD
Continued NCI CTCAE Grade 3 or 4 treatment-related SAEs/AEs ≥28 days.	Discontinue study medication

AE: adverse event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; QD: once daily; SAE: serious adverse event.
(a) Dose not to be decreased below 100 mg QD.

(2) Dose Modification for Hematologic Toxicities

The dose interruption/modification criteria for hematologic parameters will be based on blood counts and are outlined in Table 8.b.

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 reduction(s), the patient must permanently discontinue treatment with niraparib.

Table 8.b Dose Interruption, Resume or Reduction for Hematologic Toxicities

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

CBC: complete blood cell count.
*For patients with platelet count ≤10,000/μL prophylactic platelet transfusion per guidelines may be considered. For patients taking anticoagulation or antiplatelet drugs consider of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤20,000/μL (before platelet count decreased ≤10,000/μL).

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. When the treatment

is re-started after the AE resolution, weekly blood draws for CBC will be also required for an additional 4 weeks to ensure safety of the restarted dose. Monitoring every 4 weeks may resume thereafter.

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

The patient must be referred to a hematologist for further evaluation (1) if transfusions are required on 1 or more occasions or (2) if the treatment-related hematologic toxicities have not recovered to NCI CTCAE Grade 1 or less after 4 weeks interruption with sufficient supportive care. If a diagnosis of myelodysplastic syndrome (MDS)/acute myeloblastic leukemia (AML) is confirmed by a hematologist, the patient must permanently discontinue study treatment.

(3) Other

If a secondary cancer (new malignancies other than MDS/AML) is diagnosed while on study, the patient must permanently discontinue study treatment.

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

8.2.2 Re-Escalation After Dose Reduction

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

8.2.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Niraparib will be administered in continuous cycles; therefore, study drug should be administered continuously unless TEAEs occur that meet the dose modification criteria outlined in Section 8.2.1.

If dose interruption was required due to TEAE at the beginning of a Cycle, the Cycle should not be postponed. Once the patient recovers from the TEAE, the study treatment will be resumed in the middle of the cycle, without waiting for the first day of the next Cycle.

However, the timing of efficacy and safety evaluations will not be affected by the dose interruption or dose reduction.

8.3 Excluded Concomitant Medications and Procedures

The following medications, procedures and foods are prohibited from the time of signing the informed consent through the treatment discontinuation visit:

- Other anticancer therapies other than study treatment, with the exception as follows:
  - 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 for the treatment of brain or leptomeningeal metastases or other diseases (Section 7.2, Exclusion Criteria 4). Temporary steroid use will be permitted for treatment of AEs or for prophylaxis. Of note,

topical steroids such as intraarticular, intranasal, eye-drops, and inhalation are permitted without limitation.

- Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of PD is present.

- Conventional chemotherapy drugs, live virus and bacterial vaccines increased risk of infection have been observed. Effects with niraparib are unknown and therefore they should not be administered to patients 4 weeks before initial administration of niraparib and during the study.
- Prophylactic cytokine (granulocyte colony-stimulating factor [GCSF]) administration should not be given in Cycle 1. Prophylactic cytokine may be administered in Cycle 2 onwards according to local guidelines, etc.

The following medications, procedures, and foods should be used with caution during the study treatment period:

- Drugs that are substrates for cytochrome P450 (CYP) 1A2 (Appendix F) (niraparib is a CYP1A2 inducer).
- Drugs that are inhibitors or substrates for P-glycoprotein (P-gp) (niraparib is a substrate for P-gp).
- Anticoagulation and antiplatelet drugs (niraparib potential risk includes thrombocytopenia).
- Drugs associated with QT interval (QTc) prolongation (Appendix G) (Niraparib has been associated with QT prolongation when co-administered with medications known to cause QTc prolongation.)

8.4 Permitted Concomitant Medications and Procedures

For patients with platelet count ≤10,000/μL prophylactic platelet transfusion per guidelines may be considered.

8.5 Precautions and Restrictions

8.5.1 Pregnancy and Contraception

Niraparib is clastogenic and is expected to exhibit embryo-fetal toxicity based on the mechanism of action. Therefore, female patients participating in this study should avoid becoming pregnant. Nonsterilized female patients of reproductive age group should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or

- If they are of childbearing potential*, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception** at the same time, from the time of signing of the ICF through 180 days after the last dose of study drug, or
- Agree to practice true abstinence from the time of signing of the ICF through 180 days after the last dose of study drug, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

*Women of childbearing potential are defined as any sexually active female subjects who meet both of the following criteria:

- Those who have not undergone hysterectomy or bilateral oophorectomy.
- Those who have not had natural menopause for 12 consecutive months or longer.

  Note: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

**Examples of highly effective contraception methods are listed below:

- Hormonal birth control pills.
- Intrauterine device.
- Intrauterine hormone-releasing system.

8.5.2 Other Precautions and Restrictions

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

8.6 Blinding and Unblinding

This is an open-label study.

8.7 Description of Investigational Agents

Niraparib capsule contains 100 mg of niraparib (free form). The hard capsules have a white body with a printed black bar, and a purple cap with a printed white bar.

Refer to the Investigator's Brochure for further details.

8.8 Preparation, Reconstitution, and Dispensation

Detailed instructions for dispensing niraparib tablets are provided in the Pharmacy Manual. Niraparib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling niraparib.

8.9 Packaging and Labeling

Niraparib capsules are packaged in a high-density polyethylene (HDPE) white bottle with a two-piece, pulp-backed, heat-induction-foil inner seal, tamper-proof cap. Each bottle contains 93 capsules. The label text of the study drug will comply with the national legislation to meet all requirements in Japan.

8.10 Storage, Handling, and Accountability

Investigational study drug must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed to the patients and returned to the sponsor or its designated disposal vendor, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

Niraparib capsules must be stored at 2°C to 25°C. Refer to the Pharmacy Manual for further details.

8.11 Other Protocol-Specified Materials

Not applicable.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the sponsor's medical monitor for this study, other third-party vendors, and the list of investigators may be found in the protocol annex or the Study Manual.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator or subinvestigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB).

9.3 Treatment Group Assignments

Not applicable.

9.4 Study Procedures

Refer to the Schedule of Events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.4.2 Patient Demographics

The date of birth, race and sex of each subject are to be recorded during the Screening period. If available, the data on whether individual subjects have *BRCA* mutations will also be collected.

9.4.3 Medical History

During the Screening period, all concurrent conditions will be collected for each subject. Also, medical histories that are considered to be clinically useful by the investigator will be collected.

As the information about the underlying disease, the following data will be collected and recorded specifically: the date of initial diagnosis, the type of tumor, the stage of disease at the initial diagnosis, the results of histology at diagnosis and grade.

During screening, the following medications are to be recorded as prior medications based on hearing from the subjects:

- All non-chemotherapeutic medications given to subjects within 14 days before Cycle 1 Day 1.

- All chemotherapeutic agents and treatment given to subjects after the initial diagnosis, its start and end dates and the best response to each treatment.
- All prior surgeries for the underlying disease.

In addition, CA-125 values at start and complete date of the last platinum-based regimens.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events (Appendix A).

9.4.5 Patient Height

Height will be measured at screening only. Weight will be measured at the times specified in the Schedule of Events (Appendix A).

9.4.6 Vital Signs

Vital signs include diastolic and systolic blood pressure, pulse rate and body temperature (axillary) measured at the times specified in the Schedule of Events (Appendix A). Subjects must be resting in a sitting position for 10 minutes prior to obtaining vital signs. This measurement method will be used throughout the study. To determine the effects of niraparib on the cardiovascular system, blood pressure will be measured prior to obtaining blood samples.

If blood pressure exceeds 150/100 mmHg or diastolic blood pressure exceeds 20 mmHg from baseline despite the subject has no history of hypertension, blood pressure must be re-measured within 10 minutes for confirmation.

If there was a change in blood pressure from prior to study drug administration, which was judged by the investigator as an AE, such change will be recorded in the eCRF.

9.4.7 ECOG Performance Status

ECOG performance status will be assessed and recorded according to (Appendix E) at the times specified in the Schedule of Events (Appendix A).

The investigator will evaluate the performance status.

9.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential (defined in Section 8.5.1) within 7 days before Cycle 1 Day 1, and negative results must be obtained before the first dose of study drug. Subsequently, serum or urine pregnancy tests will be performed every three cycles during the study treatment, and negative results must be obtained before the study drug administration.

9.4.9 Concomitant Medications and Procedures

Medications used by the subject and therapeutic procedures completed by the subject will be recorded in the eCRF from the time of signing the informed consent through 30 days after the last dose of study drug or the start of subsequent antitumor therapy, whichever comes first. See Section 8.3 and Section 8.4 for medications and therapies that are prohibited or allowed during the study.

All medications other than the study drug (including Chinese herbal medicine and other non-traditional remedies) and treatment used by subjects during the study period should be investigated and recorded by hearing from the subjects. For each medication, the nonproprietary name, the start and end date and the purpose of use will be recorded.

9.4.10 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and serious AEs (SAEs).

For any suspected case of MDS/AML or second primary 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 (WHO) criteria, and other sample testing reports related to MDS/AML or secondary cancer (new malignancies other than MDS/AML).

9.4.11 Enrollment

A subject is considered to be enrolled in the study when the sponsor sends an enrollment sheet back to the investigational site. Procedures for completion of the enrollment information are described in the Study Manual.

Initial dose of niraparib must be administered within 5 days of the patient enrollment.

9.4.12 Electrocardiogram

A 12-lead ECG will be performed at time points specified in the Schedule of Events (Appendix A) and the results will be evaluated at each study site. The heart rate, RR, PR, QRS, QT, and corrected QT (QTcF) intervals will be recorded in the eCRF.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally before administration of the study drug.

9.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained on the same day, before administration of the study drug, as specified in the Schedule of Events (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	**Serum Chemistry**	
• Erythrocyte • Hematocrit • Hemoglobin • Leukocytes with differential (ANC, basophil count, eosinophil count, absolute lymphocyte count, monocyte count) • Platelet count • MCV (optional) (a)	• Albumin • ALP • ALT • Amylase • AST • Total bilirubin Direct bilirubin • Urea nitrogen • Calcium • Creatinine	• Chloride • GGT • Glucose • LDH • Magnesium • Inorganic phosphate • Potassium • Sodium • Protein (total protein)
Blood coagulation test	**Pregnancy test (serum, urine)**	
• aPTT • INR	• β-hCG	

ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANC: absolute neutrophil count; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; β-hCG: human chorionic gonadotropin; INR: international normalized ratio; LDH: lactate dehydrogenase; MCV: mean cell volume; PT: prothrombin time.
(a) Although mean platelet volume collection is optional, it is highly encouraged, especially for patients with high-grade thrombocytopenia.

Table 9.b Clinical Urinalysis Tests

Urinalysis	
• Bilirubin • Glucose • Ketones • Nitrite • Occult blood	• Protein • Specific gravity • Urobilinogen • Leukocyte esterase

If creatinine clearance is to be estimated, the Cockroft-Gault formula will be employed as follows:

$$Estimated\ creatinine\ clearance\ (for\ female\ patients) = [(140 - Age) * Mass(kg)\ ] / [72 * serum\ creatinine(mg/dL)]\ * 0.85$$

9.4.13.2 Serum CA-125 Assessment

Blood samples for analysis of the serum CA-125 assessment will be obtained on the same day, before administration of the study drug, as specified in the Schedule of Events (Appendix A).

If CA-125 samples for screening assessment are collected within 72 hours prior to the first dose on Cycle 1 Day 1, repeat testing is not required for Cycle 1 Day 1. CA-125 levels must be normal at screening or have a >90% decrease, and which was stable for at least 7 days (ie, no increase >15%) compared to baseline prior to their last platinum-based chemotherapy course.

Abnormal CA-125 levels on-study do not represent disease progression; however, they may prompt imaging if clinically indicated. For determination of CA-125 progression, at least 2 CA-125 values at least 1 week apart are required for confirmation.

9.4.14 Disease Assessment

Subjects will undergo computed tomography (CT) with contrast as appropriate to monitor and assess PD, using modified RECIST criteria (Version 1.1) (Appendix F). Specific disease sites that cannot be adequately imaged by CT with contrast may be documented by magnetic resonance imaging (MRI). Bone scans may be performed on subjects with bone metastases rather than contrast enhanced CT or MRI.

During the study, anatomical measurements will be collected for each target lesion using an imaging modality consistent with that used at Screening. The same method (CT with contrast, MRI or bone scan) must be consistently used on a subject throughout the study.

Objective assessments will be performed at each time point as described in the Schedule of Events (Appendix A). When possible, the same qualified physician will interpret the results to reduce variability.

Appropriate imaging evaluation at screening should include a CT/MRI of the chest, abdomen and pelvis. Imaging evaluations of other body parts are not necessary unless clinically indicated.

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.

The sizes of visible lesions will be recorded using a ruler. The sizes of palpable lesions will be recorded in the subject's source documents at the physical examination. The tumor status will be compared with that at screening, using physical findings, imaging results and ECOG performance status.

In this study, confirmation of complete or partial response is required. Complete or partial responses may be claimed only if the criteria for each are met 4 weeks or more later.

Radiographic images will be maintained at each site, and test results and physicians' findings will be filed in subject's source documents. The sponsor may request electronic images for those subjects who demonstrate tumor reduction.

9.4.15 ORR

ORR is defined as the proportion of patients achieving CR or PR as assessed by the investigator per RECIST (v.1.1) (Appendix E).

9.4.16 PFS (Definition of PD)

PFS is defined as the time from the date of enrollment to the earlier date of progression assessed by the investigator per RECIST (v.1.1) (Appendix E) or clinical criteria, or death by any cause.

PFS will be determined based on a tumor assessment by the investigator and the criteria of CA-125 progression. The date of progressive disease (PD) will be determined based on imaging assessment according to RECIST v.1.1 (Appendix 2, Table 5) criteria, preferentially. 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. PD will be determined if at least 1 of the following criteria is met:

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

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

The investigator will describe why PD was diagnosed in the eCRF. The date of PD is defined as the earliest time point when one of the PD criteria is met. When required to determine progression, CA-125 levels should be evaluated ±2 weeks from the primary PD assessments (ie, diagnostic test or clinical parameters) and must be confirmed by a second determination ≥7 days later. In case assessments of CA-125 levels occur greater than 2 weeks from the primary PD assessments, the date of the primary assessment of PD will be used to define the date of PD. GCIG criteria for

CA-125 progression are as follows: (Note: CA-125 progression alone will not be considered disease progression.)

CA-125 progression according to GCIG criteria

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

If CT/MRI shows existing (baseline) lesions which only equivocally suggest PD and additional diagnostic tests are required to determine unequivocal PD, the official date of PD will be the date PD was unequivocally determined. Alternatively with new lesions (except ascites and effusions) that are initially equivocal that are later unequivocally determined, the date of progression will be the date the lesion was initially identified.

Note: If the investigator determines clinical PD, they can consult an imaging clinician at the investigational site prior to receiving results from the central reader. Pursuant to consultation with the clinician, the investigator can keep the patient on study treatment as long as it is considered safe, or the investigator can discontinue the patient.

9.4.17 OS

OS is defined as the time from the date of enrollment 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.

9.4.18 Pharmacokinetic Measurements

Blood samples for PK analysis of niraparib will be serially collected at the time points specified in the Schedule of Events (Appendix A). The exact dates and times of administration of niraparib before collection of the blood sample for PK analysis and the exact dates and times of collection of the blood sample for PK analysis will be recorded on the eCRF.

9.5 Records of Patients who Discontinued the Study After Enrollment and Before the First Administration of Study Drug

The investigator or subinvestigator is responsible for documenting the records of all patients who signed the ICF.

The investigator or subinvestigator is responsible for the eCRF data entry, even if the patient turned out to be ineligible after enrollment and before the first administration of study drug.

The primary reason of study discontinuation after enrollment and before the first administration of study drug will be recorded in the eCRF, under the following categories:

- Death.
- Adverse event.
- Screen failure (the subject did not meet the inclusion criteria or did meet the exclusion criteria).
- Protocol deviation.
- Lost to follow-up.
- Consent withdrawal by patient.
- Termination of the whole study by sponsor.

The subject identification number of the patient who discontinued the study before the first study drug administration will not be reused.

9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed treatment if they discontinue treatment with study drug for any of the reasons outlined in Section 9.8.

Treatment will continue until PD, unacceptable toxicities, or withdrawal due to other reasons.

9.7 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study based on the patient being followed until a specific event, eg, death or until study termination, and complete the safety follow-up.

9.8 Discontinuation of Treatment With Study Drug and Patient Replacement

Treatment with study drug may be discontinued for any of the following reasons:

- AE.
  - Any treatment-related NCI CTCAE (ver. 4.03) Grade 3 or 4 non-hematologic toxicity that have not reverted to CTCAE Grade 1 or better within 28 days of dose interruption.
  - Any hematologic toxicity that have not retreated to the pre-specified level within 28 days following study drug interruption.
  - Any treatment emergent adverse event that lead to study drug interruption and restart with dose reduction occurred in a patient who has already received a minimum dose of niraparib (100 mg QD) after prior study drug interruption due to adverse event.
- Protocol deviation.
- PD.
  - Definition of PD (Section 9.4.16) as judged by the investigator or subinvestigator.

- Pregnancy.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the end-of-treatment visit will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than progressive disease before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the Schedule of Events until disease progression occurs.

9.9 Withdrawal of Patients From Study

A subject may be withdrawn from the study for any of the following reasons. However, subjects may withdraw their consent to participate in the study at any time without prejudice.

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by subject.
- Death.
- Other.

The sponsor should be notified of all subject withdrawals from the study as soon as possible. If a subject withdraws consent to participate in the study, no study data will be collected or data added to the database for this subject thereafter. However, every effort will be made to follow all subjects for safety.

9.10 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Subjects will receive a sufficient quantity of study drugs for each treatment cycle and provided a diary where the date of study drug administration will be recorded. The study site staff will check the patient diary versus the subject's supply of remaining niraparib at each study visit to ensure proper compliance with dosing. Subjects who are not compliant with the dosing schedule may be withdrawn from the study.

Tests and procedures should be performed on schedule. However, except Cycle 1 Day 1, Cycle 2 Day 1, Early Termination and follow-up 30 days after the last dose, occasional changes are allowable within a 3-day window for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a subject from beginning treatment or completing a planned procedure or assessment within 3 days of the scheduled time, the subject may continue the study at the discretion of the investigator and after consultation with the sponsor's medical monitor or designee. However, the timing of PK assessment as specified in the Schedule of Events (Appendix A) is not flexible.

The observation and test specified in the Study Treatment Discontinuation visit will be conducted within 7 days after last dose of niraparib. The observation and test specified in the 30 days after the last dose visit will be conducted at 30 days (+7 days) after the last dose of study drug administration, or beginning of subsequent anticancer therapy, whichever comes first, and the follow-up assessments will be conducted every 90 days (±7 days) from the termination day of the study drug administration.

9.11 Thirty Days Follow-up After the Last Dose

All AEs (including laboratory data specified in the schedule) and concomitant medications will be collected and recorded for each patient from the day of signing the ICF until 30 days (+7 days) after last dose of study treatment administration, or beginning of subsequent anticancer therapy, whichever comes first.

All AEs and SAEs which occurred until the visit of 30 days follow-up after the last dose will be recorded and monitored appropriately.

9.12 Posttreatment Follow-up Assessments (Progression-Free Survival and Overall Survival)

If a patient discontinues treatment for the reason other than PD, withdrawal by subject, and lost to follow-up, scans and CA-125 testing will continue to be collected for PFS evaluation.

The PFS evaluation after study treatment discontinuation will be performed at the protocol specified intervals (ie, same as an interval during study treatment) from study treatment discontinuation until progression is confirmed or until the start of subsequent anticancer treatment.

If a patient discontinues treatment for PD, follow-up information will continue to be collected for OS assessment. The OS assessment will be performed every 90 days (±7 days) following study treatment discontinuation. Following the treatment discontinuation visit, survival status will be collected for all patients using acceptable means (ie, hospital visit is not mandatory). New malignancy information will also be collected as part of this assessment.

The following information will be collected in the Post Treatment Assessments:

- MDS, AML, and secondary cancers (new malignancies other than MDS/AML) which occurred after study treatment discontinuation
- Treatment-related death

  - The death must be reported by the investigator or subinvestigator to the Takeda Global Pharmacovigilance Department or designee, same as during study treatment period (Section 10.2).

- Outcome of adverse event that occurred during the study
  - All AEs experienced by a patient will be monitored until the AE 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.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AE Definition

AE means any untoward medical occurrence in a patient or subject who has been enrolled in a study; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.2 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective 14 June 2010 [6]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported by the investigator or subinvestigator to the Takeda Global Pharmacovigilance Department or designee (contact information provided below) (see Section 10.3 for the period of observation). This should be done by faxing, calling or e-mailing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to the clinical study site. A sample of the SAE Form may be found in the Study Manual. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

[redacted]

If information not available at the time of the first report becomes available at a later date, then the investigator or subinvestigator will transmit a follow-up SAE report or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up by the investigator or subinvestigator until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial; eg, surgery was performed earlier or later than planned.

For both serious and nonserious AEs, the investigator or subinvestigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective 14 June 2010 [6].

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug?"

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug, whichever comes first, and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study drug, whichever comes first, and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 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) of niraparib. 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 (Section 10.2). AESI monitoring must occur during the study, during follow-up and after study discontinuation.

10.5 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator or subinvestigator immediately and permanently discontinue study drug. The investigator or subinvestigator must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

10.6 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail address provided below, or immediately contact the study monitor.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail address provided below, contact the study monitor, and record the event in the Overdose page of the eCRF.

Call Center	Phone Number	Email	Fax
[redacted]			

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

10.7 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs and the head of the institution, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who has been enrolled in the study.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator, subinvestigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor or designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH

E6 Section (Section 4.9.5) requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 (Section 4.9.5) states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and/or the head of the institution and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements for record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

In this study, the following 4 analysis sets are defined: safety analysis set, full analysis set, response-evaluable analysis set, and PK analysis set. The details of the definition will be provided in the SAP.

The sponsor will review the definition of any analysis set and the data handling rule and add any issue handling rule specified after study initiation, with consultation with medical expert if necessary, then the SAP will be finalized before database lock.

13.1.1.1 Safety Analysis Set

Safety analysis set is defined as patients who receive at least 1 dose of study drug.

13.1.1.2 Full Analysis Set

Full analysis set is defined as patients who receive at least 1 dose of study drug.

13.1.1.3 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.

13.1.1.4 PK Analysis Set

PK analysis set is defined as patients who receive at least 1 dose of study drug and have at least 1 concentration data of niraparib.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by dose cohort using the FAS, the safety analysis set and the PK analysis set.

13.1.3 Efficacy Analysis

PFS and OS will be analyzed using Kaplan-Meier method to provide quartiles and progression/survival rate at specified points with 95% CI using FAS. The Kaplan-Meier plot for PFS and OS will also be provided.

ORR and its two-sided 95% confidence interval will be provided using the response-evaluable analysis set. The two-sided 95% confidence interval will be calculated based on binominal distribution.

13.1.4 Pharmacokinetic Analysis

All PK analyses will be performed using the PK analysis set.

Population PK analyses will be conducted using the PK data of niraparib collected in this study. These population PK analyses may additionally include data collected in other niraparib clinical studies. The plan for the population PK analysis will be defined separately and the results reported separately.

13.1.5 Safety Analysis

13.1.5.1 Primary Endpoint analysis

The subject incidence of Grade 3 or 4 thrombocytopenia within 30 days after the initial dose of niraparib will be calculated using safety analysis set.

13.1.5.2 Secondary Endpoints analysis

The following analyses will be performed using the safety analysis set.

TEAE is defined as adverse events that occur after administration of the first dose of study drug. TEAEs will be coded using the MedDRA dictionary, and will be tabulated by preferred terms (PT) and system organ class (SOC).

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- Serious TEAEs.
- TEAEs leading to study drug discontinuation.
- TEAEs leading to study drug interruption.
- TEAEs leading to study drug reduction.

13.1.5.3 Other Endpoints Analysis

For laboratory tests, vital sign, ECG and ECOG performance status, shift tables based on changes in NCI CTCAE grade from baseline to the worst postbaseline value will be generated using the safety analysis set. For continuous variable, value at each time point and changes from baseline

will be summarized using descriptive statistics. Case plots over time for each subject will be presented.

Additional safety analyses may be performed to more clearly enumerate rates of toxicities and to further define the safety profile of niraparib QD.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 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), as described in Section 1.3.2.5. 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 [redacted] 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%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study medication, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, subinvestigator, and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator or subinvestigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without prior written agreement with the sponsor or prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change and its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and approval from IRB should be obtained.

The investigator or subinvestigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] Food and Drug Administration [FDA], the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, (ie, before shipment of the sponsor-supplied drug). The IRB approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting

the study. The ICF further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the ICF. The ICF must be approved by the IRB and the sponsor before use.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or subinvestigator to explain the detailed elements of the ICF to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject determines that he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, at the time of consent and before the subject enters into the study. The subject should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator or subinvestigator must also sign and date the ICF at the time of consent and before the subject enters into the study.

Once signed, the original ICF will be stored in the investigator's site file. The investigator or subinvestigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age and date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, (eg, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the clinical study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline *BRCA*1/2 mutation. J Clin Oncol 2015;33(3):244-50.

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[3] Kaelin WG, Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 2005;5(9):689-98.

[4] Turner N, Tutt A, Ashworth A. Hallmarks of '*BRCA*ness' in sporadic cancers. Nat Rev Cancer 2004;4(10):814-9.

[5] Abkevich V, Timms KM, Hennessy BT, Potter J, Carey MS, Meyer LA, et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. Br J Cancer 2012;107(10):1776-82.

[6] Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services Series v4.03. June 14, 2010. Publication No. 09-5410.

Appendix A Schedule of Events

	Screening	Study Treatment							Follow-Up	
Cycle (a)	**Screening (b)**	**Cycle 1**				**Cycle 2**	**Subsequent Cycles (a)**	**Study Treatment Discontinuation (visit within 7 days of last dose)**	**30 days after the last dose(c)**	**Post Treatment Assessments**
Day	**-28 to -1 Days**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**			
Study Procedures										
Informed Consent (b)	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Medical, surgical, cancer, medication history	X									
Safety Assessments/Labs/Measurements										
Physical examination	X	X	X	X	X	X	X	X		
Vital signs, height, weight(d)	X	X		X		X	X	X		
ECOG performance status	X	X				X	X	X		
12-lead ECG(e)	X							X		
Pregnancy test(f)	X						X			
Coagulation/Serum chemistry(g)	X	X		X		X	X	X	X	
Hematology(g)(h)	X	X	X	X	X	X	X	X	X	
Serum CA-125(g)(i)(j)	X(i)	X				X	X	X		X(o)
Urinalysis(k)	X									
Chest CT/MRI(l)	X									
Adverse Event(m)(n)	←								→	
Concomitant medications	←								→	
Efficacy Measurements										
Tumor Assessment(RECIST)(o)(p)	X(p)						X	X		X(o)

	Screening	Study Treatment							Follow-Up	
Cycle (a)	**Screening (b)**	**Cycle 1**				**Cycle 2**	**Subsequent Cycles (a)**	**Study Treatment Discontinuation (visit within 7 days of last dose)**	**30 days after the last dose(c)**	**Post Treatment Assessments**
Day	**-28 to -1 Days**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**			
Survival assessment(q)										X(q)
PK Measurements										
Blood sample for PK(r)		X				X	X			
Drug Administration and Accountability										
Study treatment dispensed/collected(s)		X				X	X	X(s)		

CA, cancer antigen; CBC, complete blood cell count; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ICF, informed consent form; MRI, magnetic resonance imaging; PET, positron emission tomography; PK, pharmacokinetic(s); RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

(a) Treatment cycles are 28 days long, 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, coagulation test, 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 [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) The assessment of Follow-up (30 days after the last dose) will be performed until 30 days (+7 days) after last dose of study treatment administration or beginning of subsequent anticancer therapy, whichever comes first.

(d) Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.

(e) Patients will have a 12-lead ECG at Screening and upon study treatment discontinuation. Note that the ECG is to be completed prior to blood draw for PK measurement and laboratory test.

(f) Negative serum pregnancy test required within 7 days 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). At screening, serum pregnancy test must be negative. During the study period, urine pregnancy test may also be allowed.

(g) If screening laboratory testing (serum chemistry, coagulation, and hematology) performed within 72 hours prior to the first dose on Cycle 1 Day 1, repeat testing is not required for Cycle 1 Day 1.

(h) If dose interruption or modification is required 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.

(i) CA-125 levels must be normal at screening or >90% decrease, and which was stable for at least 7 days (ie, no increase >15%) as compared with baseline prior to last platinum-based chemotherapy course. Abnormal CA-125 levels during study do not represent disease progression; however, they may prompt imaging if clinically indicated. If CA-125 samples for screening are collected within 72 hours prior to the first dose on Cycle 1 Day 1, repeated testing is not required for Cycle 1 Day 1.
(j) For determination of CA-125 progression, at least 2 CA-125 values at least 1 week apart are required for confirmation.
(k) Urinalysis parameters must include: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin.
(l) Chest CT/MRI will be performed 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.
(m) For any suspected MDS/AML, and secondary cancers (new primary malignancies other than MDS/AML) case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to WHO criteria and other sample testing results related to MDS/AML, and secondary cancers (new primary malignancies other than MDS/AML).
(n) All AEs (excluding MDS, AML, and secondary cancers [new primary malignancies other than MDS/AML]) will be recorded for each patient from the day of signing the ICF until 30 days after last dose of study treatment administration, or beginning of subsequent anticancer therapy, whichever comes first.
(o) RECIST tumor assessment via CT or MRI scan of abdomen/pelvis and clinically indicated areas required at baseline, then after every 2 cycles (ie, 8 weeks with a window of ±7 days from date of visit) through Cycle 14 (56 weeks) (ie, Day 1 of Cycle 3, Cycle 5, Cycle 7, Cycle 9, Cycle 11, Cycle 13, and Cycle 15), then after every 3 cycles (12 weeks with a window of ±7 days) until Cycle 38 (ie, Day 1 of Cycle 18, Cycle 21, Cycle 24, …, and Cycle 39), and after every 6 cycles (24 weeks with a window of ±7 days) until progression (ie, Day 1 of Cycle 45, Cycle 51, …); at this point (ie, progression), a final follow-up set of imaging is required. PET/CT may be used according to RECIST guidelines. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals in the protocol until progression is confirmed or until the start of subsequent anticancer treatment. Radiographic images will be maintained at each site, and test results and physicians' findings will be filed in subject's source documents. The sponsor may request electronic images for those subjects who demonstrate tumor reduction.
(p) 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 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 ICF must have been performed and be able to be submitted per the Sponsor-specified method.
(q) Every 90 days (±7 days) following study treatment discontinuation.
(r) Blood samples for PK collected on Cycle 1 Day 1 and Cycle 2 Day 1 collected predose (within 30 minutes) and 2 hours postdose (±15 minutes). Additional blood samples for PK on Cycle 4 Day 1 will be collected at predose within 30 minutes only. In addition, the exact time of the PK blood draw will be recorded.
(s) No new capsules dispensed (collection only).

Appendix B Responsibilities of the Investigator

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the subinvestigators and other staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all subinvestigators, colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB that conform to ICH and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid ICF is the most current version approved by the IRB. Each ICF should contain a section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a section on the uses and disclosures of a subject's personal information, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. This responsibility lies on the appropriate individual, designated by the site in Japan.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix E Response Evaluation Criteria In Solid Tumors (RECIST), Amendment V1.1

These criteria are adapted from Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

Measurability of Tumor at Baseline

Measureable

Tumor lesions

Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness recommended to be no greater than 5 mm. For a study site which defines that the slice thickness greater than 5 mm is medically acceptable, the minimum size for a measurable lesion at baseline should be twice the slice thickness used for imaging).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Tumor Response Evaluation

Target lesions

- When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means, for instance, where patients have only one or two organ sites involved a maximum of two and four lesions, respectively, will be recorded).

- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected
- Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters.

Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression".

Response Criteria

Evaluation of target lesions

- CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- PD: At least a 20% increase in the sum of 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, the sum must also demonstrate an absolute increase of at least 5 mm.
- 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

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

New lesions

- There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD.
- If a new lesion is equivocal, for example, because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Best Overall Response

- The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.
- The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.
- The best overall response across all time points is determined once all the data for the patient is known.
- In this study, confirmation of complete or partial response is required. Complete or partial responses may be claimed only if the criteria for each are met 4 weeks or more later (Table 1). In this circumstance, the best overall response can be interpreted as in Table 3.
- When SD is believed to be best response, SD criteria must be met within 4 weeks or more from baseline (minimum time interval).

Table 1 Overall Response: Patients with Target (+/-Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Confirmation
CR	CR	No	CR	≥4 weeks
CR	Non-CR/non-PD	No	PR	≥4 weeks
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	documented at least once ≥4 weeks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NE, not evaluable.

Table 2 Overall Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD(a)
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR, complete response; PD, progressive disease; NE, not evaluable.

Table 3. Best Overall Response When Confirmation of CR and PR Required

Overall response First time point	Overall response Subsequent time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR(a)
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR, complete response; PD, progressive disease; NE, not evaluable; SD, stable disease.
(a) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

- The duration of overall response is measured from the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented as assessed per RECIST (v.1.1) or clinical criteria (taking as reference for progressive disease the smallest measurements recorded on study).

Appendix F Substrate Drugs Known to be Affected by Inhibition or Induction by CYP Enzymes

P450 Isozyme	Substrate Drugs
CYP1A2	caffeine, tizanidine

CYP, cytochrome P450.
Source: MHLW DDI Guidance.
This list is not intended to be exhaustive, but is to show examples of drugs whose metabolism is significantly influenced by CYP enzyme.

Appendix G 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			

Source: Huang X, Venet F, Wang YL, et al. PD-1 expression by macrophages plays a pathologic role in altering microbial clearance and the innate inflammatory response to sepsis. Proc Natl Acad Sci U S A. 2009;106(15):6303-6308.
Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. Ann Pharmacother. 2013;47(10):1330-1341.
*Topical use only allowed for ketoconazole.
This list is not intended to be exhaustive, but is to show examples of representative drugs.

Appendix H Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment 03.

The existing texts are shown with italics and underlines, and revised text are represented with bold letters.

Page 10, Section 2.0 STUDY SUMMARY – Study Design

Page 26, Section 6.1 Overview of Study Design

Existing Text

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.

Revised Text

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 Cycle 38, and at the end of every 6 cycles (24 weeks with a window of ±7 days) until progression**. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for 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.

Rationale for Amendment

Changed a frequency of imaging for tumor assessment due to consideration for effect of long-term radiation on subject.

Page 67, Appendix A Schedule of Events

Existing Text

(o) RECIST tumor assessment via CT or MRI scan of abdomen/pelvis and clinically indicated areas required at baseline, then after every 2 cycles (ie, 8 weeks with a window of ±7 days from date of visit) through Cycle 14 (56 weeks), then after every 3 cycles (12 weeks with a window of ±7 days) *until study treatment discontinuation*; at this point, a final follow-up set of imaging is required. PET/CT may be used according to RECIST guidelines. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals in the protocol until progression is confirmed or until the start of subsequent anticancer treatment. Radiographic images will be maintained at each site, and test results and physicians' findings will be filed in subject's source documents. The sponsor may request electronic images for those subjects who demonstrate tumor reduction.

Revised Text

(o) RECIST tumor assessment via CT or MRI scan of abdomen/pelvis and clinically indicated areas required at baseline, then after every 2 cycles (ie, 8 weeks with a window of ±7 days from date of visit) through Cycle 14 (56 weeks) **(ie, Day 1 of Cycle 3, Cycle 5, Cycle 7, Cycle 9, Cycle 11, Cycle 13, and Cycle 15)**, then after every 3 cycles (12 weeks with a window of ±7 days) **until Cycle 38 (ie, Day 1 of Cycle 18, Cycle 21, Cycle 24, …, and Cycle 39), and after every 6 cycles (24 weeks with a window of ±7 days) until progression (ie, Day 1 of Cycle 45, Cycle 51, …)**; at this point **(ie, progression)**, a final follow-up set of imaging is required. PET/CT may be used according to RECIST guidelines. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals in the protocol until progression is confirmed or until the start of subsequent anticancer treatment. Radiographic images will be maintained at each site, and test results and physicians' findings will be filed in subject's source documents. The sponsor may request electronic images for those subjects who demonstrate tumor reduction.

Rationale for Amendment

Changed a frequency of imaging for tumor assessment due to consideration for effect of long-term radiation on subject.

Clarified the process for imaging.

Document History

Version	Date	Comments
original version	2018/10/05	New document
2nd version	2018/11/14	The primary purpose of this amendment is to revise the starting dose of niraparib in each subject, based on the tolerability results of niraparib in the local phase 1 study (Niraparib-1001 study).
3rd version	2019/01/18	The primary purpose of this amendment is to correct typographical errors in the Sample Size Justification, and thereby demonstrate the appropriateness of the sample size.
4th version	2021/11/09	The primary purpose of this amendment is to change a frequency of imaging for tumor assessment due to consideration for effect of long-term radiation on subject.