Report on the Deliberation Results

September 8, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Zejula Capsules 100 mg
Non-proprietary Name	Niraparib Tosilate Hydrate (JAN*)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	February 28, 2020

Results of Deliberation

In its meeting held on September 4, 2020, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

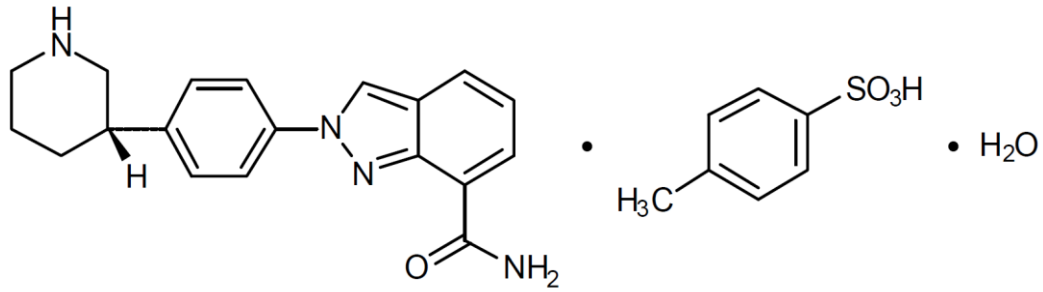
Review Report

August 24, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Zejula Capsules 100 mg
Non-proprietary Name	Niraparib Tosilate Hydrate
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	February 28, 2020
Dosage Form/Strength	Capsules, each containing 159.4 mg of niraparib tosilate hydrate (100 mg of niraparib).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{19}H_{20}N_4O \cdot C_7H_8O_3S \cdot H_2O$

Molecular weight: 510.61

Chemical name:

2-{4-[(3*S*)-Piperidin-3-yl]phenyl}-2*H*-indazole-7-carboxamide mono(4-methylbenzenesulfona te) monohydrate

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has been demonstrated to have efficacy in (a) the maintenance treatment of patients with ovarian cancer after the initial chemotherapy, (b) the maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer, and a certain level of efficacy in (c) the treatment of patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition. PMDA has also concluded that further investigation is necessary through post-marketing surveillance on bone marrow suppression, hypertension, interstitial lung disease, posterior reversible encephalopathy syndrome, secondary malignant tumor, and thromboembolism.

Indications

Maintenance treatment of ovarian cancer after the initial chemotherapy
Maintenance treatment of platinum-sensitive recurrent ovarian cancer
Treatment of platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency

Dosage and Administration The usual adult dosage is 200 mg of niraparib administered orally once daily. For adult patients with a body weight of ≥77 kg and a platelet count of ≥150,000/μL before the first dose, the recommended dose is 300 mg of niraparib administered orally once daily. The dose should be reduced, as appropriate, according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

July 14, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Zejula Capsules 100 mg
Non-proprietary Name	Niraparib Tosilate Hydrate
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	February 28, 2020
Dosage Form/Strength	Capsules, each containing 159.4 mg of niraparib tosilate hydrate (100 mg of niraparib).
Proposed Indications	Maintenance treatment of ovarian cancer after the initial chemotherapy. Maintenance treatment platinum-sensitive recurrent ovarian cancer. Treatment of advanced/recurrent ovarian cancer with homologous recombination deficiency (HRD).
Proposed Dosage and Administration	The usual adult dosage is 200 mg of niraparib administered orally once daily. For adult patients with a body weight of ≥77 kg and a platelet count of ≥150,000/μL before the first dose, the recommended dose is 300 mg of niraparib administered orally once daily. The dose should be reduced, as appropriate, according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Poly (ADP-ribose) polymerase (PARP) is an enzyme that plays a role in DNA repair. Binding to the single-strand break (SSB) site of DNA, PARP forms PAR chain with the use of nicotinamide adenine dinucleotide (NAD) as a substrate, facilitates the accumulation of factors involved in DNA repair, and thereby contributes to SSB repair (*Trends Biochem Sci*. 1995;20:405-11).

Niraparib tosilate hydrate (niraparib), a low-molecular-weight compound discovered by Merck & Co., Inc. (currently Merck Sharp and Dohme [MSD]), is an inhibitor of PARP. Niraparib inhibits SSB repair by blocking the binding of NAD to PARP and prevents the dissociation of PARP-DNA complexes (*Cancer Res.* 2012;72:5588-99), inducing double-strand breaks (DSBs) during the process of DNA replication (*Cancer Discov.* 2017;20-37). In normal cells, these DSBs are repaired by homologous recombination which is mediated by *BRCA* gene products (*BRCA*1 and *BRCA*2) or other homologous recombination repair-related factors (*Cancer Res.* 2012;72:5588-99). However, in tumor cells lacking homologous recombination repair mechanism mainly due to the mutation of *BRCA* genes or other homologous recombination repair-related genes, the administration of niraparib induces DSBs, which accumulate without being repaired, and in turn, apoptosis is induced. This series of processes is expected to suppress tumor proliferation (*J Med Chem.* 2015;58:3302-14; *Nat Rev Cancer*. 2005;5:689-98).

1.2 Development history etc.

Outside Japan, a phase I study (Study PN001) was started by TESARO in the U.S. in patients with advanced solid cancer in September 2008.

As a part of the clinical development of niraparib for the maintenance treatment of ovarian cancer after the initial chemotherapy, a foreign phase III study (PRIMA study) was started by TESARO in patients with advanced ovarian cancer in response to first-line platinum-based chemotherapy in August 2016.

As a part of the clinical development of niraparib for the maintenance treatment of platinum-sensitive recurrent ovarian cancer a foreign phase III study (NOVA study) was started in August 2013 by TESARO in patients with platinum-sensitive, relapsed, ovarian cancer who were in response to the last platinum-based chemotherapy.

As a part of the clinical development of niraparib for the treatment of recurrent ovarian cancer with homologous recombination deficiency, TESARO also started a foreign phase II study (QUADRA study) in April 2015 in patients with recurrent ovarian cancer who had a history of chemotherapy.

In the U.S., a marketing application for niraparib was filed in October 2016 with data including pivotal study from the NOVA study, and the product was approved for the following indication in March 2017: “ZEJULA is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.” Later,

additional applications were filed with (a) data mainly from the QUADRA study in April 2019 and (b) data mainly from the PRIMA study in December 2019, and the product was approved, respectively, with the indication of (a) "ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, or genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy" in October 2019; and (b) "ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy" in April 2020.

In the EU, the marketing application for niraparib was filed in October 2016 with data mainly from the NOVA study, and the product was approved in November 2017 with the indication of "Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy." Later, an additional application was filed in February 2020 with data mainly from the PRIMA study and is currently under review.

As of May 2020, niraparib has been approved in 40 countries and regions for the indication of the maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer, and in 2 countries for the indication of the treatment of recurrent ovarian cancer with homologous recombination deficiency. For the indication of the maintenance treatment of patients with ovarian cancer after the initial chemotherapy, niraparib has been approved only in the U.S.

In Japan, a phase I study (Study 1001) was started by the applicant in patients with advanced solid cancer in April 2018. The applicant also started, in December 2018, a phase II study (Study 2001) in patients with platinum-sensitive and relapsed ovarian cancer who were in response to the last platinum-based chemotherapy and a phase II study (Study 2002) in patients with recurrent ovarian cancer who had a history of chemotherapy.

A marketing application for niraparib has been filed with data mainly from the PRIMA, NOVA, and QUADRA studies and Studies 2001 and 2002.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale brown powder. The properties of the drug substance, including description, solubility, hygroscopicity, melting point/thermal analysis, dissociation constant, and distribution coefficient were determined. The drug substance has been found in a monohydrate form, [redacted], and amorphous form. However, it has been confirmed that the monohydrate form is produced at the commercial scale and that the monohydrate form remained unchanged in the stability test.

The chemical structure of the drug substance has been elucidated with elementary analysis, mass spectrometry, ultraviolet and visible absorption spectrometry, infrared spectrophotometry (IR), nuclear magnetic resonance (NMR) analyses (^{1}H-, ^{13}C-, and ^{15}N-NMR), and single-crystal X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized from [redacted] and [redacted] as starting substances.

The quality control strategy was formulated by addressing the following with a quality by design (QbD) approach (Table 1).

- Identification of critical quality attributes (CQAs).
- Identification of critical process parameters (CPPs) and the investigation of acceptable ranges for process parameters based on a quality risk assessment and design of experiments.

Table 1. Outline of the control strategy for the drug substance

CQA	Control methods
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The following steps are defined as the critical process steps: the reduction of [redacted] and deprotection of [redacted]; the synthesis of [redacted] by amidation from [redacted] and obtaining of the crude drug substance by salification of [redacted]; obtaining of [redacted] by purification of [redacted]; and [redacted]. Process controls and action limits are specified for all steps except for packaging, labeling, and test steps. [redacted], [redacted], and [redacted] are controlled as a critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and liquid chromatography [LC]), purity (related substances [LC], *R*-enantiomer [LC], residual solvents [gas chromatography (GC)], and elemental impurities [inductively coupled plasma-mass spectrometry]), water content, residue on ignition, particle size, crystal form, and assay (LC).

2.1.4 Stability of drug substance

The main stability studies performed for the drug substance are shown in Table 2. The drug substance was found to be stable. The photostability testing showed that the drug substance is photostable.

Table 2. Stability studies for the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 batches at pilot scale	25°C	60% RH	Low-density polyethylene bag (double-layer) + high-density polyethylene drum	48 months
Accelerated testing	3 batches at pilot scale	40°C	75% RH		6 months

Accordingly, a re-test period of 48 months was proposed for the drug substance when stored in a double-layer low-density polyethylene bag and a high-density polyethylene drum at room temperature. The long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release hard capsule containing 159.4 mg of the drug substance (100 mg of niraparib). It contains lactose hydrate and magnesium stearate as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process consisting of the following steps: [redacted], mixing of [redacted], mixing of [redacted], encapsulation, [redacted], and primary and secondary packaging/labeling.

The [redacted], [redacted], and [redacted] steps were defined as critical steps. Process control is specified for [redacted], [redacted], and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (IR and LC), purity (degradation product [LC] and elemental impurities [inductively coupled plasma-mass spectrometry]), water content, uniformity of dosage units (strength uniformity test [LC]), dissolution (LC), and assay (LC).

2.2.4 Stability of drug product

The main stability studies performed for the drug product are shown in Table 3. The drug product was found to be stable. The photostability testing showed that the drug product is photolabile.

Table 3. Stability studies for the drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 batches at commercial scale	5°C	−	Blister packaging ([redacted] and aluminum foil)	18 months
Accelerated testing		25°C	60% RH		6 months

−, Not adjusted.

Accordingly, in compliance with the ICH Q1E Guideline, a shelf-life of 24 months was proposed for the drug product when stored in a blister packaging ([redacted] and

aluminum foil) at 2°C to 8°C, protected from light. The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In this section, the dose and concentration of niraparib and its metabolites are expressed as free base.

3.1 Primary pharmacodynamics

3.1.1 Inhibitory effects of niraparib on PARP

3.1.1.1 *In vitro* (CTD 4.2.1.1-1, 4.2.1.1-2, 4.2.1.1-3, and 4.2.1.1-4)

The inhibitory effects of niraparib on human PARP-1, 2, 3, 4, and 5a (recombinant proteins) were evaluated with the uptake of ^{3}H-labeled NAD as an index. The IC_{50} of niraparib in human PARP-1, 2, 3, 4, and 5a are shown in Table 4.

Table 4. Inhibitory effects of niraparib on human PARPs

	n	IC_{50} value (nmol/L)
PARP-1	9	3.76 ± 1.6
PARP-2	5	2.15 ± 0.70
PARP-3	7	1,250 ± 34.0
PARP-4	5	334 ± 101
PARP-5a	6	567 ± 381

Mean ± standard deviation

The inhibitory effects of niraparib on 13 types of human PARPs (recombinant proteins) were evaluated based on the uptake of biotinylated oxidized NAD as index. The IC_{50} of niraparib in human PARP-1, 2, 3, 5a, 5b, and 10 are shown in Table 5. The IC_{50} of niraparib in human PARP-6, 7, 8, 11, 12, 14, or 15 could not be determined.

Table 5. Inhibitory effects of niraparib on human PARPs

	IC_{50} value (nmol/L)		IC_{50} value (nmol/L)
PARP-1	2.8	PARP-5a	1,400
PARP-2	0.6	PARP-5b	1,400
PARP-3	5,200	PARP-10	2,100

n = 1

The inhibitory effects of niraparib and M1 (a metabolite of niraparib [see Section 4.3.1]) on human PARP-1 and 2 (recombinant proteins) were evaluated based on the uptake of biotinylated oxidized NAD as index. The IC_{50} value of niraparib (n = 1) in human PARP-1 and 2 was 1.1 and 0.4 nmol/L, respectively. The IC_{50} of M1 in human PARP-1 or 2 could not be determined.

The inhibitory effects of niraparib on PAR chain formation were evaluated with HeLa cells, a human cervical cancer cell line. The IC_{50} of niraparib (n = 18) was determined as 4 ± 2.6 nmol/L (mean ± standard deviation).

3.1.1.2 *In vivo* (CTD 4.2.1.1-13)

The inhibitory effects of niraparib[1] on PARP-1 and 2 in tumor tissues were evaluated based on the uptake of ^{3}H-labeled NAD as index in nude mice (5/group), subcutaneously transplanted with MDA-MB-436 cells, a human breast cancer cell line with *BRCA1* mutation. In the niraparib 0,[2] 50, and 100 mg/kg groups, the activity of the uptake of NAD[3] (mean ± standard error) at 4 hours post-dose was 105.0% ± 14%, 5.80% ± 2%, and 5.50% ± 3%, respectively.

3.1.2 Inhibitory effects of niraparib on the proliferation of tumor in malignant tumor cell cline

3.1.2.1 *In vitro* (CTD 4.2.1.1-6)

The inhibitory effects of niraparib on the proliferation of tumor cells were evaluated with HeLa cells and A549 cells, a human non-small cell lung cancer cell line, both in which the expression of *BRCA* gene was reduced by knocking down of *BRCA* gene by shRNA based on the reductase activity of live cells as index. The IC_{50} values of niraparib are shown in Table 6

Table 6. Inhibitory effects of niraparib on the proliferation of tumor in cell lines

Cell line	*BRCA* gene	n	IC_{50} value (nmol/L)
HeLa	Wild-type	52	852 ± 262
	BRCA1-deficient	52	34 ± 17
A549	Wild-type	3	1,760 ± 670
	BRCA2-deficient	3	11 ± 5

Mean ± standard deviation

The inhibitory effects of niraparib on the proliferation of human malignant tumor cells with *BRCA* mutation were evaluated based on the reductase activity of live cells as index. The IC_{50} values of niraparib are shown in Table 7.

Table 7. Inhibitory effects of niraparib on the proliferation of tumor cells for each cell line

Cell line	Tumor type	*BRCA* mutation	n	IC_{50} value (nmol/L)
MDA-MB-436	Breast cancer	*BRCA1*	6	18 ± 3
SUM149PT			9	24 ± 7
SUM1315MO2			3	20 ± 6
CAPAN-1	Pancreatic cancer	*BRCA2*	6	73 ± 22

Mean ± standard deviation

3.1.2.2 *In vivo* (CTD 4.2.1.1-10)

The inhibitory effects of niraparib[1] on the proliferation of tumor cells were evaluated in severe combined immunodeficient (SCID) mice (1 to 6/group) bearing orthotopic xenografts derived from 27 patients with ovarian cancer. Day 0 was defined as the day the tumor diameter measured 0.5 to 1 cm. Niraparib[4] 60 mg/kg was administered QD from Day 1 (the day of the start of administration) for up to 28 days, and the tumor cross-section area was measured. Individual tumor grafts were subjected to the evaluation of homologous recombinant repair ability using Myriad myChoice HRD CDx (Myriad Genetic Laboratories), with the

[1] Although niraparib hydrochloride was used, whether the dosage was expressed as a free base or the hydrochloride form is unknown.
[2] Although water was used as a vehicle, details, for instance, sterilized water or purified water, are unknown.
[3] The activity of uptake of NAD = {(uptake of NAD for the PAR chain in tumors in the niraparib group)/(uptake of NAD for the PAR chain in tumors in the vehicle group)} × 100
[4] The types of salt used or dosage (expressed as a free base or the hydrochloride form) were unspecified.

genomic instability scores based on loss of heterozygosity (LOH), telomeric allelic imbalance (TAI),[5] and large-scale state transition (LST)[6] and the presence of *BRCA* mutation. The results are shown in Table 8.

Table 8. Inhibitory effects of niraparib on the proliferation of tumor cells in SCID mice bearing orthotopic xenografts derived from patients with ovarian cancer

Tumor graft	*BRCA* mutation	GIS*1	HRD*2	n	Ratio of tumor cross-section area*3	Tumor response*4
PH054	*BRCA1*	70	Positive	6	0.08 ± 0.157	PR
PH039	−	67		5	0.14 ± 0.117	
PH088	*BRCA1*	51		5	0.17 ± 0.249	
PH242	−	51		1	0.24	
PH013	−	79		2	0.353, 0.369	
PH077	*BRCA2*	65		5	0.41 ± 0.392	
PH056	−	84		1	0.617	
PH038	−	76		4	1.11 ± 0.598	SD
PH095	*BRCA2*	79		5	2.05 ± 0.213	PD
PH063	−	51		3	2.14 ± 0.293	
PH233	−	64		1	2.92	
PH061	−	49		3	3.43 ± 2.24	
PH134	−	72		2	3.41, 4.57	
PH249	−	62		1	4.59	
PH231	−	86		2	4.51, 6.82	
PH291	−	53		2	8.90, 12.31	
PH331	−	28	Negative	5	1.35 ± 0.431	
PH235	−	29		3	1.42 ± 0.334	
PH048	−	17		4	1.42 ± 1.09	
PH044	−	38		1	2.50	
PH087	−	16		5	1.45 ± 0.580	
PH080	−	33		2	1.27, 1.78	
PH098	−	0		4	2.33 ± 1.06	
PH026	−	22		4	2.71 ± 0.906	
PH045	−	13		2	1.93, 5.03	
PH247	−	34		3	5.31 ± 1.24	
PH081	−	17		1	7.38	

Mean ± standard deviation; Individual values when n = 1 or 2; −, Not applicable; *1, Mean scores calculated for LOH, TAI, and LST using Myriad myChoice HRD CDx (Myriad Genetic Laboratories) [see Section 7.R.5.3]; *2, Determined as positive for *tBRCA* mutation or HRD with GIS of ≥42 for tumor tissues tested by Myriad myChoice HRD CDx (Myriad Genetic Laboratories) [see Section 7.R.5.3]; *3, A ratio of tumor cross-section area = (tumor cross-section area on the end day of the measurement)/(tumor cross-section area on Day 0); *4, Response was assessed as PR, SD, and PD, respectively, for the ratio of tumor cross-section area of <0.7, 0.7 to 1.2, and >1.2.

3.2 Secondary pharmacodynamics

3.2.1 Effects of niraparib on receptors, ion channels, enzymes, and transporters (CTD 4.2.1.2-1)

The inhibitory effects of niraparib on 168 types of receptors, ion channels, enzymes, and transporters were evaluated using radiolabeled ligands. Transporters with IC_{50} of niraparib <5 μmol/L are shown in Table 9.

[5] Allelic imbalance in chromosomal terminus including telomeric regions (*Cancer Discov.* 2012;2: 366-75).
[6] Chromosomal region of 1×10^7 bases with sequences different from those of the allele caused by mutation, such as translocation (*Cancer Res.* 2012;72: 5454-6).

Table 9. Inhibitory effects of niraparib on receptors

	IC_{50} value (μmol/L)
Dopamine transporter	0.051
Norepinephrine transporter	0.239
Serotonin transporter	0.363
MAO-B	0.751
$5\text{-}HT_4$	0.976
L-type calcium channel (benzodiazepine-binding site)	3.22

n = 1

The results revealed that the IC_{50} of niraparib in these transporters, etc. was lower than the C_{max} (3.7 μmol/L)[7)] of niraparib at the recommended human clinical dose. Psychoneurotic adverse events (e.g., insomnia and anxiety) were reported in the clinical studies [see Section 7.3]. Given these, the applicant explained that appropriate cautionary advice would be given to healthcare professionals via the package insert, etc. to call attention to these adverse events.

3.3 Safety pharmacology

3.3.1 Effects of niraparib on the central nervous system (CTD 4.2.1.3-5)

A single oral dose of niraparib 5, 10, or 30 mg/kg was administered to rats (16 per group), and the effects of niraparib on the central nervous system were evaluated with the functional observational battery. No effects of niraparib were observed.

3.3.2 Cardiovascular effects

3.3.2.1 Effects of niraparib on hERG potassium currents (CTD 4.2.1.3-1)

The effects of niraparib on human ether-à-go-go related gene (hERG) potassium currents were evaluated with the human embryonic kidney (HEK) 293 cell line transfected with hERG. The inhibition rate of hERG potassium current by niraparib 3, 10, 30, and 100 μmol/L was 11.0% ± 0.5%, 37.9% ± 0.8%, 69.3% ± 0.8%, and 91.4% ± 0.9% (mean ± standard error, n = 3), respectively. The inhibitory effects were statistically significant at all concentrations as compared with the control, a buffered saline solution of 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid containing 0.3% dimethyl sulfoxide (DMSO) ($p < 0.05$, the Dunnett's multiple comparison test). The IC_{50} was 15.2 μmol/L.

3.3.2.2 Effects of niraparib on heart rate, blood pressure, and electrocardiographic parameters (CTD 4.2.1.3-3)

A single oral dose of niraparib 3, 6, and 15 mg/kg was sequentially administered to dogs (n = 8) at a-week interval to evaluate the effects of niraparib on blood pressure (systolic, diastolic, and mean blood pressure), heart rate, and electrocardiographic parameters (PR interval, QRS width, QT interval, and QTc interval). Niraparib 15 mg/kg increased blood pressure (systolic, diastolic, and mean blood pressure).

[7)] C_{max} on Day 21 of treatment with oral niraparib 300 mg QD in Study 1001 in Japanese patients with advanced solid cancer.

Given that hypertension was reported in the clinical studies as well [see Section 7.R.2.3], the applicant explained that cautionary advice on hypertension will be given appropriately via the package insert, etc. to healthcare professionals.

3.3.3 Effects of niraparib on the respiratory system (CTD 4.2.1.3-4)

A single oral dose of niraparib 10, 50, or 100 mg/kg was administered to rats (6 per group) to evaluate the effects of niraparib on respiratory rate, tidal volume, and minute ventilation. No effects of niraparib were observed.

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the applicant's explanation about the nonclinical pharmacology of niraparib is acceptable, except for the aspects discussed in the following subsection.

3.R.1 Mechanism of action and efficacy of niraparib

The applicant's explanation about the action mechanism and efficacy of niraparib for ovarian cancer:
PARP, an enzyme involved in DNA repair, binds to the SSB site of DNA, forms PAR chain with the use of NAD as a substrate to facilitate the accumulation of factors involved in DNA repair, and thereby contributes to SSB repair (*Trends Biochem Sci.* 1995;20:405-11).

Niraparib, a low-molecular-weight compound, is an inhibitor of PARP. Niraparib inhibits SSB repair by blocking the binding of NAD to PARP [see Section 3.1.1] and prevents the dissociation of PARP-DNA complexes (*Cancer Res.* 2012;72:5588-99), inducing DSBs during the process of DNA replication (*Cancer Discov.* 2017;7:20-37). In normal cells, these DSBs are repaired by homologous recombination which is mediated by *BRCA* gene products (*BRCA*1 and *BRCA*2) or homologous recombination repair-related factors (*Cancer Res.* 2012;72:5588-99). However, in tumor cells lacking homologous recombination repair mechanism due to mutation of *BRCA* genes or other homologous recombination repair-related genes, the administration of niraparib induces DSBs, which accumulate without being repaired, and in turn, apoptosis is induced. This series of processes is expected to suppress tumor proliferation (*J Med Chem.* 2015;58:3302-14; *Nat Rev Cancer.* 2005;5:689-98).

Platinum sensitivity and indicators related to genome instability are candidate indicators that may reflect the deficiency in homologous recombinant repair in tumor cells (*Nat Rev Cancer.* 2016;16:110-20). Platinum agents form a cross-linked structure within the DNA strands and generate DSBs during the DNA replication. Tumor cells sensitive to platinum agents, however, may deteriorate the DSB repair function (*Cancer Discov.* 2017;7:20-37), suggesting that platinum sensitivity reflects the deficiency in homologous recombination repair. Myriad myChoice HRD CDx (Myriad Genetic Laboratories), which was used in the clinical studies for niraparib, is a test system to evaluate the genome instability based on LOH, TAI, and LST. LOH, TAI, and LST were reported to have occurred in tumor cells with a deficiency in homologous recombination repair due to mutations of homologous recombination repair-related genes (*Br J Cancer.* 2012;107:1776-82, *Cancer*

Discov. 2012;2:366-75) and the LOH, TAI, and LST-based scores that comprise GIS were correlated with functional deficiencies in *BRCA1/2* (*Breast Cancer Res.* 2014;16:475).

The above-mentioned action mechanism of niraparib and the following observations indicate that niraparib is expected to have efficacy in the treatment of ovarian cancer with a deficiency in homologous recombination repair.

- Niraparib's antiproliferative effect on tumor cells were observed in SCID mice subcutaneously transplanted with tumor grafts from patients with ovarian cancer with *BRCA* mutation [see Section 3.1.2.2].
- Niraparib's antiproliferative effect on tumor cells were observed in SCID mice subcutaneously transplanted with tumor grafts from some patients with ovarian cancer found to be HRD positive based on GIS [see Section 3.1.2.2].

The applicant's explanation about differences in pharmacological characteristics between niraparib and olaparib, an approved PARP inhibitor:

- Niraparib has been reported to exhibit higher inhibitory activity against the dissociation of PARP-DNA complexes than olaparib (*Cancer Res.* 2012;72:5588-99).
- Niraparib has been reported to have higher membrane permeability than olaparib, which may be contributory to higher concentration ratio of niraparib in tumors to that in blood (*Oncotarget.* 2018;9:37080-96).

PMDA's view:

The applicant's explanation is generally acceptable. However, the relationship between the GIS calculated with LOH, TAI, and LST-based scores and the inhibitory effects of niraparib on the proliferation of tumor cells remain unclear. Relevant information and findings on pharmacological characteristics of niraparib, including differences from olaparib, may be useful for the prediction of efficacy and the selection of eligible patients in its clinical use. Therefore, investigation should be continued and new findings should be appropriately communicated to healthcare professionals once available.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

In this section, the dose and concentration of niraparib are expressed as free base.

The pharmacokinetics (PK) of niraparib in animals was evaluated in rats, dogs, and other animals. The plasma protein binding, drug-metabolizing enzymes, and transporters for niraparib were evaluated with human and animal biomaterials.

4.1 Absorption

4.1.1 Single-dose studies

Male dogs were administered a single intravenous dose of niraparib 1 mg/kg or a single oral dose of niraparib 3 mg/kg to evaluate the plasma niraparib concentrations (Table10). A 6-day interval was interposed between the intravenous dosing and oral dosing. The bioavailability (BA) of oral niraparib 3 mg/kg was 57%. The applicant explained that the tissue distribution of niraparib was considered high because of the high volume of distribution of niraparib at steady state (Vd_{ss}) as compared with blood volume in dogs (90 mL/kg) (*Pharm Res.* 1993;10:1093-5).

Table 10. PK parameters of niraparib (Male dogs, single intravenous or oral dose)

Dosage (route)	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vd_{ss} (L/kg)
1 mg/kg (intravenous)	3	513 ± 73	0.033 (0.033, 0.033)	559 ± 133	6.1 ± 1.9	31 ± 7.2	12.3 ± 0.58
3 mg/kg (oral)	3	187 ± 50	0.5 (0.5, 0.5)	946 ± 155	–	–	–

Mean ± standard deviation; * Median (range); –, Not calculated

4.1.2 Repeated-dose studies

Male and female dogs were administered niraparib 1.5, 4.5, and 12 mg/kg orally QD for 90 days to evaluate plasma niraparib concentrations, etc (Table 11). The C_{max} and AUC_{24h} of niraparib generally increased in a dose-proportional manner with the doses tested. No clear effects of repeated dosing on the C_{max} or AUC_{24h} of niraparib were observed. No clear sex differences were observed for the C_{max} or AUC_{24h} of niraparib.

Table 11. PK parameters of niraparib (Male and female dogs, repeated dosing for 90 days)

Dosing date (day)	Dosage (mg/kg)	n	C_{max} (ng/mL)		t_{max}* (h)		AUC_{24h} (ng·h/mL)	
			Male	Female	Male	Female	Male	Female
1	1.5	4	31.5 ± 6.9	38.3 ± 7.3	2 (2, 4)	2 (2, 2)	234 ± 45	274 ± 46
	4.5	4	101 ± 31	137 ± 25	2 (1, 4)	2 (1, 2)	721 ± 84	918 ± 184
	12	6	378 ± 66	361 ± 44	2 (2, 4)	2 (1, 4)	2,690 ± 300	2,580 ± 310
90	1.5	4	33.3 ± 8.9	34.3 ± 11.4	2 (2, 2)	2 (2, 2)	261 ± 18	285 ± 90
	4.5	4	111 ± 25	94.2 ± 11.5	2 (2, 2)	2 (2, 4)	855 ± 92	857 ± 166
	12	6	276 ± 82	246 ± 68	3 (2, 4)	2 (2, 4)	2,410 ± 460	2,180 ± 250

Mean ± standard deviation; * Median (range)

4.1.3 Membrane permeability in *in vitro* studies

The membrane permeability of niraparib was evaluated with the Caco-2 cells, a human colonic cancer cell line. The $P_{app\ A\ to\ B}$ of niraparib 37.5 µmol/L was 11.6×10^{-6} cm/sec. The applicant explained that the membrane permeability of niraparib was considered high, based on the results and as compared with the $P_{app\ A\ to\ B}$ of highly membrane-permeable minoxidil 10 µmol/L of 4.52×10^{-6} cm/sec.

4.2 Distribution

4.2.1 Tissue distribution

The applicant considers that niraparib is distributed to the brain and the cerebrospinal fluid, based on the following study results.

- Male rats were administered a single oral dose of niraparib 10 or 30 mg/kg to determine the niraparib concentrations in the brain and plasma. The ratio of AUC_{24h} of niraparib in the brain to that in the plasma

was 0.85 and 0.88 following the administration of niraparib 10 and 30 mg/kg, respectively.

- Male monkeys were administered a single oral dose of niraparib 10 mg/kg to determine the niraparib concentrations in the cerebrospinal fluid and plasma. The ratio of AUC_{inf} of niraparib in the cerebrospinal fluid to that in the plasma was 0.19.

4.2.2 Plasma protein binding

Plasmas of rats, dogs, monkeys, and humans were incubated with niraparib (1 to 50 µmol/L) for 20 hours at 37°C to evaluate the plasma protein binding of niraparib by an equilibrium dialysis method. The protein-unbound fraction of niraparib in plasma was 15.7% to 16.2% in rats, 27.5% to 28.4% in dogs, 16.7% to 17.7% in monkeys, and 16.0% to 17.6% in humans.

Human serum albumin (600 µmol/L) and human α1-acid glycoprotein (25 µmol/L) were incubated with niraparib (1 and 10 µmol/L) for 6 hours at 37°C to evaluate the binding of niraparib to human serum albumin and human α1-acid glycoprotein by an equilibrium dialysis method. The unbound fraction of niraparib to human serum albumin and human α1-acid glycoprotein was 42.8% to 43.5% and 79.6% to 84.8%, respectively. According to the applicant, the results suggest that niraparib binds mainly to serum albumin in human plasma.

4.2.3 Distribution in blood cells

Bloods of rats, dogs, and humans were incubated with niraparib (1 and 10 µmol/L) for 30 minutes at 37°C to evaluate the distribution of niraparib in blood cells. The ratio of the concentration of niraparib in blood to that in plasma was 1.1 to 1.2 in rats, 1.4 to 1.8 in dogs, and 1.7 in humans. According to the applicant, the results suggest that niraparib is distributed to blood cells.

4.2.4 Placental and fetal transfer

The possibility of placental and fetal transfer of niraparib has not been investigated. According to the applicant, the physio-chemical properties of niraparib (including the protein-unbound fraction of niraparib in human plasma [see Section 4.2.2] and its molecular weight [free base] of 320) suggest that niraparib may cross the placenta and transfer to the fetus [see Section 5.R.1].

4.3 Metabolism

4.3.1 *In vitro*

Hepatic microsomes of rats, dogs, and humans were incubated with ^{14}C-niraparib (10 µmol/L) for 2 hours at 37°C in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) to investigate the niraparib metabolites. M1 (a carboxylate form) and M2 (an oxidant form) were detected in rats, dogs, and humans. M3 and M8 (oxidant forms) were also detected in rats and humans.

Hepatocytes of rats, dogs, and humans were incubated with ^{14}C-niraparib (10 µmol/L) for 2 hours at 37°C to evaluate the niraparib metabolites. M1, M2, and M10 (glucuronate conjugates of M1) were detected in rats, dogs, and humans. M8 was also detected in rats and humans.

Based on the following observations, the applicant explains that niraparib is metabolized mainly by carboxylesterase (CES) and that CYP3A and CYP1A2 also partially contribute to the metabolism of niraparib.

- Human hepatic microsomes were incubated with niraparib (10 μmol/L) for 1 hour at 37°C in the presence of CES inhibitors (phenylmethylsulfonyl fluoride and bis[4-nitrophenyl] phosphate), paraoxonase inhibitors (ethylenediaminetetraacetic acid and 5,5'-dithiobis[2-nitrobenzoic acid]), or a butyrylcholinesterase inhibitor (eserine). The formation of M1 was inhibited by ≥98% in the presence of the CES inhibitors but not clearly inhibited in the presence of the paraoxonase inhibitors or the butyrylcholinesterase inhibitor.
- Human hepatic microsomes were incubated with niraparib (25 μmol/L) for 1 hour at 37°C in the presence of monoclonal antibodies to CYP isoforms (CYP1A, CYP2C, CYP2D6, and CYP3A) or NADPH. The formation of M2 was inhibited by 55%, 27%, and 13% in the presence of the monoclonal antibodies to the CYP1A, CYP2D6, and CYP3A, respectively, but was not clearly inhibited in the presence of the monoclonal antibody to CYP2C. The formation of M3 was inhibited by 27% and 46% in the presence of the monoclonal antibodies to CYP1A and CYP3A, respectively, but was not clearly inhibited in the presence of monoclonal antibodies to CYP2C or CYP2D6.

4.3.2 *In vivo*

Bile duct-cannulated male rats were administered a single intravenous dose of ^{14}C-niraparib 3 mg/kg to evaluate metabolites in the plasma, urine, feces, and bile. Unchanged niraparib, M1, and M10 were detected in the plasma up to 10 hours post-dose. Unchanged niraparib was mainly detected in the urine and feces up to 24 hours post-dose (19.3% and 21.8% of administered radioactivity, respectively), and unchanged niraparib, M4 (an oxidant form), M11 (a mercapturic acid conjugate), and M5 (an oxidant form) were mainly detected in the bile up to 10 hours post-dose (3.8%, 3.3%,[8)] and 3.1%, respectively).

Bile duct-cannulated male dogs were administered a single intravenous dose of ^{14}C-niraparib 2 mg/kg to evaluate metabolites in the plasma, urine, feces, and bile. Unchanged niraparib, M1, and M10 were detected in the plasma up to 10 hours post-dose. M1 was mainly detected in the urine up to 24 hours post-dose and the feces up to 48 hours post-dose (46.9% and 4.4% of administered radioactivity), and M20 (an oxidant form) was mainly detected in the bile up to 24 hours post-dose (4.0% of administered radioactivity).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

The applicant's explanation:

The following observations suggest that niraparib and its metabolites are excreted mainly in the urine, feces, and bile to the same extent in rats and mainly in urine in dogs.

- Bile duct-cannulated male rats were administered a single intravenous dose of ^{14}C-niraparib 3 mg/kg. The

[8)] The value represents the sum of the percent recovered relative to the administered radioactivity dose for M4 and M11 because these metabolites coeluted.

urinary and fecal excretion of radioactivity (the percent recovered relative to the administered radioactivity dose) up to 120 hours post-dose was 25.6% and 29.8%, respectively, and the biliary excretion of radioactivity up to 48 hours post-dose was 23.6%.

- Bile duct-cannulated male dogs were administered a single intravenous dose of ^{14}C-niraparib 2 mg/kg. The urinary and fecal excretion of radioactivity (the percent recovered relative to the administered radioactivity dose) up to 120 hours post-dose was 53.4% and 8.5%, respectively, and the biliary excretion of radioactivity up to 72 hours post-dose was 18.1%.

4.4.2 Excretion in milk

The excretion of niraparib in milk has not been investigated. Meanwhile, with the physio-chemical properties of niraparib (including the protein-unbound fraction of niraparib in human plasma [see Section 4.2.2] and its molecular weight [free base] of 320) taken into account, the applicant explained that appropriate cautionary advice would be given in the package insert on possible excretion of niraparib in milk in lactating women.

4.5 Pharmacokinetic interactions

4.5.1 Inhibition of enzymes

The applicant's explanation:

The pharmacokinetic interactions mediated by inhibition of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) by niraparib and M1 are unlikely to occur in clinical use of when niraparib, based on the following results of investigation, and in light of the C_{max} of niraparib and M1 (3.7 and 4.0 μmol/L,[9)] respectively) in the steady state after repeated oral dosing of niraparib 300 mg.

- Human hepatic microsomes were incubated with niraparib (0.05 to 100 μmol/L) or M1 (0.1 to 10 μmol/L) in the presence of substrates of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[10)] or NADPH to evaluate the inhibitory effects of niraparib and MI on individual CYP isoforms. Niraparib and M1 did not clearly inhibit the metabolism of any substrates of the CYP isoforms.
- Human hepatic microsomes were incubated with niraparib (10 or 50 μmol/L) in the presence of NADPH and then with the substrate of CYP3A (testosterone) to evaluate the time-dependent inhibitory effects of niraparib on CYP3A. Niraparib did not clearly inhibit the metabolism of the substrate of CYP3A in a time-dependent manner.
- Genetic recombinant UGT isoforms (UGT 1A1, 1A4, 1A9, and 2B7) were incubated with niraparib (0.33 to 400 μmol/L) in the presence of the substrates of the UGT isoforms[11)] or UDPGA to evaluate the inhibitor effects of niraparib on the UGT isoforms. Niraparib did not clearly inhibit the metabolism of any substrates of the UGT isoforms.

[9)] C_{max} on Day 21 of treatment with oral niraparib 300 mg QD in Japanese patients with advanced solid cancer in Study 1001

[10)] In the evaluation of inhibitory effects of niraparib, phenacetin, bupropion, paclitaxel, diclofenac, *S*-mephenytoin, dextromethorphan, and testosterone were used as substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, respectively. In the evaluation of inhibitory effects of M1, the same substrates used in the evaluation of the inhibitory effects of niraparib were used for CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6, amodiaquine was used as a substrate of CYP2C8, and testosterone and midazolam were used as substrates of CYP3A.

[11)] β-estradiol, trifluoperazine, propofol, and zidovudine were used as substrates of UGT 1A1, 1A4, 1A9, and 2B7, respectively.

4.5.2 Enzyme induction

The applicant's explanation:

The pharmacokinetic interactions mediated by the induction of CYP1A2 and CYP3A by niraparib and M1 are unlikely to occur in clinical use of niraparib, based on the following observations and the C_{max} of niraparib and M1 (3.7 and 4.0 μmol/L,[9)] respectively) in the steady state after repeated oral dose of niraparib 300 mg.

- Human hepatocytes were incubated in the presence of niraparib (0.1 to 20 μmol/L) for 48 hours to evaluate the expression of mRNA of CYP isoforms (CYP1A2 and CYP3A) and their enzyme activity. The expression of mRNA of CYP1A2 increased in a niraparib-concentration-dependent manner, and niraparib showed an induction effect of approximately up to 13% of that of the positive control (omeprazole, 50 μmol/L). For the enzyme activity of CYP1A2, niraparib showed an induction effect of approximately up to 26% of that of the positive control (omeprazole, 50 μmol/L). Meanwhile, niraparib did not clearly induce the expression of mRNA or the enzyme activity of CYP3A4.
- Human hepatocytes were incubated in the presence of niraparib (100 to 400 μmol/L) for 24 hours to evaluate the enzyme activity of CYP3A. Niraparib did not clearly induce the enzyme activity of CYP3A.
- Human hepatocytes were incubated in the presence of M1 (0.1 to 10 μmol/L) for 24 hours to evaluate the enzyme activity of CYP isoforms (CYP1A2 and CYP3A). M1 did not clearly induce the enzyme activity of CYP1A2 or CYP3A.

4.5.3 Transporters

The applicant's explanation about the pharmacokinetic interactions through transporters by niraparib and M1:

The following results of the investigation indicate that niraparib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, MRP2, or BSEP and instead is a substrate of P-gp and BCRP. Also, these results show that M1 is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MRP2, or BSEP but is a substrate of MATE1 and MATE2-K. However, the absolute BA of niraparib in humans [see Section 6.1.2.1], etc. suggest that the combination of niraparib with a P-gp or BCRP inhibitor is unlikely to cause clinically significant pharmacokinetic interactions in their clinical use. In addition, the extremely low pharmacological activity of M1 relative to that of niraparib [see Section 3.1.1.1], etc. suggest that the combination of niraparib with a MATE1 or MATE2-K inhibitor is unlikely to cause clinically significant pharmacokinetic interactions in their clinical use.

- Madin-Darby canine kidney (MDCK) cells expressing human P-gp or BCRP were used to evaluate the P-gp- or BCRP-mediated transport of niraparib[12)] (0.4 to 40 μmol/L). The efflux ratio of niraparib in cells expressing P-gp to that in cells not expressing P-gp ranged from 26.8 to 131, and the transport of niraparib (4 μmol/L) was inhibited by 99.7% in the presence of a P-gp inhibitor (valspodar, 1 μmol/L). The efflux ratio of niraparib in cells expressing BCRP to that in cells not expressing BCRP ranged from 3.72 to 12.1, and the transport of niraparib (4 μmol/L) was inhibited by 50.7% in the presence of a BCRP inhibitor

[12)] M1 was also subjected to the assessment. However, because of its low permeability, whether M1 was a substrate of Pgp and BCRP was not evaluable.

(Ko143, 0.5 μmol/L).

- HEK293 cells expressing human OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K were used to evaluate the transport of niraparib and M1 (0.4 to 40 μmol/L[13)] for both) for each transporter. The ratio of the uptake rate of niraparib in cells expressing the transporter to that in cells not expressing the transporter was <2. The ratio of the uptake rate of M1 in cells expressing MATE1 and MATE2-K to that in cells not expressing MATE1 and MATE2-K was 7.28 and 2.23, respectively. The ratio of the uptake rate of M1 in cells expressing OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2 to that in cells not expressing OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2 was <2.
- Membrane vesicles expressing human MRP2 were used to evaluate the MRP2-mediated transport of niraparib and M1 (0.068 to 6.8 μmol/L for both). The uptake rate of niraparib and M1 in membrane vesicles expressing MRP2 to that in membrane vesicles not expressing MRP2 in the presence of ATP was both <2.
- Membrane vesicles prepared from Sf9 insect ovary-derived cells expressing human BSEP were used to evaluate the BSEP-mediated transport of niraparib and M1 (0.4 to 40 μmol/L for both). The ratio of the uptake rate of niraparib and M1 in membrane vesicles expressing BSEP to that in membrane vesicles not expressing BSEP in the presence of ATP was both <2.

Based on (a) the C_{max} of niraparib and M1 after administration of niraparib 300 mg of 3.7 and 4.0 μmol/L,[9)] respectively, and (b) the estimated niraparib concentration in the gastrointestinal tract of 3,750 μmol/, as well as the following observations, the inhibitory action of niraparib against OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MRP2, and BSEP and that of M1 against P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, MRP2, and BSEP are unlikely to cause pharmacokinetic interactions in its clinical use. In contrast, the inhibitory action of niraparib against P-gp, BCRP, OCT1, MATE1, and MATE2-K may cause pharmacokinetic interactions.

- MDCK cells expressing human P-gp or BCRP were used to evaluate the inhibitory effects of niraparib (1.65 to 400 μmol/L) and M1 (375 μmol/L) on the P-gp- or BCRP-mediated transport of the substrates[14)] of individual transporters. Niraparib inhibited the transport of the substrates of P-gp and BCRP with a respective IC_{50} of 161 and 5.80 μmol/L. In contrast, M1 did not clearly inhibit the transport of the substrate of P-gp or BCRP.
- HEK293 cells expressing human OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K were used to evaluate the inhibitory effects of niraparib and M1 on the OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1-, OCT2-, MATE1-, or MATE2-K-mediated transport of their substrates,[15)] at a concentration of 263 μmol/L[16)] for both niraparib and M1. Niraparib inhibited the transport of substrates of OCT1, MATE1, and MATE2-K with a respective IC_{50} of 34.1μmol/L, 0.179 μmol/L, and

13) Transport was evaluated with niraparib at 0.068 to 6.8 μmol/L and M1 at 0.68 μmol/L for MATE1 and MATE2-K.
14) Digoxin (10 μmol/L) and cladribine (10 μmol/L) were used as a substrate of P-gp and BCRP, respectively.
15) Agents used as substrates were atorvastatin (0.15 μmol/L) for OATP1B1 and OATP1B3, para-aminohippuric acid (10 μmol/L) for OAT1, furosemide (5 μmol/L) for OAT3, 1-methyl-4-phenylpyridinium (5 μmol/L) for OCT1 and OCT2, and metformin (50 μmol/L) for MATE1 and MATE2-K.
16) Transport was evaluated with niraparib and M1 at 34 μmol/L for OAT1, OAT3, and OCT2, with niraparib at 1.65 to 400 μmol/L for OCT1, and with niraparib at 0.140 to 34 μmol/L and M1 at 34 μmol/L for MATE1 and MATE2-K.

<0.140 μmol/L. In contrast, niraparib did not clearly inhibit the transport of the substrate of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2, and M1 did not clearly inhibit the transport of the substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K.

- Membrane vesicles expressing human MRP2 were used to evaluate the inhibitory effects of niraparib and M1 (1.23 to 300 μmol/L for both) on the MRP2-mediated transport of 5(6)-carboxy-2'7'-dichlorofluorescein (5 μmol/L). Neither niraparib nor M1 clearly inhibited the transport of the substrate of MRP2.
- Membrane vesicles prepared from Sf9 cells expressing human BSEP were used to evaluate the inhibitory effects of niraparib and M1 (1.40 to 340 μmol/L for both) on the BSEP-mediated transport of ^{3}H-labelled taurocholic acid (1 μmol/L). Neither niraparib nor M1 clearly inhibited the transport of the substrate of BSEP.

4.R Outline of the review conducted by PMDA

Based on the submitted data and review shown in the sections below, PMDA has concluded that the applicant's explanation about non-clinical pharmacokinetics of niraparib is acceptable.

4.R.1 Pharmacokinetic interactions

Results of the *in vitro* studies suggest that clinical use of niraparib may cause pharmacokinetic interactions through its inhibition of P-gp, BCRP, OCT1, MATE1, and MATE2-K [see Section 4.5.3].

According to the applicant, although the precise evaluation of the pharmacokinetic interactions mediated by the above-mentioned transporters is difficult because of the small number of patients who concomitantly received the substrates of these transporters, the pharmacokinetic interactions are unlikely to pose a problem in clinical use of niraparib, based on of the following observation.

- In a foreign phase II study (QUADRA study) and foreign phase III studies (NOVA and PRIMA studies), no particular concerns were raised on the safety in the combination use of niraparib with a substrate of P-gp, BCRP, OCT1, MATE1, or MATE2-K.

PMDA's view:

The applicant's explanation is generally acceptable. Meanwhile, given the importance of information about the pharmacokinetic interactions of niraparib through P-gp, BCRP, OCT1, MATE1, or MATE2-K in terms of the proper use of niraparib, currently available information should be communicated to healthcare professionals, while information collection is continued. Any useful information should be appropriately provided to healthcare professionals once available.

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, niraparib (tosilate hydrate) is used, unless otherwise specified. The doses and concentrations of niraparib are expressed as free base.

Unless otherwise specified, 0.5% methylcellulose solution and DMSO were used as a vehicle in *in vivo* and *in vitro* studies, respectively.

5.1 Single-dose toxicity

No single-dose toxicity study was conducted. However, the acute toxicity of niraparib was evaluated based on the results from the toxicity studies in rats and dogs (Table 12). In these studies, niraparib hydrochloride was used.

Table 12. Single-dose toxicity studies

Test system	Route	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached data CTD
Female rats (Sprague Dawley)	Oral	0, 10, 100, 750	The acute toxicity was evaluated in a 7-day repeated-dose toxicity study. Death/moribund euthanasia: 750 (5 of 5 animals), decreased spontaneous motility; abdominal distension; atrophy of skeletal muscles; decreased lymphocytes in the spleen; mucosal atrophy of the large intestine; and glandular dilatation of the glandular stomach mucosa. ≥10: Decreased neutrophils, eosinophils, monocytes, and lymphocytes. ≥100: Decreased food consumption; salivation; decreased red blood cells, hemoglobin, hematocrit, blood reticulocytes, and platelets; increased blood ALP; decreased hematopoietic cells in the bone marrow; and mucosal necrosis of the small intestine.	750	4.2.3.2-1 Reference data
Female dogs (beagles)	Oral	4.5 to 13.5 to 40.5	The acute toxicity was evaluated in a 9-day repeated-dose toxicity study. [a)] ≥4.5: Decreased blood reticulocytes; and decreased hematopoietic cells in the bone marrow [b)] ≥13.5: Decreased white blood cells and neutrophils 40.5: Vomiting; weight loss; and decreased red blood cells, hemoglobin, and hematocrit.	>40.5	4.2.3.2-4 Reference data

a) Niraparib was administered QD at 4.5 mg/kg/day on Days 1 to 3, 13.5 mg/kg/day on Days 4 to 6, and 40.5 mg/kg/day on Days 7 to 9. b) Identified by histopathological examinations after the completion of the administration period.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in rats (4- and 13-week) and dogs (4- and 13-week) (Table 13). Effects on the bone marrow and testes were observed after the administration of niraparib. The C_{max} and $AUC_{0\text{-}24h}$ of niraparib at the no-observed-adverse-effect level (NOAEL) seen in the repeated-dose toxicity studies in rats (13-week) and dogs (13-week) (10 mg/kg/day in rats and 4.5 mg/kg/day in dogs) was 0.474 μg/mL and 5.38 μg·h/mL, respectively, in rats and 0.103 μg/mL and 0.856 μg·h/mL, respectively, in dogs, which were approximately 0.40 and 0.27 times higher, respectively, in rats and approximately 0.087 and 0.043 times higher, respectively, in dogs than the clinical exposure.[17)]

[17)] C_{max} (1.18 μg/mL) and $AUC_{0\text{-}24h}$ (19.75 μg·h/mL) of niraparib after the oral administration of niraparib 300 mg QD in Japanese patients with advanced solid cancer in Study 1001 ·

Table 13. Repeated-dose toxicity studies

Test system	Route	Duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Male and female rats (Sprague-Dawley)	Oral	4 weeks (QD) + 2-week interruption	0, 5, 10, 50	Death: 50 (5 of 15 males); decreased spontaneous motility; piloerection; jerky movement; increased respiratory rate; swelling of the muzzle/auricle; salivation; formless stools; and septic embolus/septic necrosis of organs. ≥10: Increased urine output (males) 50: Decreased weight gain/food consumption; pallor fundus; decreased red blood cells, hemoglobin, hematocrit, blood reticulocytes, white blood cells, neutrophils, lymphocytes, monocytes; increased platelets; increased blood urea nitrogen and potassium; increased blood ALP (males); decreased blood globulin; increased urine output (females); increased heart weight; decreased thymus weight; single-cell necrosis of the small intestinal crypt; villous atrophy of the small intestinal crypt (males); centrilobular hepatocellular degeneration of the liver; enlargement of Kupffer cells and hepatocellular vacuolation of the liver (males); single-cell necrosis of the salivary gland (males); decreased cells in the splenic red pulp (males); decreased lymphocytes and histiocytosis of the spleen and lymph nodes (males); decreased lymphocytes of the thymus; decreased hematopoietic cells in the bone marrow; enlargement of the adrenal cortex (males); and decreased seminiferous epithelial cells of the testes. Reversibility: Reversible [a)]	Male: 5 Female: 10	4.2.3.2-2
Male and female rats (Sprague-Dawley)	Oral	13 weeks (QD) + 4-week interruption	0, 5, 10, 30/20 (males),[b)] 30 (females)	Death: 30 (2 of 21 females) ≥10: decreased red blood cells (males)[c)]; increased platelets (males)[c)]; and decreased hematopoietic cells in the bone marrow (males).[c)] 30/20 (males) and 30 (females): Decreased weight gain/food consumption; pallor (males); decreased red blood cells (females); decreased hemoglobin, hematocrit, white blood cells, neutrophils, lymphocytes, and monocytes; increased platelets (females); decreased weight of testes/epididymis; decreased hematopoietic cells in the bone marrow (females); decreased cells in the splenic red pulp; decreased seminiferous epithelial cells of the testes; and oligozoospermia and residual cells of the epididymis. Reversibility: Reversible	10	4.2.3.2-3
Male and female dogs (Beagles)	Oral	4 weeks (QD) + 2-week interruption	0, 3, 6, 15	≥6: Decreased seminiferous epithelial cells of the testes 15: Decreased red blood cells, hemoglobin, hematocrit, and blood reticulocytes. Reversibility: Reversible	Males: 3 Females: 6	4.2.3.2-5
Male and female dogs (Beagles)	Oral	13 weeks (QD) + 4-week interruption	0, 1.5, 4.5, 12	12: Decreased red blood cells, hemoglobin, and hematocrit; decreased blood reticulocytes (males); decreased hematopoietic cells in the bone marrow; decreased seminiferous epithelial cells of the testes; and oligozoospermia of the epididymis. Reversibility: Reversible	4.5	4.2.3.2-6

a) At the end of the recovery period, (a) thickening of the cardiac arterial medium and (b) increased femoral trabecular bone were observed. However, the changes were not considered to be toxicity in light of (a) its seriousness, the presence or absence of related findings, and (b) the view on these changes as compensatory changes due to decreased hematopoietic cells. b) Hematological examinations at Week 4 showed marked decreases in red blood cell parameters in the male animals receiving niraparib 30 mg/kg, for which niraparib was interrupted for 5 days from Days 29 to 33 and was then administered at 20 mg/kg/day on Days 34 to 90. c) The change was considered to be niraparib-related but was not regarded as toxicity on the basis of the incidence, seriousness, and the presence or absence of related findings.

5.3 Genotoxicity

In vitro studies included bacterial reverse mutation tests and a chromosomal aberration assay with mammalian cultured cells, and as an *in vivo* study, a micronucleus test in rodents were conducted (Table 14). In the bacterial reverse mutation tests, the preincubation method using niraparib hydrochloride showed positive results, while the preincubation or plate method using niraparib (tosilate hydrate) showed negative results. Based on these results, niraparib was considered to have no ability to induce reverse mutation. Meanwhile, the chromosomal aberration assay with mammalian cultured cells and the micronucleus test in rodents yielded positive results. Based on the results, niraparib was considered to have an ability to induce chromosomal aberration and have genotoxicity. The C_{max} and $AUC_{0\text{-}24h}$ of niraparib at the maximum dose (5 mg/kg), at which no micronucleus induction was observed in the micronucleus test in rodents, was 0.327 μg/mL and 1.34 μg·h/mL, respectively, and was approximately 0.28 and 0.068 times higher than the clinical exposure,[17] respectively.

Table 14. Genotoxicity studies

Study type			Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Results	Attached data CTD
In vitro	Bacterial reverse mutation tests (Preincubation method)	*Salmonella typhimurium*: TA98, TA100, TA1535, and TA97a. *Escherichia coli*: WP2*uvrA* pKM101	S9−	0,[a] 30, 100, 300, 1,000, 3,000,[b] 6,000[b]	Positive (Increased number of revertant colonies for TA98 line) [c]	4.2.3.3.1-1 Reference data
			S9+	0,[a] 30, 100, 300, 1,000, 3,000,[b] 6,000[b]		
		Salmonella typhimurium: TA98	S9−	0, 30, 100, 300, 1,000, 2,000, 3,000[b]	Positive [c]	
			S9+	0, 30, 100, 300, 1,000, 2,000, 3,000		
		Salmonella typhimurium: TA98, TA100, TA1535, and TA97a. *Escherichia coli*: WP2*uvrA* pKM101	S9+	0, 30, 100, 300, 1,000, 3,000,[b] 6,000[b]	Negative	
			S9+	0, 30, 100, 300, 1,000, 3,000,[b] 6,000[b]		
		Salmonella typhimurium: TA98	S9−	0, 30, 100, 300, 1,000, 2,000, 3,000[b]	Negative	
			S9+	0, 30, 100, 300, 1,000, 2,000, 3,000		
	Bacterial reverse mutation tests (Plate method)	*Salmonella typhimurium*: TA98, TA100, TA1535, and TA1537. *Escherichia coli*: WP2*uvrA*	S9−	0, 5, 15, 50, 150, 500, 1,500,[b] 5,000[b]	Negative	4.2.3.3.1-2
			S9+	0, 5, 15, 50, 150, 500, 1,500,[b] 5,000[b]		
	Chromosomal aberration assays with mammalian cultured cells	CHO cells	S9− (4 hours)	0, 5, 10, 15	Positive (Structural alteration)	4.2.3.3.1-3
			S9+ (4 hours)	0, 10, 30, 45		
			S9− (20 hours)	0, 1, 2, 3		
In vivo	Micronucleus test in rodents	Male and female rats (Sprague Dawley) Bone marrow		0, 5, 10, 50 (Oral, 4 weeks)	≥10: Positive	4.2.3.3.2-1

a) Distilled water was used as a vehicle. b) Cell proliferation was inhibited. c) Niraparib hydrochloride was used.

5.4 Carcinogenicity

No carcinogenicity study was performed for niraparib because niraparib is an anticancer drug to treat patients with advanced cancer.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity study was performed for niraparib because niraparib is an anticancer drug to treat patients with advanced cancer, and is expected to adversely affect embryo-fetal development due to its pharmacological activity.

According to the applicant, the following points suggest that niraparib may affect fertility and early embryonic development to implantation, pre- and postnatal development, and embryo-fetal development.

- Niraparib is genotoxic [see Section 5.3].
- In repeated-dose toxicity studies, effects of niraparib on fast-dividing cells (e.g., bone marrow and testes) were observed [see Section 5.2].
- Dually PARP-1 and PARP-2-deficient mice have been reported to die at the early stage of the gastrulation process, which suggests that PARP activity is considered to be essential for embryo-fetal development (*EMBO J.* 2003;22:2255-63).

5.6 Other toxicity studies

5.6.1 Photosafety testing

Results of an *in vitro* phototoxicity study with murine fibroblast lines suggest that niraparib may induce phototoxicity. However, based on results from an *in vivo* phototoxicity study in pigment rats, it was concluded that niraparib is not phototoxic (Table 15).

Table 15. Photosafety testing

Study type	Test system	Study methods	Main findings	Attached data CTD
in vitro	Murine fibroblast lines Balb/c 3T3	0.100 to 5.62 µg/mL (with UVR [a)]) 0.100 to 5.62 µg/mL (without UVR)	Possibly phototoxic (with a photostimulation factor of >5 [b)])	4.2.3.7.7-1
in vivo	Female pigmented rats (Long-Evans)	Niraparib 0, 10, 50, and 100 mg/kg/day was orally administered for 3 days, and then UVR was performed. [c)] Examinations including assessment of skin reaction, ophthalmological examinations, and to histopathological examinations (eyeballs) were performed.	Not phototoxic	4.2.3.7.7-2

a) Ultraviolet radiation (UVR) (UVA [5 J/cm^2] and UVB [19 mJ/cm^2]) for approximately 30 minutes. b) The possibility was indicated that niraparib might have inhibited the repair of DNA damaged by UVR and have induced cell death. c) UVR (UVA [10.29 to 10.535 J/cm^2], UVB [144.9 to 148.35 mJ/cm^2], and visible light) for 42 to 43 minutes

5.6.2 Toxicity study on impurities

In compliance with the ICH Q3A Guidelines, general toxicity was evaluated for an impurity of the drug substance (*R*-enantiomer) which should be subjected to safety evaluation. Based on results from the repeated-

dose toxicity study of the drug substance containing the impurity [see Section 5.2],[18] it was concluded that the containing of the impurity would pose no safety concerns.

5.R Outline of the review conducted by PMDA

Based on the submitted data and review shown in the sections below, the applicant's explanation about the toxicity of niraparib was acceptable. The conclusion on the effects of niraparib on bone marrow which were characteristic of treatment with niraparib in the repeated-dose studies is described in Section 7.R.2.2 Bone marrow suppression, in consideration of the results of clinical studies for the safety of niraparib.

5.R.1 Use of niraparib in pregnant or possibly pregnant women

The applicant's explanation about the use of niraparib in pregnant or possibly pregnant women:

Niraparib is considered to adversely affect embryo-fetal development [see Sections 4.2.4 and 5.5], and the use of niraparib in pregnant or possibly pregnant women is thus not recommended. However, given the poor prognosis and the nature of ovarian cancer, it is considered acceptable to use niraparib with due care in pregnant or possibly pregnant women who are fully informed of the potential risks for the fetus in association with treatment with niraparib, only if the expected therapeutic benefits outweigh the possible risks associated with the treatment. In the package insert, the results, etc. of genotoxicity studies of niraparib will be provided, along with cautionary advice on possible adverse effects of niraparib on embryo-fetal development.

PMDA accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

In this section, the doses and concentrations of niraparib are expressed as free base.

6.1 Biopharmaceutic studies and associated analytical methods

Niraparib is available in capsules (10 mg capsules and 100 mg capsules) as oral formulation, and PK, etc. were evaluated for the capsule formulation (Table 16). The formulation proposed for marketing is 100 mg capsules.

Table 16. Formulation used in clinical studies

Formulation	Study
10 mg capsules	Foreign phase I studies (Studies PN001 and PN014) and foreign phase Ib studies (Studies PN008 and PN011)
100 mg capsules	A Japanese phase I study (Study 1001), Japanese phase II studies (Studies 2001 and 2002), foreign phase I studies (Studies PN001 and 5015-C), a foreign phase Ib study (Study PN008), a foreign phase II study (QUADRA study), foreign phase III studies (Studies 5011-C1 and 5011-C2 and NOVA and PRIMA studies)

6.1.1 Assay

Niraparib in human plasma was quantitated by liquid chromatography/tandem mass spectrometry (LC-MS/MS) with a lower limit of quantification of 1 ng/mL.[19]

[18] A 13-week repeated-dose toxicity study with the drug substance (batch No.: [redacted]) containing *R*-enantiomer at 0.10% in rats

[19] Plasma samples were quantitated by assays with a lower limit of quantification of 5 ng/mL in Studies 1001, 2001, and 2002 and the PRIMA study.

6.1.2 Foreign clinical studies

6.1.2.1 Foreign phase I study (CTD 5.3.1.1-1: Study 5015-C Part 1 [January to July 2015])

An open-label study was conducted to evaluate the absolute BA of niraparib in 6 patients with advanced solid cancer (6 patients in the PK analysis set). A single dose of niraparib 300 mg was orally administered, and 2 hours later, a single dose of ^{14}C-niraparib 100 µg was to be intravenously administered.

The absolute BA [90% CI] calculated based on the least-squares mean of AUC_{inf} of niraparib was 71.3% [61.7, 83.4].

6.1.2.2 Foreign phase III study (CTD 5.3.3.4-1: Study 5011-C2[20)] [August 2013 to October 2015])

A 2-group, 2-period crossover study was conducted to evaluate the effects of foods on the PK of niraparib in 17 patients with ovarian cancer (16 patients in the PK analysis set). A single dose of niraparib 300 mg was orally administered under fasted conditions[21)] or 5 minutes after a high-fat meal[22)] with a 6-day interval between the administration periods.

The median t_{max} of niraparib was 3.1 and 6.1 hours under fasted conditions and after a high-fat meal, respectively. The ratio of least-squares means of [90% CI] of C_{max} and AUC_{inf} of niraparib administered under fasted conditions to that after a high-fat meal was 0.785 [0.695, 0.886] and 1.10 [0.997, 1.22], respectively.

The applicant's explanation about food effects on the PK of niraparib based on the above results:
The gastric emptying rate decreased after a high-fat meal, suggesting a possibility of delayed t_{max} and decreased C_{max}. However, given no clear relationship seen between the C_{max} and the efficacy of niraparib [see Section 6.2.6.1], decreased C_{max} after the administration of niraparib with meals is unlikely to be clinically significant in the clinical use of niraparib, and niraparib can be administered regardless of the state of food intake.

6.1.3 Effects of gastric pH on the PK of niraparib

According to the applicant's explanation, increased gastric pH levels with the administration of medications such as proton pump inhibitors are unlikely to affect the PK of niraparib, based on the stable solubility of niraparib (1.05 to 1.77 mg/mL) regardless of the pH levels within the range of 1.0 to 6.8.

6.2 Clinical pharmacology

The PK of niraparib in patients with cancer was evaluated for niraparib monotherapy.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.5.2-2: Study 1001 Ongoing since April 2018 [data cutoff on [redacted], 20[redacted]])

[20)] This study was a part of the NOVA study and was conducted as a sub-study to evaluate the food effects on the PK of niraparib.
[21)] Subjects took niraparib after a ≥10 hour (overnight) fasting period that was followed by a ≥2 hour fasting period.
[22)] Approximately 50% of the total calories (about 800 to 1,000 kcal) are attributed to fat.

An open-label, uncontrolled study was conducted to evaluate factors including PK of niraparib in 9 patients with advanced solid cancer (9 patients in the PK analysis set). Multiple doses of niraparib 200 or 300 mg were administered orally QD to evaluate parameters including plasma niraparib concentrations.

The PK parameters of niraparib are shown in Table 17. The accumulation rate of niraparib[23)] after the administration of niraparib 200 and 300 mg was 2.64 and 3.65, respectively.

Table 17. PK parameters of niraparib

Dose (mg)	Dosing date (day)	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{24h} (ng·h/mL)
200	1	3	476.0 ± 195.1	4.00 (1.52, 4.07)	5,500 ± 2,905
	21	3	791.7 ± 387.5	3.95 (3.83, 4.03)	14,080 ± 6,493
300	1	6	550.2 ± 149.2	4.04 (2.05, 10.2)	6,660 ± 2,631
	21	4	1,180 ± 194.9	2.89 (2.88, 6.00)	19,750 ± 3,117

Mean ± standard deviation. * Median (range).

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.5.2-1: Study PN001 Part A [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to evaluate the PK, etc. of niraparib in 60 patients with advanced solid cancer (60 patients in the PK analysis set). Multiple doses of niraparib 30 to 400 mg were administered orally QC to evaluate plasma niraparib concentrations, etc.

PK parameters of niraparib are shown in Table 18. The C_{max} and AUC_{24h} of niraparib generally showed linearity for the doses tested. The accumulation rate of niraparib [23)] after the administration of niraparib 300 mg was 2.41.

Table 18. PK parameters of niraparib

Dose (mg)	Dosing date (day)	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{24h} (ng·h/mL)	$t_{1/2}$ (h)
30	1	6	47.36 ± 29.84	3.0 (1.5, 4.1)	569.6 ± 332.8	−
	21	5	104.4 ± 64.56	3.0 (1.5, 4.0)	1,603 ± 1,047	−
40	1	3	64.35 ± 36.82	3.0 (3.0, 3.1)	815.7 ± 429.0	−
	21	3	206.6 ± 69.72	2.0 (1.0, 3.0)	3,102 ± 798.4	−
60	1	7	113.7 ± 41.41	3.1 (1.5, 4.0)	1,461 ± 536.9	−
	21	6	267.2 ± 143.9	3.0 (1.5, 4.0)	4,357 ± 2,392	27.1, 72.4*2
80	1	6	170.4 ± 71.56	3.0 (3.0, 3.2)	1,954 ± 823.4	−
	21	5	376.5 ± 102.2	3.0 (1.0, 3.0)	5,603 ± 1,580	41.0 ± 3.16*3
110	1	5	329.9 ± 156.2	3.3 (3.0, 4.0)	3,524 ± 1,418	−
	21	3	564.0 ± 287.8	2.0 (1.5, 3.0)	8,159 ± 3,943	33.7, 40.1*2
150	1	6	431.4 ± 153.1	3.0 (1.5, 4.1)	5,138 ± 1,899	−
	21	4	654.1 ± 458.3	3.5 (2.0, 4.0)	10,110 ± 7,299	35.8 ± 8.44
210	1	6	591.1 ± 345.2	3.0 (2.0, 4.1)	6,952 ± 4,561	−
	21	5	1,013 ± 896.9	4.0 (2.0, 6.0)	17,570 ± 16,970	34.0 ± 10.9
290	1	5	595.5 ± 313.6	3.0 (3.0, 6.2)	6,136 ± 2,666	−
	21	3	1,392 ± 452.8	3.0 (3.0, 6.1)	21,510 ± 11,430	34.9 ± 4.93
300	1	10	769.2 ± 348.5	3.0 (1.5, 4.1)	8,672 ± 3,378	−
	21	10	1,399 ± 608.3	3.5 (2.0, 4.2)	21,410 ± 9,168	36.6 ± 5.93
400	1	6	679.7 ± 177.1	3.6 (1.5, 6.0)	8,517 ± 1,760	−
	21	4	1,425 ± 317.2	3.5 (3.0, 6.0)	25,330 ± 6,696	48.9 ± 21.6*4

Mean ± standard deviation (individual values when n = 2); *1, Median (range); *2, n = 2; *3, n = 4; *4, n = 3. −, Not calculated

23) The ratio of AUC_{24h} on Day 21 to AUC_{24h} on Day 1

6.2.2.2 Foreign phase I study (CTD 5.3.1.1-1: Study 5015-C Part 2 [June to December 2015])

An open-label, uncontrolled study was conducted to evaluate mass balance, etc. in 6 patients with advanced solid cancer (6 patients in the PK analysis set). A single dose of ^{14}C-niraparib 300 mg was orally administered to evaluate radioactivity concentrations in the blood, plasma, urine, and feces, etc.

M1 (a carboxylate form), M10 (a glucuronate conjugate of M1), a methylated form of M1, and unchanged niraparib were mainly detected in the plasma up to 168 hours post-dose (the respective percentage relative to the AUC_{168h} of the total radioactivity of 9.3%, 55.7%, 2.5%, and 2.4%). The AUC_{inf} of total radioactivity in plasma was approximately 1.7-hold higher than the AUC_{inf} in blood. Based on these findings, the applicant explained that niraparib and its metabolites were shown to be distributed mainly in plasma.

The urinary and fecal excretion rate (the percentage relative to administered radioactivity) up to 504 hours post-dose was 47.5% and 38.8%, respectively. M1, unchanged niraparib, and M10 were mainly detected in urine up to 144 hours post-dose (20.0%, 10.5%, and 6.2%, respectively). Unchanged niraparib and M1 were mainly detected in feces up to 144 hours post-dose (18.7% and 2.4%, respectively).

6.2.3 Use of niraparib in patients with renal impairment

The applicant explained that dose adjustment of niraparib would be unnecessary for patients with renal impairment in light of the following.

- Data on urinary excretion rate of unchanged niraparib in the foreign phase I study (Study 5015-C) [see Section 6.2.2.2] suggest that the contribution of renal excretion to the elimination of niraparib was small.
- A pooled analysis of data from the foreign phase II study (QUADRA study) and the foreign phase III studies (NOVA and PRIMA studies) yielded the following results: The incidence of (a) serious adverse events, (b) Grade ≥3 adverse events, (c) adverse events leading to dose reduction, and (d) adverse events leading to treatment discontinuation was (a) 28.9%, 37.4%, 44.5%, and 50.0%, (b) 66.1%, 74.7%, 80.8%, and 75.0%, (c) 58.0%, 63.5%, 66.8%, and 50.0%, and (d) 14.6%, 16.0%, 20.4%, and 25.0%, respectively, in patients with normal renal function[24] (n = 481), patients with mild renal impairment (n = 562), patients with moderate renal impairment (n = 265), and patients with severe renal impairment (n = 4), showing no clear differences between patients with normal renal function and patients with mild, moderate, or severe renal impairment.

6.2.4 A relationship between exposure to niraparib and changes in QT/QTc interval

In the foreign clinical studies (Studies 5011-C1[25] and 5011-C2 and the NOVA study), a relationship between plasma niraparib concentrations and ΔQTcF was evaluated with a linear mixed-effect model based on data from 58 patients for whom the plasma niraparib concentrations were determined at the time of

[24] Renal function was classified based on CrCL: normal renal function, CrCL of ≥90 mL/min; mild renal impairment, CrCL of ≥60 and <90 mL/min; moderate renal impairment, CrCL of ≥30 and <60 mL/min; and severe renal impairment, CrCL of <30 mL/min. No patients with severe renal impairment were enrolled in the foreign phase III studies (NOVA and PRIMA studies).

[25] This study was conducted as a sub-study of the NOVA study to evaluate the effects of niraparib on QTc intervals.

electrocardiography. No clear relationship was observed between the plasma niraparib concentrations and ΔQTcF.

Based on the above results, the applicant explained that niraparib administered according to the proposed regimen is unlikely to prolong QT/QTC interval.

6.2.5 Population pharmacokinetic analysis

A population pharmacokinetic (PPK) analysis was conducted with a non-linear mixed effect model on the PK data for niraparib (1,442 patients, 7,418 points) available from the foreign clinical studies (Study PN001, and QUADRA, NOVA, and PRIMA studies) (NONMEM Version 7.3.0). The PK of niraparib was described with the 3-compartment model with a first-order absorption process into a central compartment following a first-order elimination process and a zero-order release into the absorption compartment with lag time.

The following covariates for (a) CL/F, (b) Vc/F, (c) Vp2/F, (d) Frel, and (e) D1 of niraparib were evaluated: (a) creatinine clearance (CrCL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, albumin, performance status according to the Eastern Cooperative Oncology Group (ECOG PS), HRD, and platelet count corrected with body weight, sex, age, race, carcinoma, and body surface area; (b) body weight, sex, age, race, and albumin, (c) body weight, sex, and albumin, (d) body weight and food; and (e) sex and food. As a result, (a) CrCL and body weight corrected with albumin, age, and body surface area, (b) body weight, and (c) food were selected as significant covariates for (a) CL/F, (b) Vc/F and Frel, and (c) D1. The effects of individual covariates on exposure to niraparib (AUC in the steady state) were limited, the applicant explained that each covariate would be unlikely to have clinically significant effects on the PK of niraparib.

6.2.6 Relationship between exposure and efficacy or safety

6.2.6.1 Relationship between exposure and efficacy

Based on data available from the overall *gBRCA*-mutated cohort, the overall non-*gBRCA*-mutated cohort, and the HRD-positive group in the non-*gBRCA*-mutated cohort in the foreign phase III study (NOVA study), the niraparib group was divided by the quartile points[26] of niraparib exposure[27] (C_{max}) to estimate the progression-free survival (PFS) in each group exposed to niraparib with the Kaplan-Meier method. No clear relationship between niraparib exposure and the PFS was observed in any cohorts or groups.

Based on data available from the foreign phase III study (PRIMA study), the niraparib group was divided by the quartile points[28] of niraparib exposure[29] (mean plasma concentration[30]) to estimate the PFS in each group

[26] The range of C_{max} (ng/mL) based on quartile points in (a) the *gBRCA*-mutated cohort, (b) the non-*gBRCA*-mutated cohort, and (c) the non-*gBRCA* mutated and HRD-positive group was (a) ≥23 and ≤379, >379 and ≤532, >532 and ≤692, and >692, (b) ≥2.05 and ≤390, >390 and ≤574, >574 and ≤774, and >774, and (c) ≥3.21 and ≤366, >366 and ≤552, >552 and ≤763, and >763, respectively.
[27] Estimated from the PKK analysis using a non-linear mixed-effect model based on data for the PK of niraparib (480 patients, 3,923 points) available from the foreign clinical studies (Study PN001 and the NOVA study) (NONMEM Version 7.3).
[28] The range of the mean plasma concentration (ng/mL) based on quartile points in the respective groups was 42.1 to 278, 278 to 375, 375 to 528, and 528 to 1,260.
[29] Estimated from the PPK analysis [see Section 6.2.5].
[30] Calculated as a mean AUC per day until the earlier of the occurrence of an event, treatment discontinuation, or treatment withdrawal.

with exposed to niraparib with the Kaplan-Meier method. No clear relationship between niraparib exposure and PFS was identified.

6.2.6.2 Relationship between exposure and safety

Based on data available from the foreign phase III study (PRIMA study), a relationship was evaluated between niraparib exposure[28] (AUC[31]) and the occurrence of all-grade or Grade ≥3 platelets decreased, anemia, neutrophils decreased, hypertension, and fatigue with a univariate logistic regression model. With an increase in niraparib exposure, increased incidences of all-grade or Grade ≥3 platelets decreased, anemia, neutrophils decreased, and fatigue, and all-grade hypertension were suggested. Meanwhile, no clear relationship was observed between niraparib exposure and the incidence of Grade ≥3 hypertension.

6.2.7 Difference in PK of niraparib between Japanese and non-Japanese patients

No obvious differences were observed in niraparib exposure (C_{max} and AUC_{24h}) after the oral administration of niraparib 300 mg QD in the Japanese phase I study (Study 1001 [see Section 6.2.1.1]) and the foreign phase I study (Study PN001 [see Section 6.2.2.1]). The applicant explained that no clear differences were observed in the PK of niraparib between Japanese and non-Japanese patients.

6.R Outline of the review conducted by PMDA

Based on the submitted data and review shown in the following subsection, PMDA has concluded that the applicant's explanation about the clinical pharmacology, etc. of niraparib was acceptable.

6.R.1 Use of niraparib in patients with hepatic impairment

The applicant's explanation about the use of niraparib in patients with hepatic impairment:

Given that CES plays a major role in the metabolism of niraparib [see Section 4.3.1], hepatic impairment may affect the PK of niraparib when CES expressed in the liver is involved in the metabolism of niraparib. However, no dose adjustment is considered necessary in patients with mild hepatic impairment, based on the following observations. Meanwhile, because niraparib has never been used in patients with moderate or severe hepatic impairment, caution should be exercised in the use of niraparib in this patient population, and such information should be communicated.

- In the PPK analysis, AST, ALT, ALP, and bilirubin were not selected as significant covariates for the PK parameters of niraparib [see Section 6.2.5].
- The pooled analysis of data from the foreign phase II study (QUADRA study) and the foreign phase III studies (NOVA and PRIMA studies) revealed that the incidence of (a) serious adverse events, (b) Grade ≥3 adverse events, (c) adverse events leading to dose reduction, and (d) adverse events leading to treatment discontinuation was (a) 34.6% and 45.2%, (b) 72.3% and 77.4%, (c) 62.8% and 55.5%, and (d) 15.8% and 21.2%, respectively, in patients with normal hepatic function[32] (n = 1,168) and patients with mild

[31] The AUC during the period until the first occurrence of the event for patients experiencing the event, and the AUC during the period until the end of treatment for patients not experiencing the event

[32] Classified based on the NCI-ODWG criteria. No patients with moderate or severe hepatic impairment were included in the pooled analysis.

hepatic impairment (n = 146). No clear differences were observed between the patients with normal hepatic function and patients with mild hepatic impairment.

Currently, a clinical study (Study 003) is underway to evaluate the PK of niraparib in patients with moderate hepatic impairment. The results of the study will be provided to healthcare professionals as soon as available.

PMDA accepted the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

Data from 7 studies, i.e., 1 Japanese phase I study, 2 Japanese phase II studies, 1 foreign phase I study, 1 foreign phase II study, and 2 foreign phase III studies listed in Table 19, were submitted for the evaluation of efficacy and safety. Data from 6 studies, i.e., 2 foreign phase I studies, 2 foreign phase Ib studies, and 2 foreign phase III studies listed in Table 19, were submitted as reference data.

Table 19. List of clinical studies for efficacy and safety

Data category	Region	Study	Phase	Patient population	Number of subjects enrolled	Outline of dosage regimen	Main endpoints
Evaluation	Japan	1001	I	Patients with advanced solid cancer	9	Niraparib 200 or 300 mg was orally administered QD.	Safety Tolerability
		2001	II	Patients with platinum-sensitive, relapsed, ovarian cancer in response to their last platinum-based chemotherapy	19	Niraparib 300 mg was orally administered QD.	Safety
		2002	II	HRD-positive patients with platinum-sensitive recurrent ovarian cancer who had received 3 or 4 previous chemotherapy regimens	20	Niraparib 300 mg was orally administered QD.	Efficacy Safety
	Outside Japan	PN001	I	Patients with advanced solid cancer	104	Niraparib 30, 40, 60, 80, 110, 150, 210, 290, 300, or 400 mg was orally administered QD.	Safety Tolerability PK
		QUADRA	II	Patients with recurrent ovarian cancer who had received ≥3 previous chemotherapy regimens	463	Niraparib 300 mg was orally administered QD.	Efficacy Safety
		NOVA	III	Patients with platinum-sensitive, relapsed, ovarian cancer in response to their last platinum-based chemotherapy	553 (a) 372 (b) 181	(a) Niraparib 300 mg was orally administered QD. (b) Placebo was orally administered QD.	Efficacy Safety
		PRIMA	III	Patients with advanced ovarian cancer in response to first-line platinum-based chemotherapy	Fixed starting dose: (a) 317 (b) 158 Individualized starting dose: (a) 170 (b) 88	Fixed starting dose: (a) Niraparib 300 mg was orally administered QD. (b) Placebo was orally administered QD. Individualized starting dose: (a) Niraparib 200 or 300 mg was orally administered QD. (b) Placebo was orally administered QD.	Efficacy Safety
Reference data	Outside Japan	5015-C	I	Patients with advanced solid cancer	Run-in period: 12 (a) 6 (b) 6 Continuous treatment period: 11	Run-in period: A single dose of niraparib 300 mg was orally administered, and 2 hours later, a single dose of ^{14}C-niraparib 100 µg was intravenously administered (Part 1). A single dose of ^{14}C-niraparib 300 mg was orally administered (Part 2) Continuous treatment period: Niraparib 300 mg was orally administered QD	PK
		PN014	I	Patients with advanced solid cancer	19	In a 4-week cycle, temozolomide 150 mg/m^2 was orally administered QD on Days 4 to 8, and niraparib (a) 70 mg or (b) 80 mg was orally administered QD on Days 1 and 2. Subsequently, niraparib (a) 30 or 70 mg or (b) 40 mg was orally administered QD on Days 3 to 8	Safety Tolerability
		PN008	Ib	Patients with advanced solid cancer	12	In a 3-week cycle, carboplatin with the target AUC level of 5 mg·min/mL was intravenously administered on Day 3, and niraparib 40, 60, 80, or 110 mg was orally administered QD on Day1 1 to 4.	Safety Tolerability
		PN011	Ib	Patients with advanced solid cancer	6	In a 4-week cycle, the liposomal formulation of doxorubicin hydrochloride 40 mg/m^2 was intravenously administered on Day 3, and niraparib 80 mg on Days 1 and 2 and 30 or 40 mg on Days 3 to 16 was orally administered QD.	Safety Tolerability
		5011-C1	III	Patients with ovarian cancer	26	Niraparib 300 mg was orally administered QD.	Safety Efficacy
		5011-C2	III	Patients with ovarian cancer	17	A single dose of niraparib 300 mg was administered under fasted conditions or with high-fat meal and then was administered in a crossover manner on Day 8. Niraparib 300 mg was orally administered QD from Day 15 onwards.	PK

The individual clinical studies are summarized below. Major adverse events other than deaths observed in these studies are summarized in Section "7.3 Adverse events observed in clinical studies," and study results for the PK of niraparib are described in Sections "6.1 Biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese phase I study (CTD 5.3.5.2-2: Study 1001 [Ongoing since April 2018 (data cutoff on [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted in 1 site in Japan to evaluate the safety and tolerability, etc. of niraparib in patients with advanced solid cancer (target sample size, 6 to 12 patients).

Niraparib 200 or 300 mg was orally administered QD and to be continued until disease progression or the discontinuation criteria were met.

All 9 patients enrolled in this study (3 in the niraparib the niraparib 200 mg cohort and 6 in the niraparib 300 mg cohort) received niraparib and were included in the safety analysis set.

The period from the start to Day 21 of the administration of niraparib was specified as a period for the evaluation of the dose-limiting toxicity (DLT) in the niraparib 200 and 300 mg cohorts. DLT was observed in 1 of 6 patients (Grade 4 platelet count decreased) in the niraparib 300 mg cohort.

The safety analysis revealed no deaths during the administration of niraparib or within 28 days after the completion of the administration.

7.1.1.2 Japanese phase II study (CTD 5.3.5.2-3: Study 2001 [December 2018 to March 2019 (data cutoff for efficacy on November 11, 2019, and data cutoff for safety on March 17, 2019)])

An open-label, uncontrolled study was conducted in 15 sites in Japan to evaluate the safety of niraparib in patients with platinum-sensitive,[33)] relapsed, high-grade serous or *gBRCA*-mutated,[34)] ovarian cancer (including primary peritoneal cancer and fallopian tube cancer) who had received ≥2 platinum-based chemotherapy regimens[35)] and were in response to their last platinum-based chemotherapy (target sample size, 15 patients).

Niraparib 300 mg was orally administered QD. The treatment was continued until disease progression or the discontinuation criteria were met.

All 19 patients who were enrolled in this study received niraparib and were included in the safety analysis set.

33) A platinum-free interval (PFI) of ≥180 days
34) Patients were judged to be eligible for participation in the clinical study when they were determined to have *gBRCA* mutation during the examination before enrollment.
35) Patients with no history of prior treatment with PARP inhibitors were enrolled.

The primary endpoints of this study were the number of patients experiencing Grade 3 or 4 thrombocytopenia developing within 30 days after the start of administration of niraparib and its incidence.

The safety analysis identified Grade 3 or 4 thrombocytopenia developing within 30 days after the start of administration of niraparib in 6 patients with an incidence of 31.6%. No deaths occurred during the administration of niraparib or within 30 days after the completion of the administration.

7.1.1.3 Japanese phase II study (CTD 5.3.5.2-2: Study 2002 [December 2018 to July 2019 (data cutoff on July 1, 2019)])

An open-label, uncontrolled study was conducted in 17 sites in Japan to evaluate the efficacy and safety of niraparib in patients with HRD-positive,[36)] platinum-sensitive,[33)] relapsed, high-grade serous ovarian cancer (including primary peritoneal cancer and fallopian tube cancer) who had received 3 or 4 chemotherapy regimens[35)] and had responded to their last platinum-based chemotherapy (target sample size, 16 patients).

Niraparib 300 mg was orally administered QD and continued until disease progression or the discontinuation criteria were met.

All 20 patients who were enrolled in this study received niraparib and were included in the efficacy and safety analysis sets.

The primary endpoint of this study was the response rate assessed by the investigators based on the Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1.

The primary endpoint of this clinical study, the results of the investigator-assessed response rate based on the RECIST ver. 1.1, are shown in Table 20. The lower limit of the 90% CI was higher than the prespecified threshold response rate (5%[37)]) (data cutoff on July 1, 2019).

Table 20. Best overall response and response rate
(RECIST ver.1.1, efficacy analysis set, investigator-assessed, data cutoff on July 1, 2019)

Best overall response	Number of subjects (%)
	n = 20
CR	1 (5.0)
PR	6 (30.0)
SD	11 (55.0)
PD	2 (10.0)
Response (CR + PR) (response rate [90% CI*] (%))	7 (35.0 [17.7, 55.8])

* Exact method.

The safety analysis revealed no deaths during the administration of niraparib or within 30 days after the completion of the administration.

36) Defined as HRD-positive when *tBRCA* was detected or GIS was ≥42 with tests on tumor specimens by Myriad myChoice HRD CDx (Myriad Genetic Laboratories).

37) The threshold response rate was specified to be 5% based on the response rate of 11.9% and 2.9% for chemotherapy in patients with relapsed ovarian cancer who had received 3 or ≥4 chemotherapy regimens, respectively (*Eur J Obstet Gynecol Reprod Biol.* 2013;166:94-8).

7.1.2 Foreign clinical studies

7.1.2.1 Foreign phase I study (CTD 5.3.5.2-1: Study PN001 [September 2008 to September 2011])

An open-label, uncontrolled study was conducted in 3 sites outside Japan to evaluate the safety and tolerability, etc. of niraparib in patients with advanced solid cancer (target sample size, 50 to 342 patients).

In Part A, in a 3-week cycle, niraparib 30, 40, 60, 80, 110, 150, 210, 290, 300, or 400 mg was orally administered QD, and then administration was interrupted only on Days 22 to 28 of Cycle 1. In Parts B and D, niraparib 300 mg was orally administered QD and continued until disease progression or the discontinuation criteria met. Part C was planned to enroll patients with hematopoietic malignancy, but no patients had been enrolled before discontinuation of the study.

All 104 patients enrolled in the study (60 in Part A, 40 in Part B, and 4 in Part D) received niraparib and were included in the safety analysis set.

In Part A, the DLT assessment period was specified as from the start of administration of niraparib to Day 21 of administration. DLT was observed in 1 of 6 patients (Grade 3 fatigue) in the niraparib 30 mg cohort, 1 of 7 patients (Grade 3 pneumonitis) in the niraparib 60 mg cohort, and 2 of 6 patients (Grade 4 thrombocytopenia in 2 patients) in the niraparib 400 mg cohort. The maximum tolerated dose (MTD) of niraparib was determined to be 300 mg QD.

The safety analysis revealed deaths during the administration of niraparib or within 30 days after the cessation of administration in 4 of 60 patients (6.7%) (1 patient each in the niraparib 30, 60, 210, and 400 mg cohort) in Part A and 2 of 40 patients (5.0%) in Part B. Excluding 4 patients who died of disease progression, the cause of death was sepsis in 1 patient and cerebral infarction in 1 patient in Part B, a causal relationship with niraparib was ruled out for both cases.

7.1.2.2 Foreign phase II study (CTD 5.3.5.2-1: QUADRA study [Ongoing since April 2015 (data cutoff on April 11, 2018)])

An open-label, uncontrolled study was conducted in 50 sites outside Japan to evaluate the efficacy and safety of niraparib in patients with high-grade serous recurrent ovarian cancer (including primary peritoneal cancer and fallopian tube cancer) who had received ≥3 chemotherapy regimens (target sample size, 500 patients).

Niraparib 300 mg was orally administered QD and was continued until disease progression or the discontinuation criteria were met.

Of 463 patients enrolled in the study, 47 patients who are HRD-positive[36)] and platinum-sensitive [33)] who had received 3 or 4 chemotherapy regimens and responded to their last platinum-based chemotherapy, and had not been previously treated with PARP inhibitors were included in the main efficacy analysis set. In addition, 463 patients who were enrolled in the study and received niraparib were included in the safety analysis set.

The primary endpoint of the study was the response rate assessed by the investigators based on the RECIST ver. 1.1. For the following reasons, at the start of the study, (a) the primary analysis set comprised patients with and without *BRCA* mutation who had received ≥3 chemotherapies, and (b) the specified threshold response rate was 30%.

- The foreign phase I study (Study PN001) conducted in patients with advanced solid cancer to evaluate the safety, etc. of niraparib identified some non-*BRCA*-mutated patients responding to niraparib, suggesting that the presence or absence of *BRCA* mutation does not make clear differences in the efficacy outcome of niraparib.
- The foreign phase II studies (42 studies) conducted in patients with *gBRCA*-mutated, relapsed ovarian cancer who had received 3 chemotherapy regimens to evaluate the efficacy and safety of olaparib demonstrated that the investigator-assessed response rate based on the RECIST ver. 1.1 [95% CI] was 34% [26, 42].

Afterward, however, based on the following findings became available, the protocol revision 8 (dated December 21, 20[redacted]) redefined the patient population that would better respond to niraparib as (a) the primary analysis set would comprise patients with HRD-positive[36)] and platinum-sensitive[33)] ovarian cancer who had received 3 or 4 chemotherapy regimens, responded to their last platinum-based chemotherapy, and had not been previously treated with PARP inhibitors, and (b) the threshold response rate as 10%.

- Results of the NOVA study suggest that niraparib was effective in HRD-positive[36)] platinum-sensitive[33)] patients [see Sections 7.1.2.3 and 7.R.3.3].
- In a retrospective cohort study,[38)] the response rate to chemotherapy in patients with relapsed ovarian cancer who had received 3 and 4 chemotherapy regimens[39)] was 11.9% and 2.9%, respectively (*Eur J Obstet Gynecol Reprod Biol.* 2013;166:94-8).

The results of the investigator-assessed response rate based on the RECIST ver. 1.1, the primary efficacy endpoint of this clinical study, are shown in Table 21. The lower limit of the 95% CI was higher than the prespecified threshold (10%) (data cutoff on April 11, 2018).

Table 21. Best overall response and response rate
(RECIST ver.1.1, main analysis set, investigator-assessed, data cutoff on April 11, 2018)

Best overall response	Number of subjects (%)
	n = 47
CR	0
PR	13 (27.7)
SD	19 (40.4)
PD	10 (21.3)
NE	5 (10.6)
Response (CR + PR) (response rate [95% CI*] [%])	13 (27.7 [15.6, 42.6])

* Exact method

38) There is no report on the response rate to chemotherapy in patients with HRD-positive, platinum-sensitive, relapsed ovarian cancer who had been received ≥3 or 4 chemotherapy regimens. Therefore, the threshold was determined based on the reports on the response rate to chemotherapy in patients with relapsed ovarian cancer who had received ≥3 or 4 chemotherapy regimens.
39) Medications including PTX and ETP were administered.

The safety analysis revealed deaths during the administration of niraparib or within 30 days after the completion of administration in 9 of 463 patients (1.9%). Excluding 3 patients who died of disease progression, the cause of death was cardiac arrest in 2 patients, cardiopulmonary failure, gastric haemorrhage, sudden death, and hyperbilirubinaemia in 1 patient each. A causal relationship with niraparib was not ruled out for gastric haemorrhage.

7.1.2.3 Foreign phase III study (CTD 5.3.5.1-1: NOVA study [Ongoing since August 2013 (data cutoff for efficacy on May 30, 2016, and data cutoff for safety on September 15, 2017)])

A double-blind, randomized, controlled study was conducted in 128 sites outside Japan to compare the efficacy and safety of niraparib with placebo in patients with platinum-sensitive,[33)] high-grade serous or *gBRCA*-mutated[40)] relapsed ovarian cancer (including primary peritoneal cancer and fallopian tube cancer) who had received ≥2 platinum-based chemotherapy regimens[35)] and was in response to the last platinum-based chemotherapy regimen (target sample size, 490 patients).

Niraparib 300 mg or placebo was orally administered QD and was continued until disease progression or the discontinuation criteria were met.

The study was designed with a *gBRCA*-mutated cohort and a non-*gBRCA*-mutated cohort, and patients were randomized in each cohort. All 553 patients enrolled and randomized in this study (in the *gBRCA*-mutated cohort, 138 patients in the niraparib group and 65 patients in the placebo group; in the non-*gBRCA*-mutated cohort, 234 patients in the niraparib group and 116 patients in the placebo group) were included in the intention-to-treat (ITT) population and the efficacy analysis set. In the ITT population, excluding 7 patients receiving no study drug (in the *gBRCA*-mutated cohort, 2 patient in the niraparib group and 0 in the placebo group; in the non-*gBRCA*-mutated cohort, 3 patients in the niraparib group and 2 patients in the placebo group), remaining 546 patients (in the *gBRCA*-mutated cohort, 136 patients in the niraparib group and 65 patients in the placebo group; and in the non-*gBRCA*-mutated cohort, 231 patients in the niraparib group and 114 patients in the placebo group) were included in the safety analysis set.

The primary endpoint of this study was PFS assessed by the blinded independent central review (BICR) according to the RECIST ver. 1.1 alone at the start of this study, and the final analysis was scheduled to be performed when the number of PFS events in each cohort had reached 140. The first interim analysis was planned to evaluate the efficacy in the *gBRCA*-mutated cohort and scheduled to be performed when the number of PFS events in the *gBRCA*-mutated cohort had reached 85. However, a certain number of patients in the NOVA study were anticipated to have difficulty undergoing the evaluation of disease progression by imaging. Therefore, in the protocol revision 1 (dated May 3, 20[redacted]), the primary endpoint was redefined as PFS assessed

[40)] Defined as *gBRCA*-mutated when pathological mutation was detected or suspected with tests on blood specimens by Myriad Integrated BRACAnalysis (Myriad Genetic Laboratories).

by the BICR[41] according to the RECIST ver. 1.1 or clinical signs/symptoms and an increase in CA-125.[42] In addition, based on an article suggesting PARP inhibitors' potential effectiveness in patients with homologous recombination deficiency, regardless of the presence of *BRCA* mutation (*Annals of Oncology*. 2016;27:1449-55), the protocol revision 4 (dated December 4, 20[redacted]) specified a PFS analysis in the HRD-positive[36] group in the non-*gBRCA*-mutated cohort as an additional primary analysis. Afterward, the power for the *gBRCA*-mutated cohort was changed from >95% to 90% for the final analysis of the 2 cohorts at the same timing, and the final analysis was scheduled to be performed when the number of PFS events had reached approximately 100 in the *gBRCA*-mutated cohort. However, the final analysis would nearly coincide with the interim analysis scheduled at the start of this study, the interim analysis was thus canceled (the protocol revision 6, dated March 9, 20[redacted]). In the efficacy evaluation, independent hypothesis tests were planned with a one-sided significance level of 0.025 in each cohort. For the non-*gBRCA*-mutated cohort, an analysis for the overall non-*gBRCA*-mutated cohort was scheduled to be conducted when a statistically significant difference in the HRD-positive[36] group was demonstrated by stratified test procedures.

The efficacy analysis based on the primary endpoint, i.e., the primary analysis of PFS (data cutoff on May 30, 2016) yielded results shown in Table 22 and the Kaplan-Meier plots shown in Figures 1, 2, and 3. The superiority of niraparib to placebo was demonstrated in the *gBRCA*-mutated cohort and the HRD-positive group and the overall population in the non-gBRCA-mutated cohort.

[41] Defined as time from the randomization to the first onset of any of the events in the following (a), (b) and (c);
(a) Disease progression confirmed by CT or MRI according to the RECIST ver. 1.1
(b) New lesions or worsening of existing lesions identified by tests other than those in (a) (e.g., histology/ cytology, ultrasound techniques, endoscopy, PET) and an increase in CA-125 according to the GCIG criteria
(c) Worsening of clinical signs and symptoms (cancer-related pain, intestinal obstruction, decreased intestinal function, ascites, or pleural effusion) in association with the underlying disease and an increase in CA-125 according to the GCIG criteria
An increase in CA-125 according to the GCIG criteria was defined as increased CA-125 measurements obtained at 2 time points ≥1 week apart, which were ≥2 times higher than the higher of either the upper limit of the reference range or the minimum value after the first dose.

[42] An increase in CA-125 according to the GCIG criteria was defined as increased CA-125 measurements obtained at 2 time points ≥1 week apart, which were ≥2 times higher than the higher of either the upper limit of the reference range or the minimum value after the first dose.

Table 22. Results of the primary analysis of PFS (Based on BICR assessment, ITT population, data cutoff on May 30, 2016)

	gBRCA-mutated cohort		Non-*gBRCA*-mutated cohort			
			HRD-positive group		Overall cohort	
	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo
Number of subjects	138	65	106	56	234	116
Number of events (%)	59 (42.8)	44 (67.7)	56 (52.8)	45 (80.4)	125 (53.4)	88 (75.9)
Median [95% CI] (month)	21.0 [12.9, −]	5.5 [3.8, 7.2]	12.9 [8.1, 15.9]	3.8 [3.5, 5.7]	9.3 [7.2, 11.2]	3.9 [3.7, 5.5]
Hazard ratio [95% CI] *1	0.27 [0.173, 0.410]		0.38 [0.243, 0.586]		0.45 [0.338, 0.607]	
p-value (one-sided) *2	<0.0001		<0.0001		<0.0001	

-, Not estimable; *1, A stratified Cox regression model with stratifying factors including PFI (6 to <12 months or ≥12 months) before recurrence, concomitant use or nonuse of bevacizumab (BV) before or at recurrence, and best response (CR, PR) during the last platinum regimen; *2, A stratified log-rank test with stratifying factors including PFI (6 to <12 months or ≥12 months) before recurrence, concomitant use or nonuse of bevacizumab (BV) before or at recurrence, and best response (CR, PR) during the last platinum regimen. Significance level (one-sided), 0.025

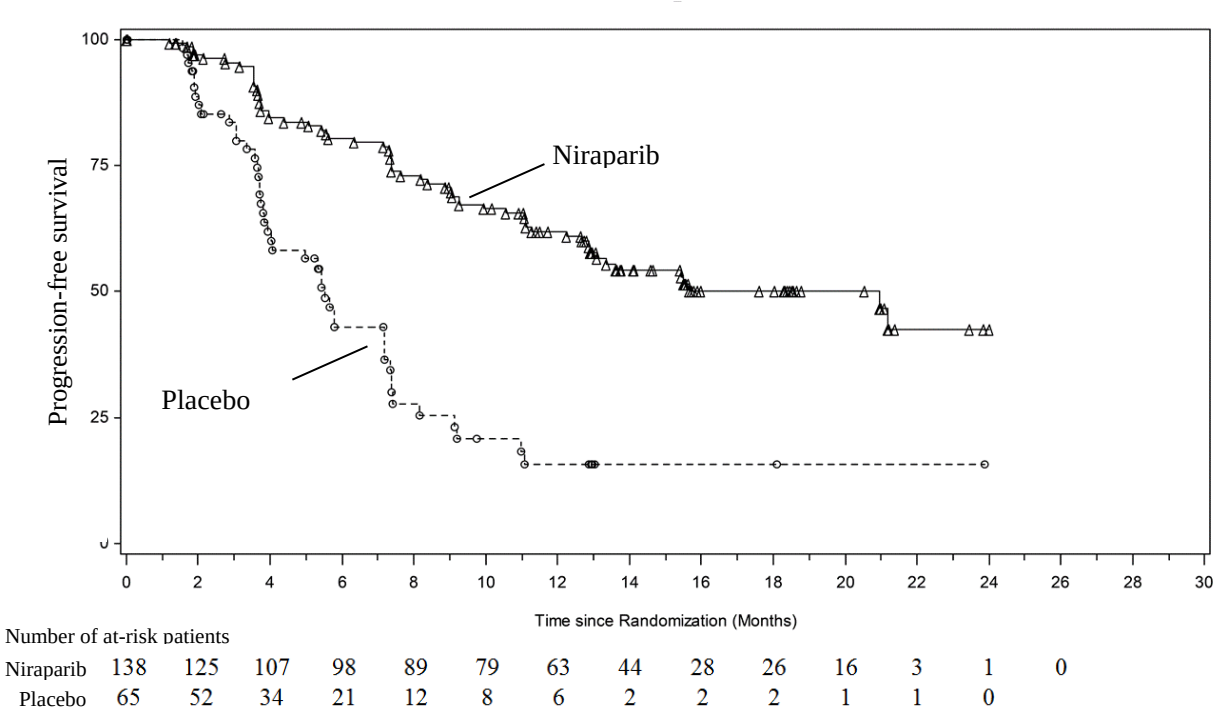


Figure 1. Kaplan-Meier plot for PFS at the primary analysis
(Based on BICR assessment, *gBRCA*-mutated cohort, data cutoff on May 30, 2016)

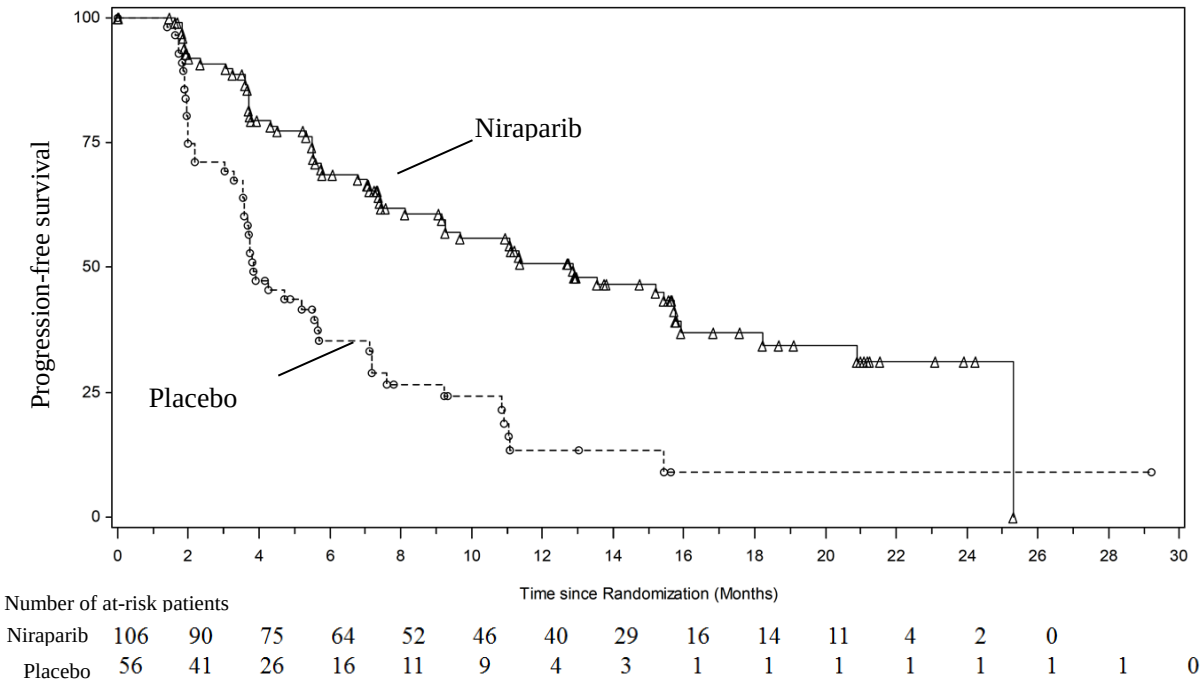


Figure 2. Kaplan-Meier plot for PFS at the primary analysis
(Based on BICR assessment, the HRD-positive group in the non-*gBRCA*-mutated cohort, data cutoff on May 30, 2016)

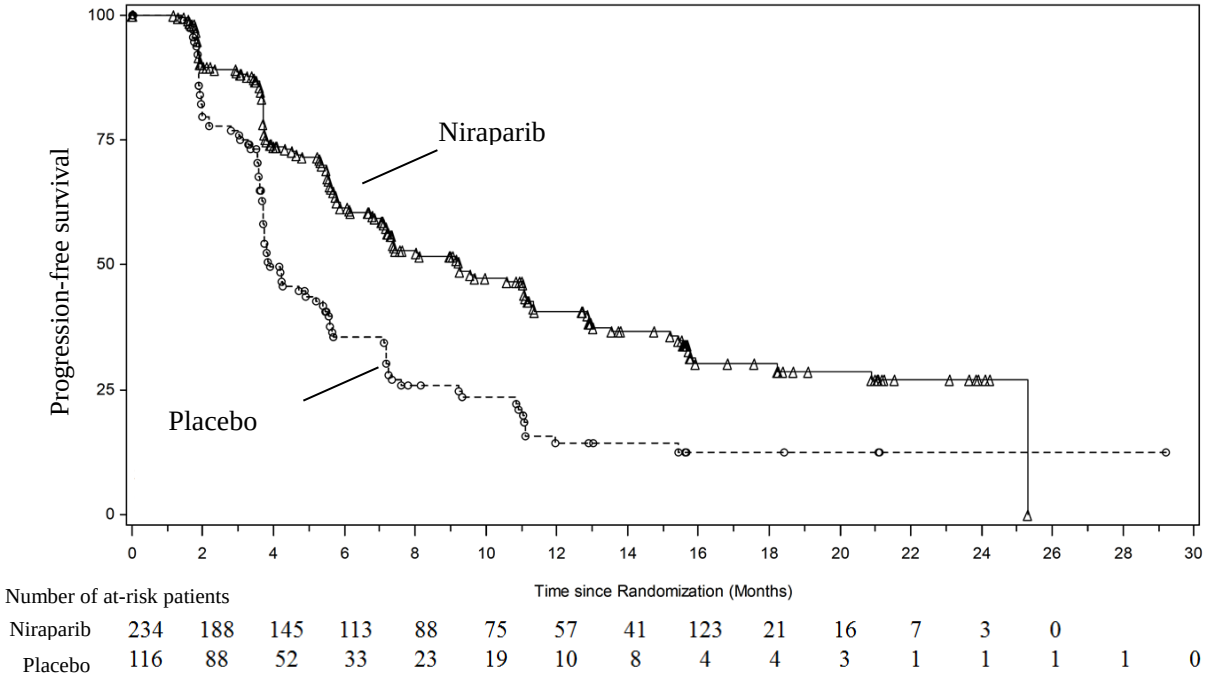


Figure 3. Kaplan-Meier plot for PFS at the primary analysis
(Based on BICR assessment, non-*gBRCA*-mutated cohort, data cutoff on May 30, 2016)

The safety analysis revealed a death during the administration of the study drug or within 30 days after the completion of administration in 1 of 367 patients (0.3%) in the niraparib group. The patient died of acute myeloid leukemia (AML), and a causal relationship with niraparib was not ruled out.

7.1.2.4 Foreign phase III study (CTD 5.3.5.1-2: PRIMA study [Ongoing since August 2016 (data cutoff on May 17, 2019)])

A double-blind, randomized, controlled study was conducted in 220 sites outside Japan to compare the efficacy and safety of niraparib to placebo in patients with high-grade serous or endometrioid ovarian cancer (including primary peritoneal cancer and fallopian tube cancer)[43] in response to first-line platinum-based chemotherapy[44] (target sample size, 620 patients).

At the start of the study, the starting dosage regimen was oral niraparib 300 mg or placebo QD (fixed starting dose). However, the exploratory analysis of the NOVA study employing the starting dose same as that in this study [see Section 7.R.6.1] revealed that (i) the incidence of events related to Grade 3 or 4 decreased platelets tended to be higher in patients with a body weight of <77 kg or a platelet count of <150,000/μL at baseline; (ii) the incidence of events related to platelets decreased was higher in patients receiving niraparib 300 mg; and (iii) no tendency toward lower efficacy was observed in patients in whom the dose of niraparib was reduced from 300 mg to 200 mg. Based on these findings, the protocol revision 2 (dated November 16, 20[redacted]) redefined the starting dose of niraparib for individual patients based on baseline body weight and the platelet count.[45] Niraparib was continued until disease progression or the discontinuation criteria were met.

Baseline body weight and platelet count	Dosage regimen
Body weight of <77 kg or a platelet count of <150,000/μL	Oral niraparib 200 mg or placebo QD
Body weight of ≥77 kg and a platelet count of ≥150,000/μL	Oral niraparib 300 mg or placebo QD

All 733 patients enrolled and randomized in the study (487 in the niraparib group and 246 in the placebo group) were included in the ITT population and in the efficacy analysis set. In the ITT population, excluding 5 patients receiving no study drug (3 in the niraparib group and 2 in the placebo group), the remaining 728 patients (484 in the niraparib group and 244 in the placebo group) were included in the safety analysis set.

The primary endpoint of this study was BICR-assessed PFS according to the RECIST ver. 1.1. At the start of this study, HRD-positive[36] patients were the target study population. However, the NOVA study demonstrated the efficacy of niraparib in the overall non-*gBRCA*-mutated cohort including the HRD-negative group [see Sections 7.1.2.3 and 7.R.3.3]. In response, in the protocol revision 2 (dated November 22, 20[redacted]) redefined

[43] Patients with cancer diagnosed as FIGO stage III or IV were enrolled if they were had received optimal debulking surgery once before enrollment. Patients with cancer stage III were excluded if had no visible residual lesion after the primary debulking surgery. Patients were eligible for participation in the study if they had not been evaluated for malignancy after neoadjuvant chemotherapy.

[44] Patients were eligible if they had received 6 to 9 cycles of the first platinum-based chemotherapy and met the following criteria:
(a) Patients who had received no bevacizumab (BV) as maintenance chemotherapy after the first chemotherapy;
(b) Patients who had completed the first BV-contained chemotherapy and had their last BV dose ≥28 days before but could not receive BV as maintenance chemotherapy due to adverse events, etc.

[45] In patients who started niraparib at 200 mg, the dose was allowed to increase to 300 mg if niraparib was not interrupted or discontinued in the first 8 weeks.

the study population, i.e., HRD-negative patients also became eligible for this study. The main analysis of PFS was scheduled to be conducted when the number of PFS events reached approximately 99 in the HRD-positive[36)] group and 255 in the overall study population. An analysis for the overall study population was to be conducted when a statistically significant difference was demonstrated in the HRD-positive[36)] group by hierarchical test procedures.

The efficacy results from the primary analysis of PFS (data cutoff on May 17, 2019) and the Kaplan-Meier plot are respectively shown in Table 23 and Figures 4 and 5, demonstrating the superiority of niraparib to placebo was demonstrated in the HRD-positive[36)] group and the overall study population.

Table 23. Results of the primary analysis of PFS (Based on BICR assessment, ITT population, data cutoff on May 17, 2019)

	HRD-positive group		Overall study population	
	Niraparib	Placebo	Niraparib	Placebo
Number of subjects	247	126	487	246
Number of events (%)	81 (32.8)	73 (57.9)	232 (47.6)	155 (63.0)
Median [95% CI] (month)	21.9 [19.3, −]	10.4 [8.1, 12.1]	13.8 [11.5, 14.9]	8.2 [7.3, 8.5]
Hazard ratio [95% CI] *1	0.43 [0.310, 0.588]		0.62 [0.502, 0.755]	
p-value (one-sided) *2	<0.0001		<0.0001	

−, Not estimable; *1, A stratified Cox proportional hazards model with stratifying factors including neoadjuvant chemotherapy (with/without), best response (CR, PR) during the platinum regimen, and status of HRD (positive/negative/unknown); *2, A stratified log-rank test with stratifying factors including neoadjuvant chemotherapy (with/without), best response (CR, PR) during the platinum regimen, and status of HRD (positive/negative/unknown); Significance level (one-sided), 0.025

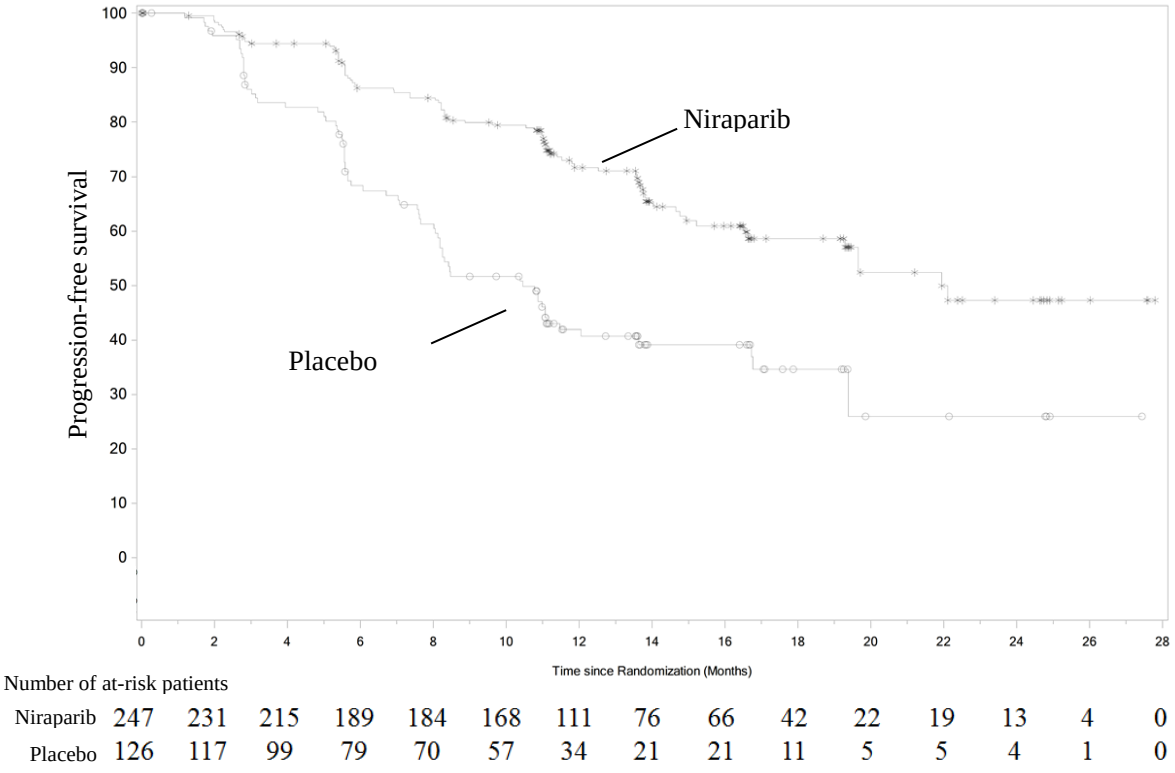


Figure 4. Kaplan-Meier plot for PFS at the primary analysis
(Based on BICR assessment, the HRD-positive group, data cutoff on May 17, 2019)

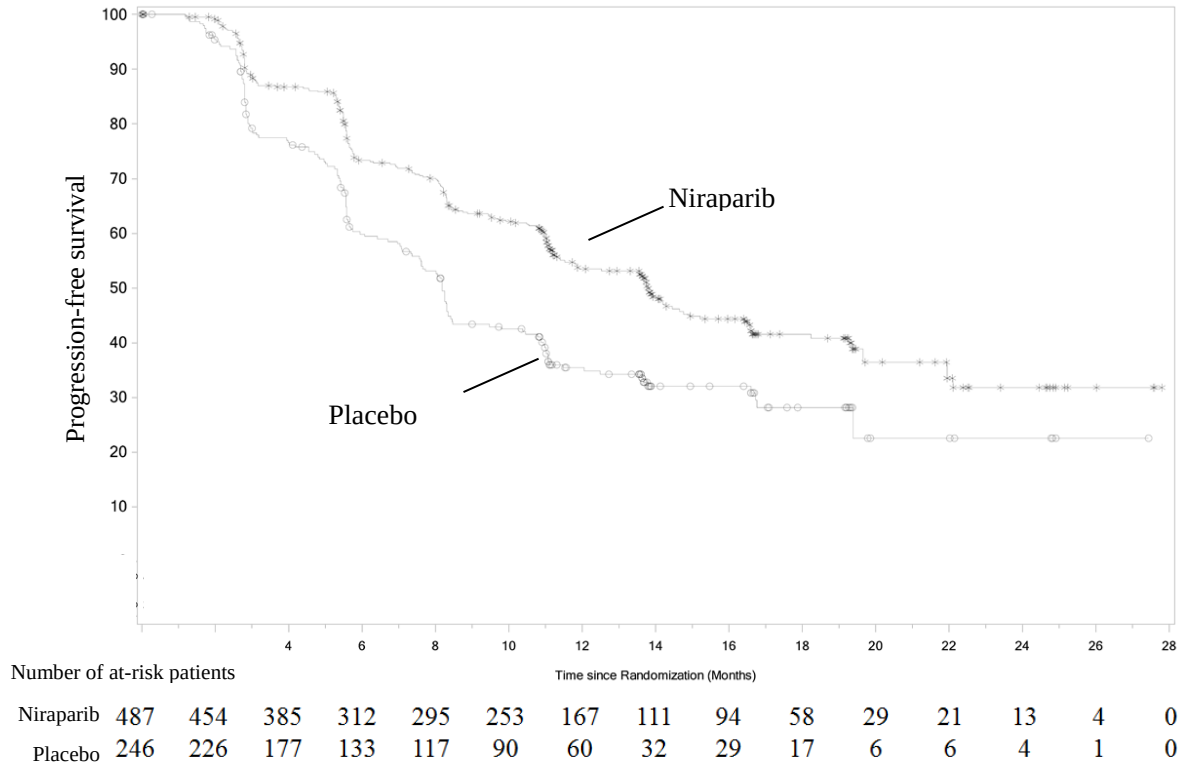


Figure 5. Kaplan-Meier plot for PFS at the primary analysis
(Based on BICR assessment, overall study population, data cutoff on May 17, 2019)

The safety analysis revealed no deaths during the administration of niraparib or within 30 days after the completion of the administration.

7.2 Reference data

7.2.1 Clinical pharmacology

Data were submitted from the following 2 clinical pharmacology studies conducted in patients with advanced solid cancer and patients with ovarian cancer [see Sections 6.1 and 6.2]. Deaths occurred during the administration of niraparib or within 30 days after the completion of the treatment in 2 patients (in 1 of 11 patients [9.1%] in Study 5015-C and 1 of 15 patients [6.7%] in Study 5011-C2). The 2 patients died of disease progression.

7.2.1.1 Foreign phase I study (CTD 5.3.1.1-1: Study 5015-C [Ongoing since January 2015 (data cutoff on September 15, 2017)])

7.2.1.2 Foreign phase III study (CTD 5.3.3.4-1: Study 5011-C2 [August 2013 to October 2015])

7.2.2 Foreign clinical studies

7.2.2.1 Foreign phase I study (CTD 5.3.5.4-3: Study PN014 [February 2011 to May 2012])

An open-label, uncontrolled study was conducted in 3 sites outside Japan to evaluate the safety, etc. of niraparib used in combination with temozolomide in patients with advanced solid cancer (target sample size, 64 patients).

A total of 19 patients enrolled and receiving the study drug (6 in the niraparib 30 mg group, 10 in the niraparib 40 mg group, and 3 in the niraparib 70 mg group) were included in the safety analysis set.

The safety analysis identified no deaths during the administration of niraparib or within 30 days after the completion of the treatment.

7.2.2.2 Foreign phase Ib study (CTD 5.3.5.4-1: Study PN008 [July 2010 to July 2011])

An open-label, uncontrolled study was conducted in 2 sites outside Japan to evaluate the safety, etc. of niraparib used in combination with carboplatin in patients with advanced solid cancer (target sample size, 105).

A total of 12 patients enrolled and receiving the study drug (3s in the niraparib 40 mg group, 3 in the niraparib 60 mg group, 3 in the niraparib 80 mg group, and 3 in the niraparib 11 mg group) were included in the safety analysis set.

The safety analysis identified no deaths during the administration of niraparib or within 30 days after the completion of the treatment.

7.2.2.3 Foreign phase Ib study (CTD 5.3.5.4-2: Study PN011 [November 2010 to August 2011])

An open-label, uncontrolled study was conducted in 3 sites outside Japan to evaluate the safety, etc. of niraparib used in combination with the liposomal formulation of doxorubicin hydrochloride in patients with advanced solid cancer (target sample size, 90 patients).

A total of 6 patients enrolled and receiving the study drug (3 in the niraparib 30 mg group and 3 in the niraparib 40 mg group) were included in the safety analysis set.

The safety analysis revealed a death of 1 patient in the niraparib 30 mg group during the administration of niraparib or within 30 days after the completion of the treatment. The patient died of disease progression.

7.2.2.4 Foreign phase III study (CTD 5.3.4.2-1: Study 5011-C1 [Ongoing since April 2015 (data cutoff on May 30, 2016)])

An open-label, uncontrolled study was conducted in 4 sites outside Japan to evaluate the efficacy and safety of niraparib in patients with ovarian cancer (target sample size, 20 patients).

A total of 26 patients enrolled and receiving niraparib in this study were included in the safety analysis set.

The safety analysis identified no deaths during the administration of niraparib or within 30 days after the completion of the treatment.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA considered that among the submitted evaluation data, the following 3 clinical studies were important in the efficacy and safety evaluations of niraparib and decided to review mainly focusing on these studies.

The efficacy and safety of niraparib in Japanese patients were decided to be evaluated mainly focusing on the data from the Japanese phase II study (Study 2002), which enrolled patient population similar to that included in the QUADRA study.

(a) The foreign phase III study (PRIMA study) to evaluate the efficacy and safety of niraparib in patients with high-grade serous or endometrioid ovarian cancer who were in response to their first-line platinum-based chemotherapy;
(b) The foreign phase III study (NOVA study) to evaluate the efficacy and safety of niraparib in patients with platinum-sensitive, relapsed, high-grade serous or *gBRCA*-mutated ovarian cancer who had received ≥2 platinum-based chemotherapy regimens and were in response to the last platinum-based chemotherapy; and
(c) The foreign phase II study (QUADRA study) to evaluate the efficacy and safety of niraparib in patients with recurrent high-grade serous ovarian cancer who had received ≥3 chemotherapy regimens.

In the PRIMA study, a fixed starting dose was specified at the beginning, but it was later individually determined in from a viewpoint of patients' safety, etc. during the study period [see Section 7.1.2.4]. PMDA asked the applicant to explain effects of this change in the starting dose on the efficacy and safety of niraparib.

The applicant's answer:

Based on the results of the exposure-response analysis of the PRIMA study [see Section 6.2.6] as well as the observations below, the change in the starting dose is considered unlikely to affect the efficacy of niraparib. In terms of safety, the individualized starting dose is considered to have contributed to reduced risk of bone marrow suppression-related events, etc.

Efficacy

- The results of PFS by starting dose setting in the PRIMA study (data cutoff on May 17, 2019) are shown in Table 24. No clear differences in the efficacy of niraparib were observed between the fixed starting dose and the individualized starting dose in the HRD-positive group and in any group of the overall study (the p-value of interaction was 0.749 and 0.296 in the HRD-positive group and the overall study population, respectively).
- Among patients with body weight of <77 kg or a platelet count of <150,000/μL at baseline, the hazard ratio [95% CI] of PFS was 0.62 [0.47, 0.83] and 0.68 [0.44, 1.06] in patients receiving niraparib at the starting dose of 300 and 200 mg, respectively, showing no clear difference between the doses.

Table 24. Results of the PFS analysis
(PRIMA study, based on BICR assessment, ITT population, data cutoff on May 17, 2019)

	Fixed starting dose		Individualized starting dose	
	Niraparib	Placebo	Niraparib	Placebo
HRD-positive group				
Number of subjects	160	83	87	43
Number of events (%)	57 (35.6)	52 (62.7)	24 (27.6)	21 (48.8)
Median [95% CI] (month)	22.1 [19.6, −]	8.4 [7.6, 13.6]	14.0 [12.5, −]	10.9 [6.1, −]
Hazard ratio [95% CI] *1	0.44 [0.298, 0.638]		0.39 [0.215, 0.723]	
p-value (two-sided) *2	<0.0001		0.0019	
Overall study population				
Number of subjects	317	158	170	88
Number of events (%)	150 (47.3)	104 (65.8)	82 (48.2)	51 (58.0)
median [95% CI] (month)	14.7 [13.6, 19.4]	8.2 [7.0, 9.8]	11.4 [9.7, 13.9]	8.2 [5.6, 10.9]
Hazard ratio [95% CI] *1	0.59 [0.457, 0.757]		0.69 [0.481, 0.982]	
p-value (two-sided) *2	<0.0001		0.0389	

−, Not estimable; *1, A stratified Cox proportional hazards model with stratifying factors including neoadjuvant chemotherapy (with/without), best response (CR, PR) during the platinum regimen, and status of HRD (positive/negative/unknown); *2. A stratified log-rank test with stratifying factors including neoadjuvant chemotherapy (with/without), best response (CR, PR) during the platinum regimen, and status of HRD (positive/negative/unknown)

Safety

- The clinical safety in patients receiving niraparib at the fixed starting dose and individualized starting dose in the PRIMA study is summarized in Table 25. The incidence of Grade ≥3 adverse events was lower in the patients receiving niraparib at the individualized starting dose than in the patients receiving niraparib at the fixed starting dose.
- The incidence of Grade ≥3 adverse events related to bone marrow suppression, including thrombocytopenia (in 114 patients receiving niraparib at the fixed starting dose [36.2%] and 25 patients

receiving niraparib at the individualized starting dose [14.8%]), anaemia (112 patients [35.6%] and 38 patients [22.5%]), platelet count decreased (51 patients [16.2%] and 12 patients [7.1%]), and neutropenia (46 patients [14.6%] and 16 patients [9.5%]), was lower by ≥5% in patients receiving niraparib at the individualized starting dose than in patients receiving niraparib at the fixed starting dose.

Table 25. Summary of clinical safety (PRIMA study, by starting dose)

	Number of subjects (%)			
	Niraparib			Placebo n = 244
	All subjects n = 484	Fixed starting dose n = 315	Individualized starting dose n = 169	
All adverse events	478 (98.8)	313 (99.4)	165 (97.6)	224 (91.8)
Grade ≥3 adverse events	341 (70.5)	239 (75.9)	102 (60.4)	46 (18.9)
Adverse events resulting in death	2 (0.4)	2 (0.6)	0	1 (0.4)
Serious adverse events	156 (32.2)	111 (35.2)	45 (26.6)	32 (13.1)
Adverse events leading to treatment discontinuation	58 (12.0)	35 (11.1)	23 (13.6)	6 (2.5)
Adverse events leading to treatment interruption	385 (79.5)	264 (83.8)	121 (71.6)	44 (18.0)
Adverse events leading to dose reduction	343 (70.9)	239 (75.9)	104 (61.5)	20 (8.2)

PMDA's view:

The applicant's explanation is acceptable and the efficacy of niraparib can be evaluated based on the data in the overall study population in the PRIMA study. Meanwhile, the safety results of niraparib should be interpreted with the effects of differences in starting dose setting taken into account.

7.R.2 Safety [for adverse events, see Section "7.3 Adverse events observed in clinical studies"]

As a result of the review shown below, PMDA considers that treatment with niraparib requires extra caution against adverse events including bone marrow suppression, hypertension, interstitial lung disease (ILD), thromboembolism, secondary malignancy, and posterior reversible encephalopathy syndrome. Caution should be exercised against these adverse events in the use of niraparib.

Besides the adverse events mentioned above, gastrointestinal disorders also deserves attention in the use of niraparib. Nevertheless, niraparib is tolerable when adverse events are monitored and managed, or other appropriate measures, such as dose reduction and interruption of niraparib, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.2.1 Safety profile of niraparib and differences in the safety of niraparib between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of niraparib treatment based on safety data available from the PRIMA, NOVA, and QUADRA studies:

The clinical safety observed in the PRIMA, NOVA, and QUADRA studies is summarized in Table 26.

Table 26. Summary of clinical safety (PRIMA, NOVA, and QUADRA studies)

	Number of subjects (%)				
	PRIMA study		NOVA study		QUADRA study
	Niraparib n = 484	Placebo n = 244	Niraparib n = 367	Placebo n = 179	n = 463
All adverse events	478 (98.8)	224 (91.8)	367 (100)	171 (95.5)	461 (99.6)
Grade ≥3 adverse events	341 (70.5)	46 (18.9)	278 (75.7)	42 (23.5)	338 (73.0)
Adverse events resulting in death	2 (0.4)	1 (0.4)	1 (0.3)	0	9 (1.9)
Serious adverse events	156 (32.2)	32 (13.1)	117 (31.9)	27 (15.1)	197 (42.5)
Adverse events leading to treatment discontinuation	58 (12.0)	6 (2.5)	60 (16.3)	4 (2.2)	98 (21.2)
Adverse events leading to treatment interruption	385 (79.5)	44 (18.0)	251 (68.4)	26 (14.5)	288 (62.2)
Adverse events leading to dose reduction	343 (70.9)	20 (8.2)	254 (69.2)	9 (5.0)	218 (47.1)

In the PRIMA study, the following adverse events (all grades) occurred at a ≥10% higher incidence in the niraparib group than in the placebo group: anaemia (307 patients [63.4%] in the niraparib group and 43 patients [17.6%] in the placebo group); nausea (278 patients [57.4%] and 67 patients [27.5%]); thrombocytopenia (222 patients [45.9%] and 9 patients [3.7%]); constipation (189 patients [39.0%] and 46 patients [18.9%]); platelet count decreased (133 patients [27.5%] and 3 patients [1.2%]); neutropenia (128 patients [26.4%] and 16 patients [6.6%]); headache (126 patients [26.0%] and 36 patients [14.8%]); insomnia (119 patients [24.6%] and 35 patients [14.3%]); vomiting (108 patients [22.3%] and 29 patients [11.9%]); decreased appetite (92 patients [19.0%] and 20 patients [8.2%]); neutrophil count decreased (82 patients [16.9%] and 5 patients [2.0%]); and white blood cell count decreased (74 patients [15.3%] and 8 patients [3.3%]). The following Grade ≥3 adverse events occurred at a ≥5% higher incidence in the niraparib group than in the placebo group: anaemia (150 patients [31.0%] and 4 patients [1.6%]); thrombocytopenia (139 patients [28.7%] and 1 patient [0.4%]); platelet count decreased (63 patients [13.0%] and 0); neutropenia (62 patients [12.8%] and 3 patients [1.2%]); and neutrophil count decreased (37 patients [7.6%] and 0). Serious adverse events with a ≥5% higher incidence in the niraparib group than in the placebo group were thrombocytopenia (59 patients [12.2%] and 0) and anaemia (27 patients [5.6%] and 0). Adverse events leading to treatment interruption with a≥5% higher incidence in the niraparib group than in the placebo group were thrombocytopenia (180 patients [37.2%] and 0), anaemia (151 patients [31.2%] and 2 patients [0.8%]), platelet count decreased (109 patients [22.5%] and 0), neutropenia (55 patients [11.4%] and 2 patients [0.8%]), and neutrophil count decreased (36 patients [7.4%] and 0). Adverse events leading to dose reduction with a ≥5% higher incidence in the niraparib group than in the placebo group were thrombocytopenia (149 patients [30.8%] and 0), anaemia (131 patients [27.1%] and 2 patients [0.8%]), platelet count decreased (90 patients [18.6%] and 0), neutropenia (39 patients [8.1%] and 3 patients [1.2%]), and neutrophil count decreased (24 patients [5.0%] and 0). No adverse events resulting in death or leading to treatment discontinuation occurred at a ≥5% higher incidence in the niraparib group than in the placebo group.

In the NOVA study, the following adverse events (all grades) occurred at a ≥10% higher incidence in the niraparib group than in the placebo group: nausea (272 patients [74.1%] in the niraparib group and 64 patients [35.8%] in the placebo group); anaemia (181 patients [49.3%] and 12 patients [6.7%]); fatigue (172 patients [46.9%] and 58 patients [32.4%]); thrombocytopenia (170 patients [46.3%] and 6 patients [3.4%]); constipation (152 patients [41.4%] and 38 patients [21.2%]); vomiting (131 patients [35.7%] and 31 patients [17.3%]);

headache (98 patients [26.7%] and 19 patients [10.6%]); decreased appetite (95 patients [25.9%] and 26 patients [14.5%]); insomnia (91 patients [24.8%] and 15 patients [8.4%]); hypertension (77 patients [21.0%] and 9 patients [5.0%]); platelet count decreased (77 patients [21.0%] and 3 patients [1.7%]); dyspnoea (72 patients [19.6%] and 15 patients [8.4%]); neutropenia (66 patients [18.0%] and 6 patients [3.4%]); cough (61 patients [16.6%] and 9 patients [5.0%]); and neutrophil count decreased (51 patients [13.9%] and 5 patients [2.8%]). The following Grade ≥3 adverse events of occurred at a of ≥5% higher incidence in the niraparib group than in the place group: thrombocytopenia (106 patients [28.9%] and 1 patient [0.6%]); anaemia (92 patients [25.1%] and none); neutropenia (42 patients [11.4%] and 1 patient [0.6%]); neutrophil count decreased (33 patients [9.0%] and 2 patients [1.1%]); hypertension (32 patients [8.7%] and 4 patients [2.2%]); platelet count decreased (27 patients [7.4%] and none); and fatigue (21 patients [5.7%] and none). A serious adverse event with a ≥5% higher incidence in the niraparib group than in the placebo group was thrombocytopenia (40 patients [10.9%] and none). Adverse events leading to treatment interruption and occurring at an incidence of ≥5% higher incidence in the niraparib group than in the placebo group were thrombocytopenia (115 patients [31.3%] and 1 patient [0.6%]), anaemia (72 patients [19.6%] and none), neutropenia (38 patients [10.4%] and 2 patients [1.1%]), platelet count decreased (33 patients [9.0%] and none), nausea (28 patients [7.6%] and 4 patients [2.2%]), and neutrophil count decreased (19 patients [5.2%] and none). Adverse events leading to dose reduction and occurring at a of ≥5% higher incidence in the niraparib group than in the placebo group were thrombocytopenia (112 patients [30.5%] and 1 patient [0.6%]), anaemia (66 patients [18.0%] and none), platelet count decreased (38 patients [10.4%] and none), and nausea (19 patients [5.2%] and none). No adverse events resulting in death or leading to treatment discontinuation occurred at a ≥5% higher incidence in the niraparib group than in the placebo group.

In the QUADRA study, the following adverse events (all grades) occurred at an incidence of ≥20%: nausea in 312 patients (67.4%); fatigue in 237 patients (51.2%); anaemia in 229 patients (49.5%): vomiting in 205 patients (44.3%); thrombocytopenia in 159 patients (34.3%); constipation in 159 patients (34.3%); decreased appetite in 122 patients (26.3%); platelet count decreased in 101 patients (21.8%); insomnia in 98 patients (21.2%); and abdominal pain in 97 patients (21.0%). The following Grade ≥3 adverse events of occurred at an incidence of ≥5%: anaemia in 122 patients (26.3%); thrombocytopenia in 95 patients (20.5%); nausea in 45 patients (9.7%); platelet count decreased in 42 patients (9.1%); neutropenia in 38 patients (8.2%); vomiting in 37 patients (8.0%); small intestinal obstruction in 30 patients (6.5%); abdominal pain in 29 patients (6.3%); fatigue in 29 patients (6.3%); neutrophil count decreased in 23 patients (5.0%); and hypertension in 23 patients (5.0%). Serious adverse events with an incidence of ≥5% were small intestinal obstruction in 34 patients (7.3%), thrombocytopenia in 34 patients (7.3%), and vomiting in 27 patients (5.8%). Adverse events leading to treatment interruption and occurring at an incidence of ≥5% were thrombocytopenia in 109 patients (23.5%), platelet count decreased in 59 patients (12.7%), anaemia in 57 patients (12.3%), nausea in 46 patients (9.9%), and vomiting in 41 patients (8.9%). Adverse events leading to dose reduction and occurring at an incidence of ≥5% were thrombocytopenia in 65 patients (14.0%), anaemia in 60 patients (13.0%), and platelet count decreased in 36 patients (7.8%). No adverse events resulting in death or leading to treatment discontinuation occurred at an incidence of ≥5%.

The above results suggest that no clear differences in the safety profile of niraparib exist between the niraparib group in the PRIMA and NOVA studies and the QUADRA study.

The applicant's explanation about the differences in the safety of niraparib between Japanese and non-Japanese patients based on data available from Studies 2001 and 2002, the niraparib group of the NOVA study, and the QUADRA study:

The clinical safety observed in Japanese patients in Studies 2001 and 2002 and non-Japanese patients in the QUADRA study and the niraparib group of the NOVA study is summarized in Table 27.

Table 27. Summary of clinical safety (Studies 2001 and 2002, and NOVA and QUADRA studies)

	Number of subjects (%)			
	Study 2001	Study 2002	NOVA study	QUADRA study
	n = 19	n = 20	Niraparib n = 367	n = 463
All adverse events	19 (100)	20 (100)	367 (100)	461 (99.6)
Grade ≥3 adverse events	9 (47.4)	15 (75.0)	278 (75.7)	338 (73.0)
Adverse events resulting in death	0	0	1 (0.3)	9 (1.9)
Serious adverse events	1 (5.3)	4 (20.0)	117 (31.9)	197 (42.5)
Adverse events leading to treatment discontinuation	0	1 (5.0)	60 (16.3)	98 (21.2)
Adverse events leading to treatment interruption	15 (78.9)	15 (75.0)	251 (68.4)	288 (62.2)
Adverse events leading to dose reduction	15 (78.9)	14 (70.0)	254 (69.2)	218 (47.1)

(a) Maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer

In Study 2001 and the niraparib group of the NOVA study, the following adverse events (all grades) occurred at a ≥10% higher incidence in Japanese patients than in non-Japanese patients: platelet count decreased (12 Japanese patients [63.2%] and 77 non-Japanese patients [21.0%]); neutrophil count decreased (9 Japanese patients [47.4%] and 51 non-Japanese patients [13.9%]); decreased appetite (7 Japanese patients [36.8%] and 95 non-Japanese patients [25.9%]); and white blood cell count decreased (6 Japanese patients [31.6%] and 37 non-Japanese patients [10.1%]). Grade ≥3 adverse events occurring at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were platelet count decreased (5 Japanese patients [26.3%] and 27 non-Japanese patients [7.4%]), neutrophil count decreased (4 Japanese patients [21.1%] and 33 non-Japanese patients [9.0%]), and white blood cell count decreased (2 Japanese patients [10.5%], 8 patients [2.2%]). Adverse events leading to treatment interruption and occurring at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were platelet count decreased (10 Japanese patients [52.6%] and 33 non-Japanese patients [9.0%]), neutrophil count decreased (4 Japanese patients [21.1%] and 19 non-Japanese patients [5.2%]), nausea (3 Japanese patients [15.8%] and 28 non-Japanese patients [7.6%]), malaise (1 Japanese patient [5.3%] and 1 non-Japanese patient [0.3%]), and oropharyngeal discomfort (1 Japanese patient [5.3%] and no non-Japanese patient). The following adverse events leading to dose reduction occurred at a ≥5% higher incidence in Japanese patients than in non-Japanese patients: platelet count decreased (9 Japanese patients [47.4%] and 38 non-patients [10.4%]); neutrophil count decreased (4 Japanese patients [21.1%] and 15 non-Japanese patients [4.1%]); nausea (3 Japanese patients [15.8%] and 19 non-Japanese patients [5.2%]); vomiting (2 Japanese patients [10.5%] and 8 non-Japanese patients [2.2%]); malaise (1 Japanese patient [5.3%] and 1 non-Japanese patient [0.3%]); white blood cell count decreased (1 Japanese patient [5.3%] and 1 non-Japanese patient [0.3%]); headache (1 Japanese patient [5.3%] and no non-Japanese patient); and oropharyngeal

discomfort (1 Japanese patient [5.3%] and no non-Japanese patient). No adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation occurred at a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

(b) Recurrent ovarian cancer with homologous recombination deficiency

In the QUADRA study and Study 2002, the following adverse events (all grades) occurred at a ≥10% higher incidence in Japanese patients than in non-Japanese patients: anaemia (14 Japanese patients [70.0%] and 229 non-Japanese patients [49.5%]); platelet count decreased (11 Japanese patients [55.0%] and 101 non-Japanese patients [21.8%]); headache (6 Japanese patients [30.0%] and 87 non-Japanese patients [18.8%]); neutrophil count decreased (6 Japanese patients [30.0%] and 41 non-Japanese patients [8.9%]); malaise (6 Japanese patients [30.0%] and 6 non-Japanese patients [1.3%]); palpitations (4 Japanese patients [20.0%] and 34 non-Japanese patients [7.3%]); epistaxis (3 Japanese patients [15.0%] and 22 non-Japanese patients [4.8%]); dysgeusia (3 Japanese patients [15.0%] and 20 non-Japanese patients [4.3%]); and nasopharyngitis (3 Japanese patients [15.0%] and 13 non-Japanese patients [2.8%]). Grade ≥3 adverse events occurring at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were anaemia (11 Japanese patients [55.0%] and 122 non-Japanese patients [26.3%]), platelet count decreased (6 Japanese patients [30.0%] and 42 non-Japanese patients [9.1%]), neutrophil count decreased (4 Japanese patients [20.0%] and 23 non-Japanese patients [5.0%]), and white blood cell count decreased (2 Japanese patients [10.0%] and 18 non-Japanese patients [3.9%]). Serious adverse events with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were anaemia (2 Japanese patients [10.0%] and 15 non-Japanese patients [3.2%]) and platelet count decreased (2 Japanese patients [10.0%] and 7 non-Japanese patients [1.5%]). An adverse event leading to treatment discontinuation and occurring at a ≥5% higher incidence in Japanese patients than in non-Japanese patients was white blood cell count decreased (1 Japanese patient [5.0%] and no non-Japanese patient). Adverse events leading to treatment interruption and occurring at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were anaemia (10 Japanese patients [50.0%] and 57 non-Japanese patients [12.3%]), platelet count decreased (9 Japanese patients [45.0%] and 59 non-Japanese patients [12.7%]), neutrophil count decreased (4 Japanese patients [20.0%] and 8 non-Japanese patients [1.7%]), and white blood cell count decreased (2 Japanese patients [10.0%] and 12 non-Japanese patients [2.6%]). Adverse events leading to dose reduction and occurring at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were anaemia (9 Japanese patients [45.0%] and 60 non-Japanese patients [13.0%]), platelet count decreased (8 Japanese patients [40.0%] and 36 non-Japanese patients [7.8%]), neutrophil count decreased (3 Japanese patients [15.0%] and 13 non-Japanese patients [2.8%]), nausea (2 Japanese patients [10.0%] and 20 non-Japanese patients [4.3%]), hypertension (1 Japanese patient [5.0%] and no non-Japanese patient), and lymphocyte count decreased (1 Japanese patient [5.0%] and no non-Japanese patient). No adverse events resulting in death occurred at a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:

During the treatment with niraparib, caution should be used against adverse events (e.g., events related to bone marrow suppression and hypertension) occurring at a higher incidence in the niraparib group than in the placebo group in the PRIMA and NOVA studies. The package insert should inform healthcare professionals of the

occurrence of these events appropriately. Patients with ovarian cancer in response to their first-line chemotherapy were targeted for the PRIMA study, but safety data of niraparib in Japanese patients with this condition have not been available. Besides, only a limited number of Japanese patients were enrolled in Studies 2001 and 2002. These circumstances preclude a strict comparison of differences in the safety of niraparib between Japanese and non-Japanese. However, in light of the following observations, niraparib is tolerable in Japanese patients as well when appropriate measures including treatment interruption, dose reduction, or treatment discontinuation of niraparib are taken. Meanwhile, adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients deserve attention, and the occurrence of these adverse events should be appropriately communicated to healthcare professionals via the package insert, etc.

- While bone marrow suppression-related adverse events occurred at a higher incidence in Japanese patients than in non-Japanese patients, no obvious differences were observed in the incidences of deaths or adverse events leading to treatment discontinuation between these patient groups.
- The majority of the adverse events, except for those related to bone marrow suppression, occurring at a higher incidence in Japanese patients than in non-Japanese patients were Grade ≤2.
- No clear differences were observed in the safety profiles of niraparib among the niraparib group of the PRIMA and NOVA studies and the QUADRA study.
- Although the starting dose was fixed as 300 mg in the Japanese clinical studies (Studies 2001 and 2002), the risk of adverse events related to bone marrow suppression can be reduced by the use of an individualized starting dose [see Section 7.R.6.1].

In the following sections, based on the safety results of the PRIMA, NOVA, and QUADRA studies and Studies 2001 and Study 2002, PMDA review data with a focus on adverse events with a higher incidence in the niraparib group than in the control group in the PRIMA and NOVA studies, adverse events with a higher incidence in Study 2001 or 2002 than in the QUADRA study or in the niraparib group of the NOVA study, and attention-requiring adverse events of a drug (olaparib) with an action mechanism similar to niraparib.

7.R.2.2 Bone marrow suppression

The applicant's explanation about bone marrow suppression associated with niraparib:

Tables 28 and 29 list events related bone marrow suppression falling under the MedDRA SMQ of "Haematopoietic cytopenias (broad scope)."

Table 28. Occurrence of bone marrow suppression with an incidence of ≥3% in any group (PRIMA and NOVA studies)

PT*	Number of subjects (%)							
	PRIMA study				NOVA study			
	Niraparib n = 484		Placebo n = 244		Niraparib n = 367		Placebo n = 179	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Bone marrow suppression	414 (85.5)	290 (59.9)	64 (26.2)	7 (2.9)	280 (76.3)	209 (56.9)	32 (17.9)	4 (2.2)
Anaemia	307 (63.4)	150 (31.0)	43 (17.6)	4 (1.6)	181 (49.3)	92 (25.1)	12 (6.7)	0
Thrombocytopenia	222 (45.9)	139 (28.7)	9 (3.7)	1 (0.4)	170 (46.3)	106 (28.9)	6 (3.4)	1 (0.6)
Platelet count decreased	133 (27.5)	63 (13.0)	3 (1.2)	0	77 (21.0)	27 (7.4)	3 (1.7)	0
Neutropenia	128 (26.4)	62 (12.8)	16 (6.6)	3 (1.2)	66 (18.0)	42 (11.4)	6 (3.4)	1 (0.6)
Neutrophil count decreased	82 (16.9)	37 (7.6)	5 (2.0)	0	51 (13.9)	33 (9.0)	5 (2.8)	2 (1.1)
White blood cell count decreased	74 (15.3)	12 (2.5)	8 (3.3)	0	37 (10.1)	8 (2.2)	5 (2.8)	0
Leukopenia	57 (11.8)	10 (2.1)	13 (5.3)	0	28 (7.6)	10 (2.7)	9 (5.0)	0
Lymphocyte count decreased	25 (5.2)	3 (0.6)	3 (1.2)	1 (0.4)	8 (2.2)	5 (1.4)	2 (1.1)	0
Lymphopenia	12 (2.5)	0	0	0	6 (1.6)	1 (0.3)	3 (1.7)	1 (0.6)

* The MedDRA version used was 20.0 for the PRIMA study and 18.0 for the NOVA study.

Table 29. Occurrence of bone marrow suppression with an incidence of ≥3% in any group (QUADRA study and Studies 2001 and 2002)

PT*	Number of subjects (%)					
	QUADRA study n = 463		Study 2001 n = 19		Study 2002 n = 20	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Bone marrow suppression	330 (71.3)	231 (49.9)	17 (89.5)	9 (47.4)	16 (80.0)	13 (65.0)
Anaemia	229 (49.5)	122 (26.3)	3 (15.8)	1 (5.3)	14 (70.0)	11 (55.0)
Thrombocytopenia	159 (34.3)	95 (20.5)	1 (5.3)	1 (5.3)	0	0
Platelet count decreased	101 (21.8)	42 (9.1)	12 (63.2)	5 (26.3)	11 (55.0)	6 (30.0)
Neutropenia	55 (11.9)	38 (8.2)	3 (15.8)	1 (5.3)	0	0
Neutrophil count decreased	41 (8.9)	23 (5.0)	9 (47.4)	4 (21.1)	6 (30.0)	4 (20.0)
White blood cell count decreased	55 (11.9)	18 (3.9)	6 (31.6)	2 (10.5)	4 (20.0)	2 (10.0)
Leukopenia	32 (6.9)	13 (2.8)	2 (10.5)	0	0	0
Lymphocyte count decreased	29 (6.3)	16 (3.5)	0	0	1 (5.0)	1 (5.0)
Lymphopenia	15 (3.2)	11 (2.4)	0	0	0	0

* The MedDRA ver. 21.0 was used for the QUADRA study and Studies 2001 and 2002.

In the PRIMA study, serious bone marrow suppression occurred in 106 of 484 patients (21.9%) in the niraparib group (thrombocytopenia in 59 patients, anaemia in 27 patients, platelet count decreased in 20 patients, neutropenia in 6 patients, febrile neutropenia in 3 patients, myelodysplastic syndrome, neutropenic sepsis, neutrophil count decreased, and pancytopenia in 1 patient each [including patients experiencing multiple events]). Among them, a causal relationship with niraparib was not ruled out in 105 patients in the niraparib group (thrombocytopenia in 59 patients, anaemia in 26 patients, platelet count decreased in 20 patients, neutropenia in 6 patients, febrile neutropenia in 3 patients, myelodysplastic syndrome, neutropenic sepsis, neutrophil count decreased, and pancytopenia in 1 patient each [including patients experiencing multiple events]) (No such events occurred in the placebo group). Bone marrow suppression led to treatment discontinuation in 32 of 484 patients (6.6%) in the niraparib group (thrombocytopenia in 18 patients, anaemia in 9 patients, neutropenia in 6 patients, neutrophil count decreased and platelet count decreased in 3 patients each, leukopenia and white blood cell count decreased in 1 patient each [including patients experiencing multiple events]) (No such events occurred in the placebo group). Bone marrow suppression led to treatment interruption in 337 of 484 patients (69.6%) in the niraparib group (thrombocytopenia in 180 patients, anaemia in 151 patients, platelet count decreased in 109 patients, neutropenia in 55 patients, neutrophil count decreased in 36 patients, leukopenia in 9 patients, white blood cell count decreased in 7 patients, febrile neutropenia in 2

patients, haemoglobin decreased, lymphocyte count decreased, lymphopenia, monocyte count decreased, neutropenic sepsis, pancytopenia, and red blood cell count decreased in 1 patient each [including patients experiencing more than one event)). Bone marrow suppression led to treatment interruption in 4 of 244 patients (1.6%) in the placebo group (anaemia and neutropenia in 2 patients each). Bone marrow suppression led to dose reduction in 317 of 484 patients (65.5%) in the niraparib group (thrombocytopenia in 149 patients, anaemia in 131 patients, platelet count decreased in 90 patients, neutropenia in 39 patients, neutrophil count decreased in 24 patients, white blood cell count decreased in 5 patients, febrile neutropenia, leukopenia, lymphocyte count decreased, neutropenic sepsis, and pancytopenia in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to dose reduction in 5 of 244 patients (2.0%) in the placebo group (neutropenia in 3 patients and anaemia in 2 patients). No bone marrow suppression resulted in death.

In the NOVA study, serious bone marrow suppression occurred in 56 of 367 patients (15.3%) in the niraparib group (thrombocytopenia in 40 patients, anaemia in 15 patients, myelodysplastic syndrome in 3 patients, neutropenia and pancytopenia in 2 patients each, febrile neutropenia, neutrophil count decreased, and platelet count decreased in 1 patient each [including patients experiencing multiple events]). Among them, a causal relationship with niraparib was not ruled out in 56 patients in the niraparib group (thrombocytopenia in 40 patients, anaemia in 15 patients, myelodysplastic syndrome in 3 patients, neutropenia and pancytopenia in 2 patients each, neutrophil count decreased and platelet count decreased in 1 patient each [including patients experiencing more than one event]) (No such event occurred in the placebo group). Bone marrow suppression led to treatment discontinuation in 28 of 367 patients (7.6%) in the niraparib group (thrombocytopenia in 7 patients, platelet count decreased in 6 patients, anaemia in 5 patients, neutrophil count decreased in 4 patients, neutropenia in 3 patients, myelodysplastic syndrome in 2 patients, and pancytopenia in 1 patient) and 1 of 179 patients (0.6%) in the placebo group (thrombocytopenia in 1 patient). Bone marrow suppression led to treatment interruption 194 of 367 patients (52.9%) in the niraparib group (thrombocytopenia in 115 patients, anaemia in 72 patients, neutropenia in 38 patients, platelet count decreased in 33 patients, neutrophil count decreased in 19 patients, leukopenia in 10 patients, white blood cell count decreased in 5 patients, haemoglobin decreased and lymphocyte count decreased in 2 patients each, myelodysplastic syndrome and pancytopenia in 1 patient each [including patients experiencing multiple events]) and 2 of 179 patients (1.1%) in the placebo group (neutropenia in 2 patients and thrombocytopenia in 1 patient [including patients experiencing multiple events]). Bone marrow suppression led to dose reduction in 211 of 367 patients (57.5%) in the niraparib group (thrombocytopenia in 112 patients, anaemia in 66 patients, platelet count decreased in 38 patients, neutropenia in 17 patients, neutrophil count decreased in 15 patients, haemoglobin decreased and leukopenia in 3 patients each, pancytopenia and white blood cell count decreased in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to dose reduction in 3 of 179 patients (1.7%) in the placebo group (neutrophil count decreased in 2 patients and thrombocytopenia in 1 patient). No bone marrow suppression resulted in death.

In the QUADRA study, serious bone marrow suppression occurred in 58 of 463 patients (12.5%) (thrombocytopenia in 34 patients, anaemia in 15 patients, neutropenia in 11 patients, platelet count decreased

in 7 patients, leukopenia and lymphopenia in 3 patients each, neutrophil count decreased and pancytopenia in 2 patients each, bone marrow failure, haemoglobin decreased, myelodysplastic syndrome, and normochromic anaemia in 1 patient each [including patients experiencing multiple events]). Among them, a causal relationship with niraparib was not ruled out in 57 patients (thrombocytopenia in 34 patients, anaemia in 15 patients, neutropenia in 11 patients, platelet count decreased in 7 patients, leukopenia in 3 patients, lymphopenia, neutrophil count decreased, and pancytopenia in 2 patients each, bone marrow failure, haemoglobin decreased, myelodysplastic syndrome, and normochromic anaemia in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to treatment discontinuation in 28 of 463 patients (6.0%) (thrombocytopenia in 16 patients, anaemia in 7 patients, platelet count decreased in 3 patients, neutropenia and neutrophil count decreased in 2 patients each, bone marrow failure, haemoglobin in 1 patient, and pancytopenia in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to treatment interruption in 192 of 463 patients (41.5%) (thrombocytopenia in 109 patients, platelet count decreased in 59 patients, anaemia in 57 patients, neutropenia in 19 patients, leukopenia in 12 patients, neutrophil count decreased in 8 patients, leukopenia in 7 patients, haemoglobin decreased in 4 patients, lymphopenia in 2 patients, lymphocyte count decreased and pancytopenia in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to dose reduction in 165 of 463 patients (35.6%): thrombocytopenia in 65 patients, anaemia in 60 patients, platelet count decreased in 36 patients, neutropenia in 16 patients, neutrophil count decreased in 13 patients, white blood cell count decreased in 4 patients, haemoglobin decreased in 2 patients, leukopenia and lymphopenia in 1 patient each [including patients experiencing multiple events]). No bone marrow suppression resulted in death.

In Study 2001, serious bone marrow suppression occurred in 1 of 19 patients (5.3%, thrombocytopenia in 1 patient), and a causal relationship with niraparib was not ruled out for the event. Bone marrow suppression led to treatment interruption in 13 of 19 patients (68.4%) (platelet count decreased in 10 patients, neutrophil count decreased in 4 patients, anaemia, neutropenia, thrombocytopenia, and white blood cell count decreased in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to dose reduction in 13 of 19 patients (68.4%) (platelet count decreased in 9 patients, neutrophil count decreased in 4 patients, anaemia, neutropenia, thrombocytopenia, and white blood cell count decreased in 1 patient each [including patients experiencing multiple events). No bone marrow suppression resulted in death or led to treatment discontinuation.

In Study 2002, serious bone marrow suppression occurred in 4 of 20 patients (20.0%, anaemia and platelet count decreased in 2 patients each), and a causal relationship with niraparib was not ruled out in any cases. Bone marrow suppression led to treatment discontinuation in 1 of 20 patients (5.0%: neutrophil count decreased, platelet count decreased, and white blood cell count decreased in 1 patient each (multiple events occurred in the patient). Bone marrow suppression led to treatment interruption in 13 of 20 patients (65.0%): anaemia in 10 patients, platelet count decreased in 9 patients, neutrophil count decreased in 4 patients, white blood cell count decreased in 2 patients, lymphocyte count decreased in 1 patient (including patients experiencing multiple events). Bone marrow suppression led to dose reduction in 11 of 20 patients (55.0%): anaemia in 9 patients, platelet count decreased in 8 patients, neutrophil count decreased in 3 patients, lymphocyte count

decreased, and white blood cell count decreased in 1 patient each (including patients experiencing multiple events). No bone marrow suppression resulted in death.

The median (range) time to the first onset of bone marrow suppression was 21 days (1 to 421 days) in the niraparib group of the PRIMA study, 21.5 days (-41[46] to 683 days)[47] in the niraparib group of the NOVA study, 20.5 days (1 to 336 days) in the QUADRA study, 15 days (8 to 29 days) in Study 2001, and 22.0 days (8 to 88 days) in Study 2002.

The occurrence of bone marrow suppression in the PRIMA study is summarized for each starting dose group in Table 30.

Table 30. Occurrence of bone marrow suppression with an incidence of ≥3% in any group (PRIMA study, by starting dose)

PT (MedDRA ver. 20.0)	Number of subjects (%)					
	Niraparib					
	Overall n = 484		Fixed starting dose n = 315		Individualized starting dose n = 169	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Bone marrow suppression	414 (85.5)	290 (59.9)	286 (90.8)	213 (67.6)	128 (75.7)	77 (45.6)
Anaemia	307 (63.4)	150 (31.0)	223 (70.8)	112 (35.6)	84 (49.7)	38 (22.5)
Thrombocytopenia	222 (45.9)	139 (28.7)	165 (52.4)	114 (36.2)	57 (33.7)	25 (14.8)
Platelet count decreased	133 (27.5)	63 (13.0)	95 (30.2)	51 (16.2)	38 (22.5)	12 (7.1)
Neutropenia	128 (26.4)	62 (12.8)	87 (27.6)	46 (14.6)	41 (24.3)	16 (9.5)
Neutrophil count decreased	82 (16.9)	37 (7.6)	61 (19.4)	28 (8.9)	21 (12.4)	9 (5.3)
White blood cell count decreased	74 (15.3)	12 (2.5)	51 (16.2)	7 (2.2)	23 (13.6)	5 (3.0)
Leukopenia	57 (11.8)	10 (2.1)	37 (11.7)	7 (2.2)	20 (11.8)	3 (1.8)
Lymphocyte count decreased	25 (5.2)	3 (0.6)	16 (5.1)	2 (0.6)	9 (5.3)	1 (0.6)

In the niraparib group of the PRIMA study, serious bone marrow suppression occurred in 79 of 315 patients (25.1%) in the fixed starting dose group (thrombocytopenia in 52 patients, anaemia in 13 patients, platelet count decreased in 15 patients, neutropenia in 4 patients, febrile neutropenia in 2 patients, myelodysplastic syndrome, neutrophil count decreased, and pancytopenia in 1 patient each [including patients experiencing multiple events]). Serious bone marrow suppression occurred in 27 of 169 patients (16.0%) in the individualized starting dose group (anaemia in 14 patients, thrombocytopenia in 7 patients, platelet count decreased in 5 patients, neutropenia in 2 patients, febrile neutropenia and neutropenic sepsis in 1 patient each [including patients experiencing multiple events]). A causal relationship was not ruled out in 79 patients in the fixed starting dose group (thrombocytopenia in 52 patients, anaemia in 13 patients, platelet count decreased in 15 patients, neutropenia in 4 patients, febrile neutropenia in 2 patients, myelodysplastic syndrome, neutrophil count decreased, and pancytopenia in 1 patient each [including patients experiencing multiple events]) and 26 patients in the individualized starting dose group (anaemia in 13 patients, thrombocytopenia in 7 patients, platelet count decreased in 5 patients, neutropenia in 2 patients, febrile neutropenia and neutropenic sepsis in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to treatment discontinuation in 21 of 315 patients (6.7%) in the fixed starting dose group (thrombocytopenia in 14 patients,

46) In the NOVA study, collected events included those occurred before starting the treatment with niraparib and were assessed by investigators as related to niraparib. Therefore, some events showed a time to the first onset time by a negative value.

47) The median (range) time to the first onset of events in the NOVA study was 22.0 days (1 to 683 days) when only based on bone marrow suppression-related events which occurred after the start of treatment with niraparib.

anaemia and neutropenia in 4 patients each, neutrophil count decreased and platelet count decreased in 2 patients each, leukopenia and white blood cell count decreased in 1 patient each [including patients experiencing multiple events]) and 11 of 169 patients (6.5%) in the individualized starting dose group (anaemia in 5 patients, thrombocytopenia in 4 patients, neutropenia in 2 patients, neutrophil count decreased and platelet count decreased in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to treatment interruption in 238 of 315 patients (75.6%) in the fixed starting dose group (thrombocytopenia in 140 patients, anaemia in 114 patients, platelet count decreased in 80 patients, neutropenia in 38 patients, neutrophil count decreased in 29 patients, leukopenia in 7 patients, white blood cell count decreased in 5 patients, febrile neutropenia in 2 patients, haemoglobin decreased, lymphocyte count decreased, lymphopenia, pancytopenia, and red blood cell count decreased in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to treatment interruption in 99 of 169 patients (58.6%) in the individualized starting dose group (thrombocytopenia in 40 patients, anaemia in 37 patients, platelet count decreased in 29 patients, neutropenia in 17 patients, neutrophil count decreased in 7 patients, leukopenia in 2 patients, white blood cell count decreased in 2 patients, monocyte count decreased and neutropenic sepsis in 1 patient each [including patients experiencing multiple events]). Bone marrow suppression led to dose reduction in 226 of 315 patients (71.7%) in the fixed starting dose group (thrombocytopenia in 120 patients, anaemia in 98 patients, platelet count decreased in 67 patients, neutropenia in 26 patients, neutrophil count decreased in 19 patients, white blood cell count decreased in 3 patients, febrile neutropenia, leukopenia, lymphocyte count decreased and pancytopenia in 1 patient each [including patients experiencing multiple events). Bone marrow suppression led to dose reduction in 91 of 169 patients (53.8%) in the individualized starting dose group (anaemia in 33 patients, thrombocytopenia in 29 patients, platelet count decreased in 23 patients, neutropenia in 13 patients, neutrophil count decreased in 5 patients, white blood cell count decreased in 2 patients, and neutropenic sepsis in 1 patient [including patients experiencing multiple events]). No bone marrow suppression resulted in death.

PMDA's view:
In the PRIMA study, the incidences of Grade ≥3 or serious bone marrow suppression-related adverse events were lower in the individualized starting dose group than in the fixed starting dose group, but the incidence of bone marrow suppression was higher in the niraparib group than in the placebo group. Given these, caution should be exercised against bone marrow suppression such as thrombocytopenia and anemia during treatment with niraparib. Healthcare professionals should be informed of the occurrence of bone marrow suppression in the clinical studies appropriately via the package insert, etc.

7.R.2.3 Hypertension

The applicant's explanation about hypertension associated with niraparib:
Hypertension-related events falling under the MedDRA SMQ "Hypertension (narrow scope)" were aggregated.

The occurrence of hypertension in the PRIMA, NOVA, and QUADRA studies and Studies 2001 and 2002 are summarized in Tables 31 and 32. No hypertension was reported in Study 2001.

Table 31. Occurrence of hypertension (PRIMA and NOVA studies)

PT*	Number of subjects (%)							
	PRIMA study				NOVA study			
	Niraparib n = 484		Placebo n = 244		Niraparib n = 367		Placebo n = 179	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hypertension	86 (17.8)	30 (6.2)	17 (7.0)	3 (1.2)	79 (21.5)	34 (9.3)	10 (5.6)	4 (2.2)
Hypertension	82 (16.9)	29 (6.0)	17 (7.0)	3 (1.2)	77 (21.0)	32 (8.7)	9 (5.0)	4 (2.2)
Blood pressure increased	5 (1.0)	1 (0.2)	0	0	1 (0.3)	0	1 (0.6)	0
Hypertensive crisis	0	0	0	0	2 (0.5)	2 (0.5)	0	0

* The MedDRA version used was 20.0 for the PRIMA study and 18.0 for the NOVA study.

Table 32. Occurrence of hypertension (QUADRA study and Study 2002)

PT*	Number of subjects (%)			
	QUADRA study n = 463		Study 2002 n = 20	
	All grades	Grade ≥3	All grades	Grade ≥3
Hypertension	63 (13.6)	24 (5.2)	3 (15.0)	1 (5.0)
Hypertension	61 (13.2)	23 (5.0)	3 (15.0)	1 (5.0)
Blood pressure increased	2 (0.4)	1 (0.2)	0	0
Hypertensive crisis	0	0	0	0

* The MedDRA ver. 21.0 was used for the QUADRA study and Study 2002.

In the PRIMA study, serious hypertension occurred in 1 of 484 patients (0.2%) in the niraparib group (hypertension in 1 patient), and its causal relationship with niraparib was ruled out. No serious hypertension occurred in the placebo group. Hypertension led to treatment interruption in 8 of 484 patients (1.7%) in the niraparib group (hypertension in 8 patients) and 1 of 244 patients (0.4%) in the placebo group (hypertension in 1 patient). Hypertension led to dose reduction in 4 of 484 patients (0.8%) in the niraparib group (hypertension in 4 patients). No such events occurred in the placebo group. No hypertension resulted in death or led to treatment discontinuation.

In the NOVA study, serious hypertension occurred in 1 of 367 patients (0.3%) in the niraparib group (hypertensive crisis in 1 patient), and its causal relationship with niraparib was not ruled out. No serious hypertension occurred in the placebo group. Hypertension led to treatment discontinuation in 1 of 367 patients (0.3%) in the niraparib group (hypertensive crisis in 1 patient). No hypertension led to treatment discontinuation in the placebo group. Hypertension led to treatment interruption in 5 of 367 patients (1.4%) in the niraparib group (hypertension in 5 patients) and 1 of 179 patients (0.6%) in the placebo group (hypertension in 1 patient). Hypertension led to dose reduction in 5 of 367 patients (1.4%) in the niraparib group (hypertension in 5 patients). No hypertension led to dose reduction in the placebo group. No hypertension resulted in death.

In the QUADRA study, serious hypertension occurred in 8 of 463 patients (1.7%, hypertension in 8 patients), and its causal relationship with niraparib was not ruled out in 2 of the 8 patients (hypertension in 2 patients). Hypertension led to treatment discontinuation in 1 of 463 patients (0.2%, hypertension in 1 patient). Hypertension led to treatment interruption in 9 of 463 patients (1.9%, hypertension in 8 patients and blood pressure increased in 1 patient) and to dose reduction in 1 of 463 patients (0.2%, blood pressure increased in 1 patient). No hypertension resulted in death.

In Study 2002, hypertension led to treatment interruption in 1 of 20 patients (5.0%, hypertension). Hypertension led to dose reduction in 1 of 20 patients (5.0%, hypertension in 1 patient). No hypertension resulted in death, was serious, or led to treatment discontinuation.

The median (range) time to the first onset of hypertension was 56.5 days (1 to 589 days) in the niraparib group of the PRIMA study, 29.0 days (-312[46] to 947 days)[48] in the niraparib group of the NOVA study, 18.0 days (1 to 616 days) in the QUADRA study, and 29.0 days (15 to 47 days) in Study 2002.

Patients experiencing serious hypertension due to niraparib (related to niraparib) in the clinical studies of niraparib including those other than the above studies are shown in Table 33.

Table 33. List of patients experiencing serious hypertension (related to niraparib)

Study	Age	Dose (mg)	PT*1	Grade	Onset date (day)	Duration (day)	Action taken with niraparib	Outcome
NOVA	5[redacted]	300	Hypertensive crisis	3	51	6	N/A	Recovered
QUADRA	4[redacted]	300	Hypertension	3	10	5	N/A	Recovered
	5[redacted]	300	Hypertension	3	15	3	Interrupted	Recovered
PCR1002*2	UNK	UNK	Hypertension	UNK	28	UNK	Discontinued	Not recovered
	UNK	100	Hypertension	3	196	UNK	Interrupted	UNK
	8[redacted]	UNK	Hypertension	UNK	223	UNK	Continued	UNK
2017-0404*3	6[redacted]	400	Hypertension	3	1	1	Continued	Recovered
3000-02-004*4	5[redacted]	100	Hypertension	3	106	18	Discontinued	Recovered
	6[redacted]	300	Hypertension	4	20	2	Discontinued	Recovered
3000-02-005*5	6[redacted]	UNK	Hypertension	3	8	UNK	Discontinued	Not recovered
	7[redacted]	UNK	Hypertension	3	UNK	Approx. 48	Discontinued	Recovered
3000-03-005*6	8[redacted]	UNK	Hypertension	4	3	13	Discontinued	Recovered
3000-07-006*7	5[redacted]	300	Hypertension	4	UNK	2	Discontinued	Recovered with sequelae
	7[redacted]	300	Hypertension	UNK	UNK	UNK	Dose reduced	Recovered
	6[redacted]	300	Hypertension	1	UNK	UNK	UNK	UNK
	6[redacted]	300	Hypertension	2	UNK	UNK	Discontinued	Not recovered
	6[redacted]	300	Hypertension	1	UNK	UNK	Discontinued	Not recovered
	7[redacted]	200	Hypertension	UNK	20	UNK	Discontinued	UNK
	6[redacted]	300	Hypertension	UNK	UNK	UNK	Dose reduced	Recovered
3000-07-007*7	6[redacted]	UNK	Blood pressure increased	UNK	UNK	UNK	UNK	Recovered
3000-07-009*7	6[redacted]	UNK	Hypertension	3	47	13	Discontinued	Recovered
3000-07-010*7	6[redacted]	300	Hypertension	3	49	4	Discontinued	Recovered
	6[redacted]	300	Hypertensive crisis	UNK	3	UNK	Continued	Recovered
3000-07-014*7	5[redacted]	300	Hypertension	3	2	9	Discontinued	Recovered
3000-07-017*7	5[redacted]	300	Hypertension	2	17	15	Dose reduced	Recovered

*1, The MedDRA version used was 18.0 for the NOVA study, 21.0 for the QUADRA study, and 22.1 for other studies. *2, A foreign phase Ib study in patients with locally advanced or metastatic castration-resistant prostate cancer; *3, A foreign phase Ib study in patients with recurrent endometrial cancer or high-grade serous recurrent ovarian cancer; *4, A foreign phase II study in patients with advanced ovarian cancer who had received a platinum-based chemotherapy regimen and BV; *5, A foreign phase II study in patients with advanced solid cancer. *6, A foreign phase III study in patients with advanced solid cancer; *7, Compassionate Use Program

[48] The median (range) time to the first onset of hypertension that occurred after the start of treatment with niraparib in the NOVA study was 37.0 days (1 to 947 days).

PMDA asked the applicant to explain the mechanism of development and risk factors of hypertension associated with niraparib.

The applicant's answer:
Niraparib binds to the transporters of dopamine and norepinephrine, and might thus have been related to blood pressure increased. A subgroup analysis of the safety analysis set of the NOVA study revealed no clear differences in the incidence of Grade ≥3 hypertension by age, race, number of prior regimens, and other relevant parameters.

PMDA's view:
Hypertension including that of Grade ≥3 occurred at a certain percentage after the administration of niraparib in the clinical studies submitted. Serious events such as hypertensive crisis occurred, and a causal relationship with niraparib could not be ruled out for these events. Given these, caution should be exercised against hypertension during treatment with niraparib. Healthcare professionals should be informed of the occurrence of hypertension in the clinical studies appropriately via the package insert, etc.

7.R.2.4 ILD

The applicant's explanation about ILD associated with niraparib:
ILD-related events falling under the MedDRA SMQ "Interstitial lung disease (narrow scope)" were aggregated.

The occurrence of ILD in the PRIMA, NOVA, and QUADRA studies and Studies 2001 and 2002 is summarized in 34. No ILD occurred in the QUADRA study or Study 2001 or 2002.

Table 34. Occurrence of ILD (PRIMA and NOVA studies)

PT*	Number of subjects (%)							
	PRIMA study				NOVA study			
	Niraparib n = 484		Placebo n = 244		Niraparib n = 367		Placebo n = 179	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
ILD	5 (1.0)	0	0	0	2 (0.5)	0	1 (0.6)	0
Pneumonitis	4 (0.8)	0	0	0	2 (0.5)	0	1 (0.6)	0
ILD	1 (0.2)	0	0	0	0	0	0	0

* The MedDRA version used was 20.0 for the PRIMA study and 18.0 for the NOVA study.

In the PRIMA study, serious ILD occurred in 4 of 484 patients (0.8%) in the niraparib group (pneumonitis in 4 patients), and a causal relationship with niraparib was not ruled out in any cases. No serious IDL occurred in the placebo group. ILD led to treatment discontinuation in 1 of 484 patients (0.2%) in the niraparib group (pneumonitis in 1 patient). No such events occurred in the placebo group. ILD led to treatment interruption in 2 of 484 patients (0.4%) in the niraparib group (ILD and pneumonitis in 1 patient each). No such events occurred in the placebo group. ILD led to dose reduction in 1 of 484 patients (0.2%) in the niraparib group (pneumonitis in 1 patient). No such events occurred in the placebo group. No ILD resulted in death.

In the NOVA study, serious ILD occurred in 1 of 367 patients (0.3%) in the niraparib group (pneumonitis in 1 patient), for which a causal relationship with niraparib was ruled out. No serious ILD occurred in the placebo

group. ILD led to treatment interruption in 1 of 367 patients (0.3%) in the niraparib group (pneumonitis in 1 patient). No such events occurred in the placebo group. No ILD resulted in death or led to treatment discontinuation or dose reduction.

The median (range) time to the first onset of ILD was 99 days (49 to 589 days) in the niraparib group of the PRIMA study and 49.5 days (45 to 54 days) in the niraparib group of the NOVA study.

Details of patients experiencing serious ILD due to niraparib in the clinical studies of niraparib including those other than the above studies are shown in Table 35.

Table 35. List of patients with serious ILD (related to niraparib)

Study	Sex	Age	Carcinoma	Dose	PT[*1]	Grade	Onset date (day)	Duration (day)	Action taken with niraparib	Outcome
PRIMA	F	5[redacted]	Ovarian cancer	300	Pneumonitis	2	79	92	Discontinued	Recovered
	F	4[redacted]	Ovarian cancer	300	Pneumonitis	2	589	27	Continued	Recovered
	F	6[redacted]	Ovarian cancer	200	Pneumonitis	1	133	72	Continued	Recovered
	F	5[redacted]	Ovarian cancer	300	Pneumonitis	2	99	37	Dose reduced	Recovered
MK-4827-001[*2]	F	5[redacted]	Breast cancer	60	Pneumonitis	UNK	15	UNK	Discontinued	Recovered
PCR2002[*3]	M	6[redacted]	Prostate cancer	200	Pneumonitis	UNK	160	UNK	Continued	Recovering
PR-30-5011-C(a) [*4]	F	5[redacted]	Ovarian cancer	300	Pneumonitis	3	291	7	N/A	Recovered
UPCC35217[*5]	F	7[redacted]	Pancreatic cancer	300	Pneumonitis	3	113	UNK	Discontinued	UNK
3000-PN162-01-001[*6]	F	5[redacted]	Breast cancer	200	Pneumonitis	2	173	304	N/A	Recovered
3000-01-002[*7]	M	7[redacted]	Advanced solid cancer	300	Pneumonitis	2	UNK	35	Continued	Recovered
					Pneumonitis	3	UNK	1	Discontinued	Recovered
3000-02-001[*8]	M	8[redacted]	NSCLC	200	Pneumonitis	4	114	3	Continued	Recovered
3000-02-005	F	5[redacted]	Ovarian cancer	UNK	Pneumonitis	2	55	Approx. 88	Discontinued	Recovered
3000-07-010	F	6[redacted]	Ovarian cancer	300	Lung infiltrate	UNK	26	UNK	Discontinued	Recovering

*1, The MedDRA version used was 20.0 for the PRIMA study and 22.1 for other studies. *2, A foreign phase I study in patients with advanced solid cancer or hematopoietic malignancy; *A, a foreign phase Ib/II study in patients with metastatic castration-resistant prostate cancer; *4, A QTc sub-study of a foreign phase III study in patients with relapsed ovarian cancer in response to a platinum-based chemotherapy regimen; *5, A foreign phase Ib/II study in patients with unresectable pancreatic cancer without disease progression on a platinum-based chemotherapy regimen; *6, A foreign phase I/II study in patients with advanced solid cancer; *7, A foreign phase Ib study in patients with advanced solid cancer; *8, A foreign phase II study in patients with non-small cell lung cancer (NSCLC)

PMDA's view:

Serious ILD for which a causal relationship with niraparib could not be ruled out occurred in the clinical studies of niraparib, and ILD is a known risk for the approved PARP inhibitor (olaparib) (Review Report for Lynparza Tablets 100 and 150 mg, dated November 13, 2017). Given these, caution should be exercised against ILD during the treatment with niraparib. Healthcare professionals should be informed of the occurrence of ILD in the clinical studies appropriately via the package insert, etc.

7.R.2.5 Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders associated with niraparib:

Gastrointestinal disorder-related events falling under the MedDRA SOC "Gastrointestinal disorders" were aggregated.

The occurrence of gastrointestinal disorders in the PRIMA, NOVA, and QUADRA studies and Studies 2001 and 2002 is shown in Tables 36 and 37.

Table 36. Occurrence of gastrointestinal disorders with an incidence of ≥10% in any group (PRIMA and NOVA studies)

PT*	Number of subjects (%)							
	PRIMA study				NOVA study			
	Niraparib n = 484		Placebo n = 244		Niraparib n = 367		Placebo n = 179	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Gastrointestinal disorders	398 (82.2)	36 (7.4)	173 (70.9)	12 (4.9)	338 (92.1)	35 (9.5)	131 (73.2)	16 (8.9)
Nausea	278 (57.4)	6 (1.2)	67 (27.5)	2 (0.8)	272 (74.1)	12 (3.3)	64 (35.8)	2 (1.1)
Constipation	189 (39.0)	1 (0.2)	46 (18.9)	0	152 (41.4)	2 (0.5)	38 (21.2)	1 (0.6)
Vomiting	108 (22.3)	4 (0.8)	29 (11.9)	2 (0.8)	131 (35.7)	7 (1.9)	31 (17.3)	1 (0.6)
Abdominal pain	106 (21.9)	7 (1.4)	75 (30.7)	1 (0.4)	90 (24.5)	4 (1.1)	56 (31.3)	3 (1.7)
Diarrhoea	91 (18.8)	3 (0.6)	55 (22.5)	1 (0.4)	76 (20.7)	1 (0.3)	38 (21.2)	2 (1.1)
Abdominal pain upper	41 (8.5)	0	22 (9.0)	2 (0.8)	40 (10.9)	2 (0.5)	16 (8.9)	0
Dry mouth	40 (8.3)	0	6 (2.5)	0	38 (10.4)	1 (0.3)	7 (3.9)	0
Dyspepsia	34 (7.0)	0	14 (5.7)	0	45 (12.3)	0	19 (10.6)	0
Abdominal distension	32 (6.6)	0	30 (12.3)	0	30 (8.2)	0	23 (12.8)	1 (0.6)
Stomatitis	16 (3.3)	1 (0.2)	4 (1.6)	0	15 (4.1)	1 (0.3)	11 (6.1)	0

* The MedDRA version used was 20.0 for the PRIMA study and 18.0 for the NOVA study.

Table 37. Occurrence of gastrointestinal disorders with an incidence of ≥10% in any group (QUADRA study and Studies 2001 and 2002)

PT*	Number of subjects (%)					
	QUADRA study n = 463		Study 2001 n = 19		Study 2002 n = 20	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Gastrointestinal disorders	411 (88.8)	115 (24.8)	18 (94.7)	0	19 (95.0)	1 (5.0)
Nausea	312 (67.4)	45 (9.7)	13 (68.4)	0	12 (60.0)	0
Constipation	159 (34.3)	14 (3.0)	2 (10.5)	0	7 (35.0)	0
Vomiting	205 (44.3)	37 (8.0)	7 (36.8)	0	7 (35.0)	0
Abdominal pain	97 (21.0)	29 (6.3)	1 (5.3)	0	0	0
Diarrhoea	77 (16.6)	1 (0.2)	1 (5.3)	0	1 (5.0)	0
Abdominal pain upper	25 (5.4)	0	3 (15.8)	0	1 (5.0)	0
Dry mouth	23 (5.0)	0	0	0	0	0
Dyspepsia	33 (7.1)	0	1 (5.3)	0	0	0
Abdominal distension	61 (13.2)	3 (0.6)	1 (5.3)	0	0	0
Stomatitis	38 (8.2)	2 (0.4)	1 (5.3)	0	3 (15.0)	0

* The MedDRA ver. 21.0 was used for the QUADRA study and Studies 2001 and 2002.

In the PRIMA study, gastrointestinal disorders resulted in death in 1 of 484 patients (0.2%) in the niraparib group (Intestinal perforation), and its causal relationship with niraparib was ruled out. No gastrointestinal disorders resulted in death in the placebo group. Serious gastrointestinal disorders occurred in 24 of 484 patients (5.0%) in the niraparib group (small intestinal obstruction in 14 patients, intestinal obstruction in 7 patients, abdominal pain, vomiting, abdominal pain lower, diarrhoea, enteritis, small intestinal perforation, and large intestinal obstruction in 1 patient each [including patients experiencing multiple events]). Serious gastrointestinal disorders occurred in 12 of 244 patients (4.9%) in the placebo group (small intestinal obstruction in 5 patients, abdominal pain and subileus in 2 patients each, intestinal obstruction, vomiting, abdominal fat apron, abdominal pain upper, ileus, and nausea in 1 patient each [including patients experiencing multiple events]). A causal relationship with niraparib was not ruled out in 4 patients in the niraparib group (small intestinal obstruction in 2 patients, diarrhoea and enteritis in 1 patient each). Gastrointestinal disorders led to treatment discontinuation in 9 of 484 patients (1.9%) in the niraparib group (nausea in 6 patients,

abdominal pain and small intestinal obstruction in 2 patients each, diarrhoea and gastrointestinal pain in 1 patient each [including patients experiencing multiple events]) and 1 of 244 patients (0.4%) in the placebo group (ascites in 1 patient). Gastrointestinal disorders led to treatment interruption in 63 of 484 patients (13.0%) in the niraparib group (nausea and vomiting in 21 patients each, small intestinal obstruction in 10 patients, abdominal pain in 9 patients, diarrhoea in 5 patients, constipation in 4 patients, intestinal obstruction in 3 patients, abdominal pain upper in 2 patients, dyspepsia, abdominal distension, abdominal pain lower, enteritis, gastrointestinal haemorrhage, haematochezia, large intestinal obstruction, lip swelling, rectal haemorrhage, and tooth impacted in 1 patient each [including patients experiencing multiple events). Gastrointestinal disorders led to treatment interruption in 14 of 244 patients (5.7%) in the placebo group (nausea, vomiting, and small intestinal obstruction in 4 patients each, diarrhoea in 3 patients, abdominal pain in 2 patients, intestinal obstruction, dyspepsia, abdominal discomfort, abdominal fat apron, gastritis, and ileus in 1 patient [including patients experiencing multiple events]). Gastrointestinal disorders led to dose reduction in 24 of 484 patients (5.0%) in the niraparib group (nausea in 14 patients, vomiting in 7 patients, constipation in 3 patients, small intestinal obstruction in 2 patients, diarrhoea, abdominal pain, dyspepsia, enteritis, and lip swelling in 1 patient each [including patients experiencing multiple events]) and 4 of 244 patients (1.6%) in the placebo group (diarrhoea in 3 patients and small intestinal obstruction in 1 patient).

In the NOVA study, serious gastrointestinal disorders occurred in 26 of 367 patients (7.1%) in the niraparib group (small intestinal obstruction in 7 patients, constipation in 4 patients, ascites, abdominal pain, intestinal obstruction, subileus in 2 patients each, nausea in 1 patient, pancreatitis, abdominal hernia, abdominal pain upper, gastrooesophageal reflux disease, ileus paralytic, impaired gastric emptying, obstruction gastric, and vomiting in 1 patient each [including patients experiencing multiple events]). Serious gastrointestinal disorders occurred in 14 of 179 patients (7.8%) in the placebo group (small intestinal obstruction in 4 patients, nausea in 3 patients, ascites, ileus in 2 patients each, constipation, abdominal pain, pancreatitis, abdominal distension, and diarrhoea in 1 patient each [including patients experiencing multiple events]). A causal relationship with niraparib was not ruled out in 2 patients in the niraparib group (impaired gastric emptying and vomiting in 1 patient each). Gastrointestinal disorders led to treatment discontinuation in 13 of 367 patients (3.5%) in the niraparib group (nausea in 6 patients, vomiting in 3 patients, small intestinal obstruction in 2 patients, ascites, constipation, diarrhoea and intestinal obstruction in 1 patient each [including patients experiencing multiple events]) and 1 of 179 patients (0.6%) in the placebo group (small intestinal obstruction in 1 patient). Gastrointestinal disorders led to treatment interruption in 55 of 367 patients (15.0%) in the niraparib group 8nausea in 28 patients, vomiting in 22 patients, constipation in 6 patients, diarrhoea in 5 patients, abdominal pain in 3 patients, small intestinal obstruction and gastrointestinal reflux disease in 2 patients each, pancreatitis in 1 patient, abdominal distension, abdominal hernia, aphthous ulcer, duodenogastric reflux, food poisoning, intestinal obstruction, and retching in 1 patient each [including patients experiencing multiple events]). Gastrointestinal disorders led to treatment interruption in 14 of 179 patients (7.8%) in the placebo group (nausea in 4 patients, vomiting in 4 patients, small intestinal obstruction in 3 patients, abdominal pain in 2 patients, diarrhoea, pancreatitis, abdominal pain upper, ascites, and umbilical hernia in 1 patient each [including patients experiencing multiple events]). Gastrointestinal disorders led to dose reduction in 25 of 367 patients (6.8%) in the niraparib group (nausea in 19 patients, vomiting in 8 patients, diarrhoea, constipation, and

dyspepsia in 2 patients, abdominal pain, abdominal pain upper, and impaired gastric emptying in 1 patient each [including patients experiencing multiple events]) and 1 of 179 patients (0.6%) in the placebo group (diarrhoea in 1 patient). No gastrointestinal disorders resulted in death.

In the QUADRA study, gastrointestinal disorders resulted in death in 1 of 463 patients (0.2%, gastric haemorrhage), and a causal relationship with niraparib was not ruled out. Serious gastrointestinal disorders occurred in 105 of 463 patients (22.7%) (small intestinal obstruction in 34 patients, vomiting in 27 patients, nausea in 21 patients, abdominal pain in 17 patients, constipation in 10 patients, intestinal obstruction in 8 patients, ascites in 4 patients, dysphagia, ileus in, large intestinal obstruction, and rectal haemorrhage in 2 patients each, abdominal discomfort, abdominal distension, abdominal pain upper, colitis, diarrhoea, enteritis, erosive oesophagitis, gastric haemorrhage, gastritis, gastrointestinal fistula, bowel perforation, obstruction gastric, oesophageal varices haemorrhage, oesophagitis, and stomatitis in 1 patient each [including patients experiencing multiple events]). A causal relationship with niraparib was not ruled out in 28 patients (vomiting in 13 patients, nausea in 10 patients, abdominal pain in 4 patients, constipation in 3 patients, small intestinal obstruction, intestinal obstruction, dysphagia, rectal haemorrhage, colitis, diarrhoea in 1 patient, gastric haemorrhage, gastritis, gastrointestinal fistula, and oesophagitis 1 patient each [including patients experiencing multiple events]). Gastrointestinal disorders led to treatment discontinuation in 43 of 463 patients (9.3%): (vomiting in 18 patients, nausea in 14 patients, small intestinal obstruction in 12 patients, abdominal distension, abdominal pain, and intestinal obstruction in 3 patients each, colitis, diarrhoea, erosive oesophagitis, gastrointestinal fistulae, oesophagitis, and stomatitis in 1 patient each [including patients experiencing multiple events]). Gastrointestinal disorders led to treatment interruption in 105 of 463 patients (22.7%) (nausea in 46 patients, vomiting in 41 patients, small intestinal obstruction in 18 patients, abdominal pain and constipation in 16 patients each, diarrhoea in 6 patients, dysphagia, intestinal obstruction in, and stomatitis in 3 patients each, dyspepsia and rectal haemorrhage in 2 patients each, abdominal distension, abdominal pain lower, abdominal pain upper, ascites, flatulence, gastrooesophageal reflux disease, ileus, large intestinal obstruction, oesophageal varices haemorrhage, and retching in 1 patient each [including patients experiencing multiple events]). Gastrointestinal disorders led to dose reduction in 34 of 463 patients (7.3%) (nausea in 20 patients, vomiting in 10 patients, abdominal pain in 4 patients, constipation, and stomatitis, abdominal distension, diarrhoea, flatulence, and odynophagia in 1 patient each [including patients experiencing multiple events]).

In Study 2001, gastrointestinal disorders led to treatment interruption in 3 of 19 patients (15.8%, nausea in 3 patients and vomiting in 2 patients [including patients experiencing multiple events]). Gastrointestinal disorders led to dose reduction in 3 of 19 patients (15.8%, nausea in 3 patients and vomiting in 2 patients [including patients experiencing multiple events]). No gastrointestinal disorders resulted in death, were serious, or led to treatment discontinuation.

In Study 2002, serious gastrointestinal disorders occurred in 1 of 20 patients (5.0 %, ascites in 1 patient), and a causal relationship with niraparib was ruled out. Gastrointestinal disorders led to treatment interruption in 1 of 20 patients (5.0%, nausea in 1 patient and vomiting in 1 patient [multiple events occurred in the patient]). Gastrointestinal disorders led to dose reduction in 2 of 20 patients (10.0%, nausea in 2 patients and vomiting

in 1 patient [including a patient experiencing multiple events]). No gastrointestinal disorders resulted in death or led to treatment discontinuation.

The median (range) of the time to the first onset of gastrointestinal disorders was 8 days (1 to 479 days) in the niraparib group of the PRIMA study, 3 days (-29[46] to 614 days)[49] in the niraparib group of the NOVA study, 5 days (1 to 756 days) in the QUADRA study, 3.5 days (1 to 28 days) in Study 2001, and 4 days (1 to 85 days) Study 2002.

PMDA's view:
Death for which a causal relationship with niraparib could not be ruled out occurred after the administration of niraparib (gastric haemorrhage in 1 patient). The majority of gastrointestinal disorders observed were Grade ≤2. PMDA thus concluded that gastrointestinal disorders are generally controllable by interruption of niraparib, reduction of niraparib dose, or symptomatic treatment. Nevertheless, in light of the higher incidence of gastrointestinal disorders in the clinical studies, caution should be used against gastrointestinal disorders during treatment with niraparib and the occurrence of gastrointestinal disorders in the clinical studies should be communicated appropriately to healthcare professionals via the package insert, etc.

7.R.2.6 Thromboembolism

The applicant's explanation about thromboembolism associated with niraparib:
Thromboembolism-related events falling under the MedDRA SMQ of "Embolic and thrombotic events (broad scope)" were aggregated.

Tables 38 and 39 list the occurrence of thromboembolism in the PRIMA, NOVA, and QUADRA studies. No thromboembolism occurred in Study 2002.

Table 38. Occurrence of thromboembolism in ≥2 patients in either group (PRIMA and NOVA studies)

PT*	Number of subjects (%)							
	PRIMA study				NOVA study			
	Niraparib n = 484		Placebo n = 244		Niraparib n = 367		Placebo n = 179	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Thromboembolism	6 (1.2)	3 (0.6)	1 (0.4)	0	11 (3.0)	4 (1.1)	1 (0.6)	0
Pulmonary embolism	1 (0.2)	1 (0.2)	1 (0.4)	0	3 (0.8)	2 (0.5)	0	0
Embolism	1 (0.2)	1 (0.2)	0	0	1 (0.3)	1 (0.3)	0	0
Thrombosis	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Deep vein thrombosis	0	0	0	0	1 (0.3)	1 (0.3)	0	0
Myocardial infarction	0	0	0	0	0	0	0	0

* The MedDRA version used was 20.0 for the PRIMA study and 18.0 for the NOVA study.

[49] The median (range) time to the first onset of gastrointestinal disorders that occurred after the start of treatment with niraparib in the NOVA study was 3.5 days (1 to 614 days)

Table 39. Occurrence of thromboembolism in ≥2 patients in either group (QUADRA study and Study 2001)

PT*	Number of subjects (%)			
	QUADRA study n = 463		Study 2001 n = 19	
	All grades	Grade ≥3	All grades	Grade ≥3
Thromboembolism	21 (4.5)	9 (1.9)	1 (5.3)	0
Pulmonary embolism	4 (0.9)	3 (0.6)	0	0
Embolism	2 (0.4)	1 (0.2)	0	0
Thrombosis	2 (0.4)	0	0	0
Deep vein thrombosis	7 (1.5)	1 (0.2)	0	0
Myocardial infarction	3 (0.6)	2 (0.4)	0	0

* The MedDRA version used was 20.0 for the QUADRA study and 21.0 for Study 2001.

In the PRIMA study, serious thromboembolism occurred in 2 of 484 patients (0.4%) in the niraparib group (device occlusion and pulmonary embolism in 1 patient each). A causal relationship with niraparib was not ruled out in 1 patient in the niraparib group (pulmonary embolism in 1 patient). No serious thromboembolism occurred in the placebo group. Thromboembolism led to treatment interruption in 1 of 484 patients (0.2%) in the niraparib group (hemiparesis in 1 patient). No such events occurred in the placebo group. Thromboembolism led to dose reduction in 1 of 484 patients (0.2%) in the niraparib group (hemiparesis in 1 patient). No such events occurred in the placebo group. No thromboembolism resulted in death or led to treatment discontinuation.

In the NOVA study, serious thromboembolism occurred in 4 of 367 patients (1.1%) in the niraparib group (pulmonary embolism in 2 patients, peripheral artery thrombosis and transient ischaemic attack in 1 patient each), and a causal relationship with niraparib was not ruled out in 1 patient in in the niraparib group (transient ischaemic attack in 1 patient). No serious thromboembolism occurred in the placebo group. Thromboembolism led to treatment interruption occurred in 2 of 367 patients (0.5%) in the niraparib group (embolism and superior vena cava syndrome in 1 patient each). No such events occurred in the placebo group. No thromboembolism resulted in death or led to treatment discontinuation or dose reduction.

In the QUADRA study, serious thromboembolism occurred in 8 of 463 patients (1.7%; deep vein thrombosis in 4 patients, embolism, myocardial infarction, pulmonary embolism, and transient ischaemic attack in 1 patient each). Among them, a causal relationship with niraparib was not ruled out in 1 patient (myocardial infarction in 1 patient). Thromboembolism led to treatment interruption in 2 of 463 patients (0.4%, deep vein thrombosis and pulmonary embolism in 1 patient each). No thromboembolism resulted in death or led to treatment discontinuation or dose reduction.

In Study 2001, no thromboembolism resulted in death, was serious, or led to treatment discontinuation, treatment interruption, or dose reduction.

The median (range) of the time to the first onset of thromboembolism was 62.5 days (15 to 168 days) in the niraparib group of the PRIMA study, 214 days (19 to 477 days) in the niraparib group of the NOVA study, 58 days (1 to 635 days) in the QUADRA study, and 57 days (57 to 57 days) in Study 2001.

Patients experiencing serious thromboembolism (related to niraparib) in all clinical studies submitted are shown in Table 40.

Table 40. Listing of patients experiencing serious thromboembolism (related to niraparib)

Study	Age	Sex	Dose (mg)	Carcinoma	PT*	Grade	Onset date (day)	Duration (day)	Action taken with niraparib	Outcome
PRIMA	5[redacted]	F	300	Ovarian cancer	Pulmonary embolism	3	81	31	Continued	Recovered
NOVA	6[redacted]	F	300	Ovarian cancer	Transient ischaemic attack	2	156	2	Continued	Recovered
QUADRA	6[redacted]	F	300	Ovarian cancer	Myocardial infarction	3	40	1	N/A	Recovered

* The MedDRA version used was 20.0 for the PRIMA study, 18.0 for the NOVA study, and 21.0 for the QUADRA study.

PMDA asked the applicant to explain the mechanism underlying the development and risk factors of thromboembolism associated with niraparib.

The applicant's answer:
The incidence of thromboembolism in patients with ovarian cancer is 10% to 22%, which is highest among patients with solid cancer (*Gynecologic Oncology*. 2005;99:119-25). Patients with ovarian cancer seem to be at higher risk of thromboembolism related to malignancy. A relationship between niraparib and thromboembolism or the mechanism of thromboembolism associated with niraparib remains unknown, and risk factors have not been identified.

PMDA's view:
The incidence of thromboembolism was higher in the niraparib group than in the placebo group in the clinical studies submitted, and serious events were reported. The results suggest the need of caution against thromboembolism during treatment with niraparib. The occurrence of thromboembolism in the clinical studies should be communicated appropriately to healthcare professionals via the package insert, etc. A relationship between niraparib and the risk of the development of thromboembolism remains unknown at present, and therefore relevant information should be continuously collected in the post marketing setting and that valuable information should be appropriately provided to healthcare professionals once available.

7.R.2.7 Secondary malignancy

The applicant's explanation about secondary malignancy associated with niraparib:
Secondary malignancy-related events were aggregated.

The occurrence of secondary malignancy in the PRIMA, NOVA, and QUADRA studies and Studies 2001 and 2002 is shown in Tables 41 and 42. No secondary malignancy occurred in Study 2001 or 2002.

Table 41. Occurrence of secondary malignancy (PRIMA and NOVA studies)

PT*	Number of subjects (%)							
	PRIMA study				NOVA study			
	Niraparib n = 484		Placebo n = 244		Niraparib n = 367		Placebo n = 179	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Secondary malignancy	5 (1.0)	2 (0.4)	3 (1.2)	1 (0.4)	5 (1.4)	4 (1.0)	2 (1.1)	2 (1.1)
Breast cancer/Invasive breast carcinoma	2 (0.4)	1 (0.2)	1 (0.4)	0	0	0	0	0
MDS/AML	1 (0.2)	1 (0.2)	0	0	5 (1.4)	4 (1.0)	2 (1.1)	2 (1.1)
Basal cell carcinoma	1 (0.2)	0	0	0	0	0	0	0
Thyroid cancer	1 (0.2)	0	1 (0.4)	1 (0.4)	0	0	0	0
Squamous cell carcinoma	0	0	1 (0.4)	0	0	0	0	0

* The MedDRA version used was 20.0 for the PRIMA study and 18.0 for the NOVA study.

Table 42. Occurrence of secondary malignancy (QUADRA study)

PT*	Number of subjects (%)	
	QUADRA study n = 463	
	All grades	Grade ≥3
Secondary malignancy	2 (0.4)	2 (0.4)
Breast cancer/Invasive breast carcinoma	1 (0.2)	1 (0.2)
MDS/AML	1 (0.2)	1 (0.2)
Basal cell carcinoma	0	0
Thyroid cancer	0	0
Squamous cell carcinoma	0	0

* The MedDRA version used was 21.0 for the QUADRA study.

The median (range) time to the first onset of secondary malignancy was 267 days (135 to 664 days) in the niraparib group of the PRIMA study, 427 days (307 to 666 days) in the niraparib group of the NOVA study, and 65 days (65 to 391 days) in the QUADRA study.

Patients experiencing secondary malignancy (causally related to niraparib) due to niraparib in the above-mentioned clinical studies or other studies are listed in Table 43.

Table 43. List of patients experiencing serious secondary malignancy (related to niraparib)

Study	Age	Dose (mg)	PT*1	Grade	Onset date (day)	Action taken with niraparib	Outcome
PRIMA	6[redacted]	300	MDS	4	284	N/A	Not recovered
NOVA	5[redacted]	300	MDS	5	490	N/A	Death
	6[redacted]	300	MDS	4	312	Discontinued	Not recovered
			AML	5	666	N/A	Death
	4[redacted]	300	MDS	2	427	N/A	Not recovered
	6[redacted]	300	MDS	5	408	N/A	Death
QUADRA	6[redacted]	300	AML	4	65	N/A	Not recovered
			MDS	4	65	N/A	Not recovered
ENGOT-OV24-NSGO*2	6[redacted]	100	AML	UNK	631	N/A	Not recovered
3000-07-010*3	6[redacted]	300	AML	5	253	N/A	Death

*1, The MedDRA version used was 20.0 for the PRIMA study, 18.0 for the NOVA study, 21.0 for the QUADRA study, and 22.1 for other studies. *2, A foreign phase I/II study in patients with platinum-sensitive ovarian cancer; *3, Compassionate Use Program

PMDA's view:

Although the PRIMA and NOVA studies did not show no clear differences in the incidence of secondary malignancy between the niraparib group and the placebo group, clinical studies including foreign studies other than PRIMA and NOVA revealed death cases due to secondary malignancy for which a causal relationship

with niraparib could not be ruled out. Caution should be used against secondary malignancy. In particular, hematological diseases, such as myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) deserve attention, because these diseases have been more frequently reported than other secondary malignancies.

In light of the above, the occurrence of secondary malignancy in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. In addition, because secondary malignancy may occur after a long time, relevant information should be continuously collected in the post-marketing setting and valuable information should be appropriately provided to healthcare professionals as soon as available.

7.R.2.8 Posterior reversible encephalopathy syndrome

The applicant's explanation about posterior reversible encephalopathy syndrome associated with niraparib:
Posterior reversible encephalopathy syndrome-related events falling under the MedDRA PTs of "Posterior reversible encephalopathy syndrome," "Capillary leak syndrome," "Encephalopathy," "Hypertensive encephalopathy," "Leukoencephalopathy," and "Vasogenic cerebral oedema" were aggregated.

No posterior reversible encephalopathy syndrome occurred in the PRIMA, NOVA, or QUADRA study or Study 2001 or 2002.

In the clinical studies of niraparib and foreign post-marketing experience, serious posterior reversible encephalopathy syndrome was reported in 9 patients (posterior reversible encephalopathy syndrome in 4 patients, encephalopathy in 4 patients, and vasogenic cerebral oedema in 1 patient), and a causal relationship with niraparib was not ruled out in any cases. Posterior reversible encephalopathy syndrome resulted in death in 2 patients (encephalopathy in 2 patients), and a causal relationship with niraparib was not ruled out in either case.

PMDA's view:
While no posterior reversible encephalopathy syndrome was reported in the PRIMA, NOVA, or QUADRA study or Study 2001 or 2002, serious posterior reversible encephalopathy syndrome for which a causal relationship with niraparib could not be ruled out was reported in clinical studies and post-marketing experience of niraparib. Given this, the occurrence, etc. of posterior reversible encephalopathy syndrome in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc.

7.R.3 Efficacy for maintenance treatment

As a result of the review shown below, PMDA has concluded that niraparib has been demonstrated to have efficacy in the maintenance treatment of (a) patients with advanced ovarian cancer in response to first-line platinum-based chemotherapy and (b) patients with platinum-sensitive, relapsed, ovarian cancer in response to their last platinum-based chemotherapy.

7.R.3.1 Selection of the control group in the PRIMA NOVA studies

The applicant's explanation about the selection of placebo as a control in (a) the PRIMA study and (b) the NOVA study:

(a) When the PRIMA study was in the planning stage, the NCCN guidelines (v.2.2015) recommended that patients with ovarian cancer responding to their first-line platinum-based chemotherapy be followed up without receiving additional treatment until disease progression. Because there was no standard maintenance treatment recommended, placebo was selected as a control.
(b) When the NOVA study was in the planning stage, the NCCN guidelines (v.3.2012) recommended that patients with recurrent ovarian cancer responding to their platinum-based chemotherapy should be followed up without further addition of treatment until disease progression. Because there was no standard maintenance treatment recommended, placebo was selected as a control.

PMDA accepted the applicant's explanation.

7.R.3.2 Efficacy endpoints in the PRIMA and NOVA studies

The efficacy endpoint used in (a) the PRIMA study and (b) the NOVA study was (a) PFS based on the RECIST ver. 1.1 and (b) PFS based on the RECIST ver. 1.1 or clinical signs/symptoms and an increase in CA-125, respectively.

The applicant's explanation about the appropriateness of the selection of the efficacy endpoint:

(a) In patients eligible for the PRIMA study, the prolongation of PFS was an indication of prolonged time to disease progression or recurrence that would delay the onset of symptoms associated with disease progression, suggesting its clinical significance. The endpoint was thus appropriate.
(b) A certain number of patients in the NOVA study were assumed to have difficulty undergoing imaging assessment for disease progression [see Section 7.1.2.3]. Given this, and based on the following observations, it was considered appropriate to use PFS based on the RECIST ver. 1.1 or clinical signs/symptoms and an increase in CA-125 as the primary endpoint of the NOVA study.
    - In patients eligible for the NOVA study, the prolongation of PFS was an indication of prolonged time to disease progression or recurrence that would delay the onset of symptoms associated with disease progression, suggesting its clinical significance.
    - Patients eligible for the NOVA study often have peritoneal dissemination. Some patients would have difficulty undergoing imaging-based assessment of disease progression in accordance with the RECIST ver. 1.1.
    - According to the RECIST ver. 1.1, patients with a pre-treatment tumor marker exceeding the reference level can achieve CR only when the marker returns to the normal level. In light of it, it is considered appropriate to determine disease progression based on an increase in CA-125, which has been reported to be observed prior to the worsening of clinical signs or symptoms in patients with recurrent ovarian cancer, as well as clinical signs and symptoms, etc (*Lancet.* 2010;376:1155-63).

PMDA's view:

Because the treatment in the PRIMA or NOVA study was intended for life extension of the target patients, overall survival (OS) should have been the primary endpoint of the PRIMA and NOVA studies. However, the applicant's explanation about a certain clinical significance of PFS prolongation in such patients is understandable, and PFS is valid for the evaluation of the efficacy of niraparib as the primary endpoint, when used in conjunction with OS results obtained from the PRIMA and NOVA studies.

7.R.3.3 Results of efficacy evaluation in the PRIMA NOVA studies

The applicant's explanation about the results of the evaluation of the efficacy of niraparib in (a) the PRIMA study and (b) the NOVA study:

(a) PRIMA study:

In the PRIMA study, niraparib was demonstrated to be superior to placebo for the PFS assessed by the BICR based on the RECIST ver. 1.1 (the primary endpoint) in the HRD-positive group (i.e., the primary analysis set) and the overall study population [see Section 7.1.2.4]. The hazard ratio [95% CI] of PFS in the HRD-negative group was 0.68 [0.49, 0.94].

OS, a secondary endpoint of the study, was assessed by a stratified hypothesis test first in the overall study population and then in the HRD-positive group when the primary analysis of PFS showed a statistically significant difference both in the HRD-positive group and the overall study population. Further, an interim analysis of OS was scheduled to evaluate the efficacy of niraparib at the time of the primary analysis of PFS. The O'Brien-Fleming-type α-spending function based on the Lan-DeMets method was used to control the type-I error rate associated with the conduct of the interim analysis.

The results of the interim analysis of OS as the secondary endpoint (data cutoff on May 17, 2019) and the Kaplan-Meier plots are respectively shown in Table 44 and Figures 6 and 7.

Table 44. Results of the interim analysis of OS (ITT population, data cutoff on May 17, 2019)

	HRD-positive group		Overall study population	
	Niraparib	Placebo	Niraparib	Placebo
Number of subjects	247	126	487	246
Number of events (%)	16 (6.5)	10 (7.9)	48 (9.9)	31 (12.6)
Median [95% CI] (month)	30.3 [30.3, −]	− [25.0, −]	30.3 [30.3, −]	− [25.0, −]
Hazard ratio [95% CI] *1	0.61 [0.265, 1.388]		0.70 [0.442, 1.106]	
p-value (two-sided) *2	0.2323		0.1238	

−, Not estimable; *1, A stratified Cox proportional hazards model with stratifying factors including neoadjuvant chemotherapy (with/without), best response (CR, PR) during platinum therapy, and status of HRD (positive/negative/unknown); *2, A stratified log-rank test with stratifying factors including neoadjuvant chemotherapy (with/without), best response (CR, PR) during platinum therapy, and status of HRD (positive/negative/unknown)

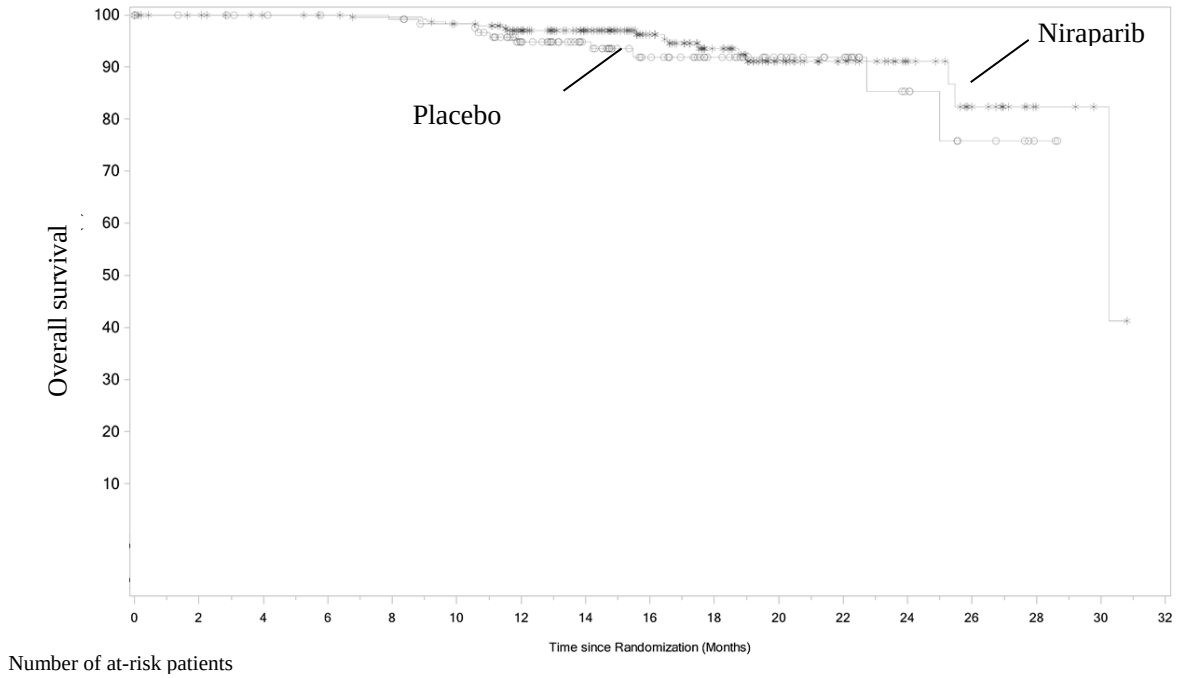


Figure 6. Kaplan-Meier plot for OS at the interim analysis (HRD-positive group, data cutoff on May 17, 2019)

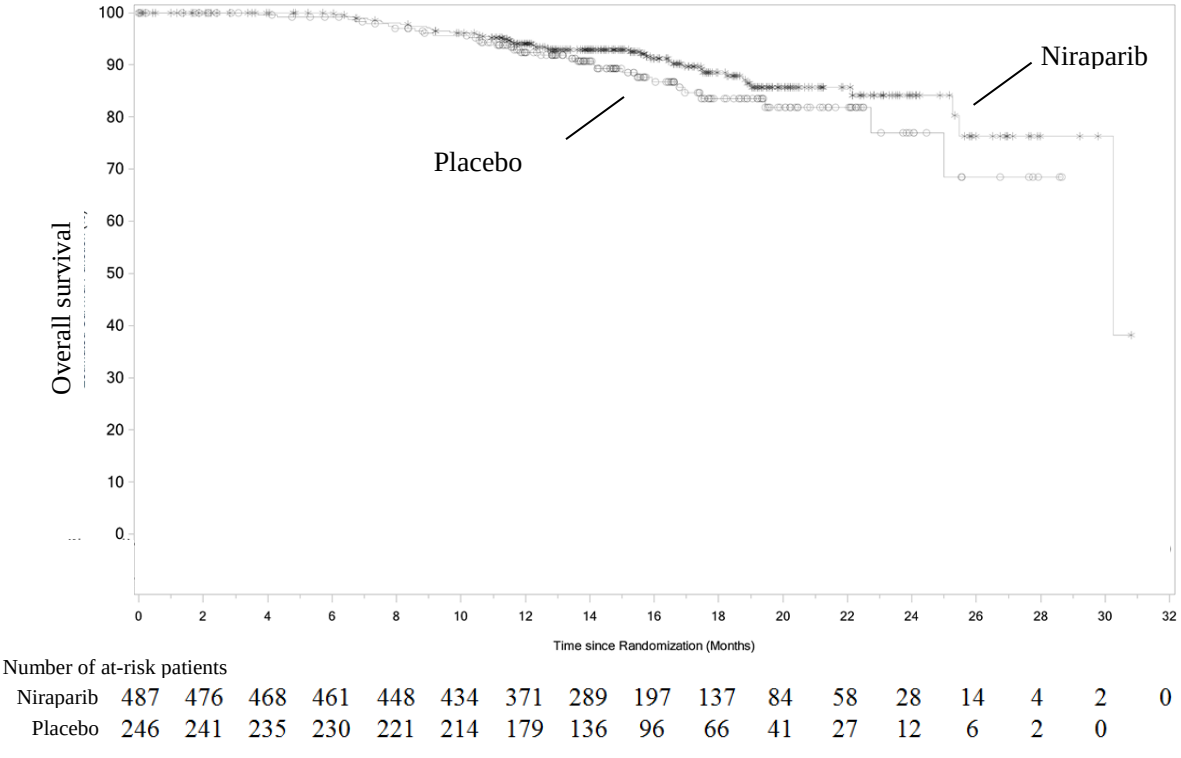


Figure 7. Kaplan-Meier plot of OS at the interim analysis (Overall study population, data cutoff on May 17, 2019)

Furthermore, the applicant provided the following explanation about the efficacy of niraparib in Japanese patients with ovarian cancer who were in response to their first-line platinum-based chemotherapy:

Although no Japanese patients were included in the PRIMA study, no clear different trend was observed in the efficacy results between the QUADRA study and Study 2002 [see Sections 7.1.1.3, 7.1.2.2, and 7.R.5.2], and no obvious differences were observed in the pharmacokinetics of niraparib between Japanese and non-Japanese patients [see Section 6.2.7]. Based on these findings, niraparib is expected to have efficacy in Japanese patients as well.

(b) NOVA study:

In the NOVA study, niraparib was demonstrated to be superior to placebo in PFS assessed by the BICR based on the RECIST ver. 1.1 or clinical signs/symptoms and an increase in CA-125 (the primary endpoint) in (i) the *gBRCA*-mutated cohort, (ii) the non-*gBRCA*-mutated cohort, and (iii) the HRD-positive group in the non-*gBRCA*-mutated cohort (the primary analysis sets) [see Section 7.1.2.3]. The hazard ratio [95% CI] of PFS assessed by the BICR in the HRD-negative group was 0.58 [0.36, 0.92].

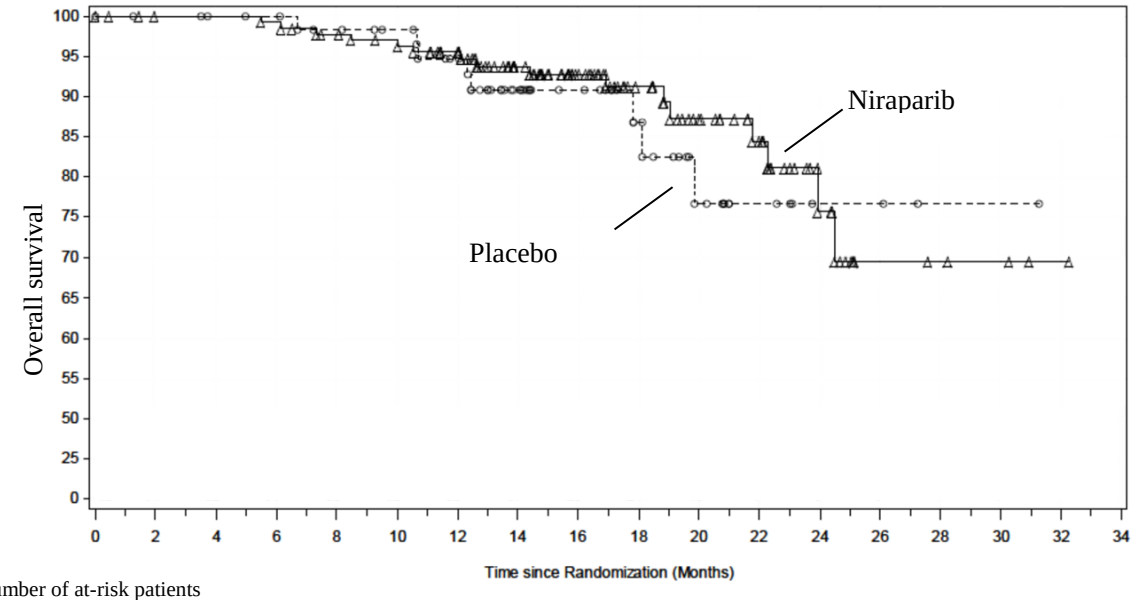
A sensitivity analysis was performed on PFS assessed by the BICR based on RECIST ver. 1.1. alone. The hazard ratio [95% CI] of PFS with niraparib relative to that with placebo in (i) the *gBRCA*-mutated cohort, (ii) the non-*gBRCA*-mutated cohort, and (iii) the HRD-positive group in the non-*gBRCA*-muted cohort, which was 0.26 [0.17, 0.41], 0.46 [0.34, 0.62], and 0.39 [0.25, 0.60], respectively, was similar to that obtained by the primary analysis.

The results of the analysis of OS as the secondary endpoint at the time of the primary analysis of PFS (data cutoff on May 30, 2016) in the NOVA study and the Kaplan-Meier plots are respectively shown in Table 45 and Figures 8, 9, and 10.

Table 45. Results of the analysis of OS (ITT population, data cutoff on May 30, 2016)

	gBRCA-mutated cohort		Non-*gBRCA*-mutated cohort			
			HRD-positive group		Overall cohort	
	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo
Number of subjects	138	65	106	56	234	116
Number of events (%)	16 (11.6)	8 (12.3)	23 (21.7)	7 (12.5)	44 (18.8)	27 (23.3)
Median [95% CI] (month)	– [24.5, −]	– [−, −]	– [28.3, −]	– [−, −]	– [28.3, −]	– [20.2, −]
Hazard ratio [95% CI] *1	0.91 [0.36, 2.28]		1.39 [0.57, 3.42]		0.74 [0.45, 1.20]	
p-value (one-sided) *2	0.8346		0.4665		0.2181	

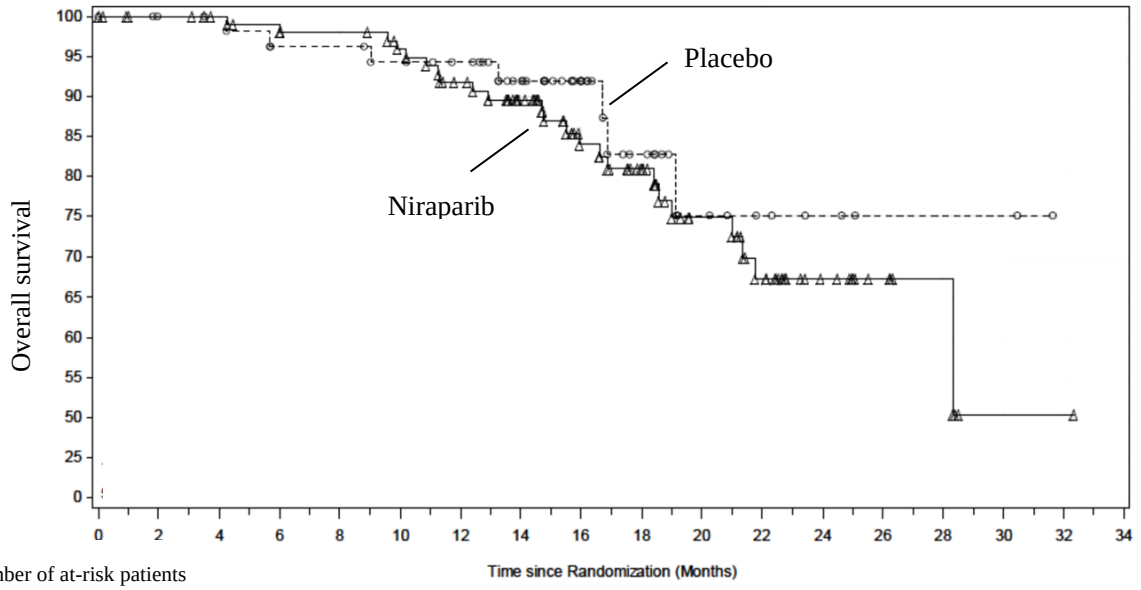
−, Not estimable; *1, A stratified Cox regression model with stratifying factors including PFI (6 to <12 months or ≥12 months) before recurrence, concomitant use of BV before or at recurrence (with/without), and best response (CR, PR) during the last platinum regimen; *2, A stratified log-rank test with stratifying factors including PFI (6 to <12 months or ≥12 months) before recurrence, concomitant use of BV before or at recurrence (yes/no), and best response (CR, PR) during the last platinum regimen



Number of at-risk patients

Niraparib	138	135	135	134	130	127	118	92	68	51	39	29	14	5	4	3
Placebo	65	64	62	61	58	55	50	37	29	21	13	7	3	3	1	1

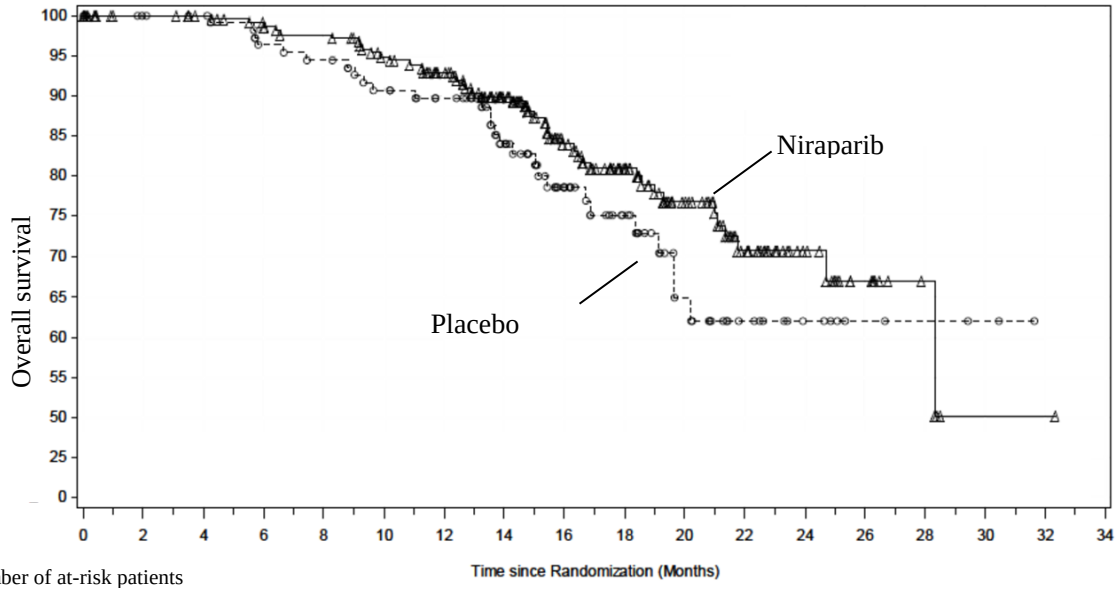
Figure 8. Kaplan-Meier plot for the analysis of OS
(*gBRCA*-mutated cohort, data cutoff on May 30, 2016)



Number of at-risk patients

Niraparib	106	103	100	98	96	92	86	73	56	46	32	25	13	7	4	1
Placebo	56	54	53	50	50	48	45	37	24	16	9	6	4	2	2	2

Figure 9. Kaplan-Meier plot for the analysis of OS
(HRD-positive group in the non-*gBRCA*-mutated cohort, data cutoff on May 30, 2016)



Number of at-risk patients

Niraparib	234	224	219	214	210	201	188	156	114	89	62	40	21	11	4	1
Placebo	116	112	110	104	102	96	90	71	50	37	23	14	8	4	3	2

Figure 10. Kaplan-Meier plot for the analysis of OS
(non-*gBRCA*-mutated cohort, data cutoff on May 30, 2016)

A non-stratified OS analysis was performed as a sensitivity analysis. The hazard ratio [95% CI] of PFS with niraparib relative to that with placebo in (i) the *gBRCA*-mutated cohort, (ii) the non-*gBRCA*-mutated cohort, and (iii) the HRD-positive group in the non-*gBRCA*-mutated cohort, which was 0.77 [0.33, 1.81], 0.73 [0.45, 1.19], and 1.42 [0.61, 3.33], respectively, was similar to that obtained by the stratified analysis.

The applicant's explanation about the point estimate of the hazard ratio of OS exceeding 1 in the HRD-positive group in the non-*gBRCA*-mutated cohort in the NOVA study:
Although it was difficult to draw a definitive conclusion because of the small number of OS events in the group, the result is attributable to the following differences in patient characteristics among the groups.

- The percentage of patients receiving a subsequent therapy following the completion of study drug treatment in the HRD-positive group in the non-*gBRCA*-mutated cohort:
  45.3% (48 of 106) of patients in the niraparib group and 73.2% (41 of 56) of patients in the placebo group

In patients receiving no subsequent treatment, no evident trend toward decreasing in the niraparib group as compared with the placebo group with a hazard ratio [95% CI] of 1.03 [0.094, 11.30].

Furthermore, the applicant provided the following explanation for the efficacy of niraparib in Japanese patients with recurrent ovarian cancer who were in response to their platinum-based chemotherapy regimen.

The percentage of PFS [95% CI] at Month 6 in the niraparib group in Study 2001 and the NOVA study (a combined analysis of the *gBRCA*-mutated and non-*gBRCA*-mutated cohorts) was 71.1% [43.7, 86.8] and 68.9%

[63.5, 73.6], respectively, showing no clear different trend. Given this, niraparib is expected to have efficacy in Japanese patients as well.

PMDA's view:
In light of the applicant's explanation above and the following observations, niraparib has been demonstrated to be effective in the maintenance treatment for both Japanese and non-Japanese patients with advanced ovarian cancer in response to first-line platinum-based chemotherapy.

- Niraparib was demonstrated to be superior to placebo in PFS assessed by the BICR based on the RECIST ver. 1.1, the primary endpoint of the PRIMA study, in the HRD-positive group and the overall study population. In addition, the prolongation of PFS was clinically significant.
- No trend toward a decrease in OS, the secondary endpoint of the PRIMA study, was observed with niraparib as compared with placebo in the HRD-positive group or the overall study population.
- No clear differences were observed in the pharmacokinetics of niraparib or the diagnosis and therapeutic system between Japanese and non-Japanese patients with ovarian cancer in response to their first-line platinum-based chemotherapy [see Section 6.2.7]. Give this, etc., niraparib is expected to have efficacy in Japanese patients as well.

With regard to the maintenance treatment in patients with platinum-sensitive, relapsed, ovarian cancer in response to their last platinum-based chemotherapy in the NOVA study, the applicant stated that the intergroup difference in a subsequent therapy following the completion of study drug treatment might have affected the OS results in the HRD-positive group in the non-*gBRCA*-mutated cohort. This explanation is understandable to some extent. Meanwhile, due to the limited number of OS events in the cohort, it is difficult to draw a conclusion, only based on the applicant's explanation, that the OS results in the HRD-positive group in the non-*gBRCA*-mutated cohort were consistent with the results in the *gBRCA*-mutated cohort and the non-*gBRCA*-mutated cohort. However, for the following reasons, etc., the efficacy of niraparib was demonstrated in Japanese patients as well in the maintenance treatment of those who were included in the NOVA study, e.g., patients with platinum-sensitive, relapsed, ovarian cancer who had received ≥2 platinum-based chemotherapy regimens and were in response to their last platinum-based chemotherapy.

- Niraparib was demonstrated to be superior to placebo in the PFS assessed by the BICR on the basis of the RECIST ver. 1.1 or clinical signs/symptoms and an increase in CA-125, which was the primary endpoint in the NOVA study, in the *gBRCA*-mutated cohort, the HRD-positive group in the non-*gBRCA*-mutated cohort, and the overall study population. In addition, the prolongation of PFS was clinically significant.
- No trend toward a decrease in OS, the secondary endpoint of the NOVA study, was observed for niraparib as compared with placebo in the *gBRCA*-mutated cohort or the non-*gBRCA*-mutated cohort.
- The results of Study 2001 allow only limited discussion about the efficacy of niraparib in Japanese patients. However, based on the reasons including the following, niraparib is expected to have efficacy in Japanese patients as well.

- No clear different trend was observed in the efficacy results between the QUADRA study and Study 2002 [see Sections 7.1.1.3, 7.1.2.2, and 7.R.5.2].
- No obvious differences were identified in the pharmacokinetics of niraparib or the diagnosis of or treatment system for patients with recurrent ovarian cancer in response to the last platinum-based chemotherapy regimen between Japanese and non-Japanese patients [see Section 6.2.7].

7.R.4 Clinical positioning and indications as maintenance treatment

7.R.4.1 Maintenance treatment of patients with ovarian cancer after the initial chemotherapy

The proposed indication for niraparib was "Maintenance treatment of patients with ovarian cancer after the initial chemotherapy." The following statements were also proposed for the "Precautions Concerning Indications" section.

- Niraparib should be used in patients with stage III or IV ovarian cancer diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) who are in response to first-line platinum-based chemotherapy.
- The selection of patients to treat with niraparib should be based on knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

As a result of its review presented in Sections "7.R.3 Efficacy for maintenance treatment" and "7.R.2 Safety" and the following subsection, PMDA has concluded that the "Indications" and "Precautions Concerning Indications" sections could be described as proposed.

7.R.4.1.1 Clinical positioning and indications of niraparib

The maintenance treatment with niraparib of patients with ovarian cancer after the initial chemotherapy is described in clinical practice guidelines or major textbooks of clinical oncology in and outside Japan as follows:

- NCCN guidelines (v. 1.2020):
  Niraparib therapy is highly recommended as maintenance treatment for patients with ovarian cancer in response after their initial chemotherapy without BV who are (i) positive for *BRCA* mutation. The therapy is also recommended as maintenance treatment for patients who are (ii) negative for *BRCA* mutation or unknown.

The applicant's explanation about the clinical positioning and indications of niraparib:
Results of the PRIMA study demonstrated that niraparib has clinical efficacy in patients diagnosed as having stage III or IV ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) who are din response to first-line platinum-based chemotherapy. Niraparib is thus considered to offer a therapeutic option for such patients. The PRIMA study excluded patients with FIGO stage ovarian cancer who had no residual lesions after the primary debulking surgery. However, according the clinical practice guidelines in and outside Japan, similar treatment is performed regardless of the presence or absence of residual lesions

after the primary debulking surgery. Therefore, the use of niraparib is considered recommendable also for such patients.

Based on the above, “Maintenance treatment of patients with ovarian cancer after the initial chemotherapy” was proposed for the indication of niraparib, along with the following advice given in the “Precautions Concerning Indications” section.

- Niraparib should be used in patients with stage III or IV ovarian cancer diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) who are in response to first-line platinum-based chemotherapy.
- The selection of patients to treat with niraparib should be based on knowledge from the “Clinical Studies” section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

While the PRIMA study targeted patients receiving no BV in the maintenance treatment after their initial chemotherapy. However, patients who had received BV in combination with platinum-based chemotherapy as their initial chemotherapy were allowed to be enrolled in the study if they had not received BV as maintenance treatment because of adverse events, etc. for ≥28 days before enrollment. PMDA asked the applicant to explain the clinical benefit of niraparib in patients with a prior history of treatment with BV.

The applicant’s explanation:
The PRIMA study enrolled 7 patients with a prior history of treatment with BV (6 [1.2%] in the niraparib group and 1 [0.4%] in the placebo group), and it was difficult to evaluate the clinical efficacy of niraparib in this limited number of patients. However, the clinical practice guidelines in Japan recommend BV monotherapy as maintenance treatment after the combination of BV and the first-line platinum-based chemotherapy. Given this situation, particular advice to discourage the use of niraparib as maintenance treatment is considered unnecessary for patients who have a prior history of treatment with BV in their initial chemotherapy.

The PRIMA study enrolled patients with high-grade serous ovarian cancer or endometrioid ovarian cancer. PMDA thus asked the applicant to explain the clinical efficacy of niraparib in patients with a histologic type and grade of malignancy other than those in patients eligible for the PRIMA study.

The applicant’s explanation:
In light of the observations below, etc., niraparib is expected to be clinically effective in patients with advanced ovarian cancer who are in response to first-line platinum-based chemotherapy, regardless of their histologic type or malignancy grade. Nevertheless, the fact that patients with high-grade serous ovarian cancer or endometrioid ovarian cancer were enrolled in the PRIMA study should be communicated to healthcare professionals, and thus this information will be included in the “Clinical Studies” section of the package insert.

- As with PARP inhibitors including niraparib, platinum agents are known to be effective for tumors with a deficiency in homologous recombination repair, and these agents are reported to have high therapeutic effect for tumors with a collapsed DNA repair mechanism mediated by homologous recombination repair due to *BRCA* gene mutation, regardless of the histologic type or grade of malignancy (*Clin Cancer Res.* 2014;20:764-75).
- The PRIMA study excluded patients with the histologic types or malignancy grade other than high-grade serous ovarian cancer or endometrioid ovarian cancer. However, 1 patient of this category was included because no histologic types or malignancy grades were specified in the inclusion criteria at the beginning of the study. This limited patient number would have precluded the evaluation of the efficacy of niraparib, but the patient yielded a result of PFS (24.9 months) suggestive of the efficacy of niraparib.

The applicant's explanation about the choice between niraparib and olaparib for patients with advanced ovarian cancer who are in response to first-line platinum-based chemotherapy:
There are no clinical study data that compare the efficacy and safety of niraparib and olaparib and, at present, the priority is not clear. However, while olaparib is recommended for patients with *BRCA*-mutated ovarian cancer (NCCN guidelines [v. 1.2020], etc), niraparib is recommended for patients with advanced ovarian cancer who are in response to first-line platinum-based chemotherapy regardless of the presence or absence of *BRCA* gene mutation. Based on the above, etc., the decision on the choice of either niraparib or olaparib will be made according to the condition of individual patients and based on the understanding of the efficacy and safety of the respective drugs.

PMDA's view:
The applicant's explanation is generally acceptable, and the indication of niraparib can be defined as "Maintenance treatment of patients with ovarian cancer after the initial chemotherapy" as proposed.

Because of limited data from clinical studies investigating the efficacy and safety of niraparib as maintenance treatment for patients with a prior history of treatment with BV and patients with ovarian cancer other than high-grade serous or endometrioid ovarian cancer, niraparib is not recommended for such patients. However, assuming that niraparib is used by physicians with adequate knowledge and experience in cancer chemotherapy, the package insert should provide information about the prior treatments, etc. of patients enrolled in the NOVA studies in the "Clinical Studies" section, along with relevant cautionary advice in the "Precautions Concerning Indications" section.

Based on the above, PMDA has concluded that the "Precautions Concerning Indications" section should include the following advice.

- Niraparib should be used in patients with stage III or IV ovarian cancer diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) who are in response to first-line platinum-based chemotherapy.

- The selection of patients to treat with niraparib should be based on knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

7.R.4.2 Maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer

The proposed indication for niraparib was "Maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer." The following statements were also proposed for the "Precautions Concerning Indications" section.

- Niraparib should be used for patients who are in response to the platinum-based chemotherapy regimen for recurrence.
- The selection of patients to treat with niraparib should be based on knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

As a result of its review presented in Sections "7.R.3 Efficacy for maintenance treatment" and "7.R.2 Safety" and the subsection below, PMDA has concluded that the indications of niraparib should be defined as proposed, along with the following cautionary advice presented in the "Precautions Concerning Indications" section.

- Niraparib should be used for patients who are in response to the platinum-based chemotherapy regimen for recurrence.
- The selection of patients to treat with niraparib should be based on knowledge from the "Clinical Studies" section, such as about time from the completion of the platinum-based chemotherapy regimen to disease progression (platinum-free interval [PFI]) and prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

7.R.4.2.1 Clinical positioning and indications of niraparib

The maintenance treatment with niraparib of patients with platinum-sensitive recurrent ovarian cancer is described as follows in clinical practice guidelines and major textbooks of clinical oncology in and outside Japan.

- NCCN guidelines (v. 1.2020):
  Niraparib is recommended as maintenance treatment for patients with platinum-sensitive recurrent ovarian cancer.

The applicant's explanation about the clinical positioning and indications of niraparib:
Results of the NOVA study demonstrated the clinical efficacy of maintenance treatment with niraparib in patients with platinum-sensitive recurrent ovarian cancer who are in response to the last platinum-based chemotherapy. Niraparib is thus considered to offer a therapeutic option for such patients.

Based on the above, “Maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer” was proposed for the indication of niraparib, along with the definition of platinum sensitivity and information related to the prior treatment of patients enrolled in the clinical studies provided in the “Clinical Studies” section and the following caution advice given in the “Precautions Concerning Indications” section.

- Niraparib should be used for patients who are in response to the platinum-based chemotherapy regimen for recurrence.
- The selection of patients to treat with niraparib should be based on knowledge from the “Clinical Studies” section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

In the NOVA study, *gBRCA*-mutated patients were all eligible for participation regardless of their histologic types, whereas among non-*gBRCA*-mutated patients, only those with high-grade serous cancer were enrolled. PMDA thus asked the applicant to explain the clinical efficacy of niraparib in patients with a histologic type or malignancy grade other than those for high-grade serous ovarian cancer.

The applicant’s response:
In the NOVA study, non-*gBRCA*-mutated patients with a histologic type or malignancy grade other than those of high-grade serous ovarian cancer were to be excluded, but 17 patients in this category (13 in the niraparib group and 4 in the placebo group) were enrolled. This limited patient number precludes the efficacy evaluation of niraparib in these patients. However, platinum agents, which are known to have an effect on tumors with a deficiency in homologous recombination repair as with PARP inhibitors including niraparib, have been reported to be therapeutically effective for tumors with a collapse of DNA repair mechanism mediated by homologous recombination repair due to *BRCA* gene mutation, regardless of histologic types or malignancy grades (*Clin Cancer Res.* 2014;20:764-75). This suggest that niraparib has promising clinical efficacy in patients with recurrent ovarian cancer in response to their platinum-based chemotherapy regimen, regardless of their histologic type or malignancy grade. Nevertheless, the fact that the eligibility for the NOVA study of non-*gBRCA*-mutated patients was limited to only those with high-grade serous ovarian cancer should be communicated to healthcare professionals and thus will be mentioned in the “Clinical Studies” section of the package insert.

In the NOVA study, patients without a prior history of treatment with any PARP inhibitors were eligible for the study. PMDA thus asked the applicant to explain the clinical efficacy of niraparib in patients with a prior history of treatment with PARP inhibitors.

The applicant’s explanation:
There are no available clinical study data on the efficacy and safety of niraparib as the maintenance treatment for patients who had previously been treated with PARP inhibitors and were eligible for the NOVA study. Therefore, niraparib is not recommendable for such patients. However, among participants in the QUADRA study, who had similar characteristics to those in the NOVA study participants, e.g., platinum sensitivity, 1 of

37 patients who had previously been treated with PARP inhibitors showed the efficacy of niraparib, despite some differences in the number of prior treatments. Give this result, etc., particular advice discouraging the use of niraparib is unnecessary for patients with recurrent ovarian cancer in response to their platinum-based chemotherapy regimen.

The applicant's explanation about the choice between niraparib and olaparib for patients with platinum-sensitive recurrent ovarian cancer who are in response to the last platinum-based chemotherapy:
No data of clinical studies comparing the efficacy and safety of niraparib and olaparib are available, and the priority remains unclear. The decision on the choice between the 2 drugs should be made according to the condition of individual patients and based on the understanding of the efficacy and safety of respective drugs.

PMDA's view:
The applicant's explanation is generally acceptable including the proposed indication of "Maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer." In addition, the definition of "platinum sensitivity" in the NOVA study [see Section 7.1.2.3] is key information for the selection patients to treat with niraparib. Thus such information should be provided in the "Clinical Studies" section of the package insert, along with relevant advice in the "Precautions Concerning Indications" section.

Because of limited data from clinical studies investigating the efficacy and safety of niraparib as maintenance treatment for patients with a prior history of treatment with PARP inhibitors and patients with non-*gBRCA*-mutated recurrent ovarian cancer with a histologic type or grade of malignancy other than high-grade serous ovarian cancer, niraparib is not recommended for such patients. However, assuming that niraparib is used by physicians with adequate knowledge and experience in cancer chemotherapy, information including prior treatment of patients enrolled in the NOVA study should be provided in the "Clinical Studies" section of the package insert, along with relevant advice in the "Precautions Concerning Indications" section.

Based on the above, PMDA has concluded that the "Precautions Concerning Indications" section should present the following cautionary advice.

- Niraparib should be used for patients who are in response to the platinum-based chemotherapy regimen for recurrence.
- The selection of patients to treat with niraparib should be based on knowledge from the "Clinical Studies" section, such as about time from the completion of the platinum-based chemotherapy regimen to disease progression (PFI) and prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

7.R.5 Efficacy, clinical positioning, and indications of niraparib in patients with recurrent ovarian cancer with homologous recombination deficiency

The proposed indication of niraparib was "Treatment of patients with advanced, recurrent ovarian cancer with homologous recombination deficiency (HRD)." The following statements were also proposed for the "Precautions Concerning Indications" section.

- Niraparib should be used for patients who have been treated with a platinum-based chemotherapy regimen.
- Niraparib should be used for patients who have been confirmed to be HRD positive by tests using approved *in vitro* diagnostics. HRD-positive and *BRCA*-mutated patients are eligible regardless of platinum sensitivity. Among HRD-positive and non-*BRCA*-mutated patients, only patients with platinum sensitivity are eligible.
- The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

As a result of its review presented in Section "7.R.2 Safety" and the sections below, PMDA has concluded that the indication of niraparib should be defined as "Treatment of patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency," along with the following advice provided in the "Precautions Concerning Indications" section.

- Niraparib should be used for patients who have been treated with 3 or more prior chemotherapy regimens.
- Niraparib should be used for patients who have been confirmed to have homologous recombination deficiency by tests using approved *in vitro* diagnostics or medical devices.
- The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about time from the completion of the platinum-based chemotherapy regimen to disease progression (PFI) and prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib as well as careful consideration of treatments other than with niraparib.

7.R.5.1 Efficacy endpoint in the QUADRA study

The applicant's explanation about the appropriateness of the primary endpoint of the QUADRA study, i.e., response rate assessed by the investigators based on the RECIST ver. 1.1:
The demonstration of efficacy of niraparib in patients enrolled in the QUADRA study would indicate niraparib's promising effect to relieve clinical symptoms associated with disease progression, which was considered clinically significant. Therefore, the primary endpoint was appropriate.

PMDA's view:
Because of unclear relationship between OS, as the true endpoint, and the response rate in patients enrolled in the QUADRA study, it is difficult to evaluate the life-extending effect of niraparib in the patients based on the response rate as the primary endpoint of the QUADRA study. However, the above applicant's point that the achievement of response in these patients has a certain clinical significance is understandable. Thus the efficacy of niraparib can be evaluated based on the response rate as the primary endpoint.

7.R.5.2 Results of the efficacy evaluation of niraparib in the QUADRA study and the clinical positioning of niraparib in patients with recurrent ovarian cancer with homologous recombination deficiency

The applicant's explanation about the results of the efficacy evaluation of niraparib in the QUADRA study:

The response rate assessed by the investigators based on the RECIST ver. 1.1 [95% CI], the primary endpoint of the QUADRA study, was 27.7% [15.6, 42.6] in the patients with HRD-positive, platinum-sensitive, recurrent, high-grade, serous ovarian cancer who had received 3 or 4 chemotherapy regimens and had not been previously treated with PARP inhibitors (the primary analysis set), and the lower limit of 95% CI was above the prespecified threshold of 10% [see Section 7.1.2.2]. In the QUADRA study, the best percentage changes in the tumor diameter (target lesion) assessed by the investigators based on the RECIST ver. 1.1 are shown in Figure 11. The median duration of response[50)] [95% CI] was 9.2 months [5.9, not estimable].

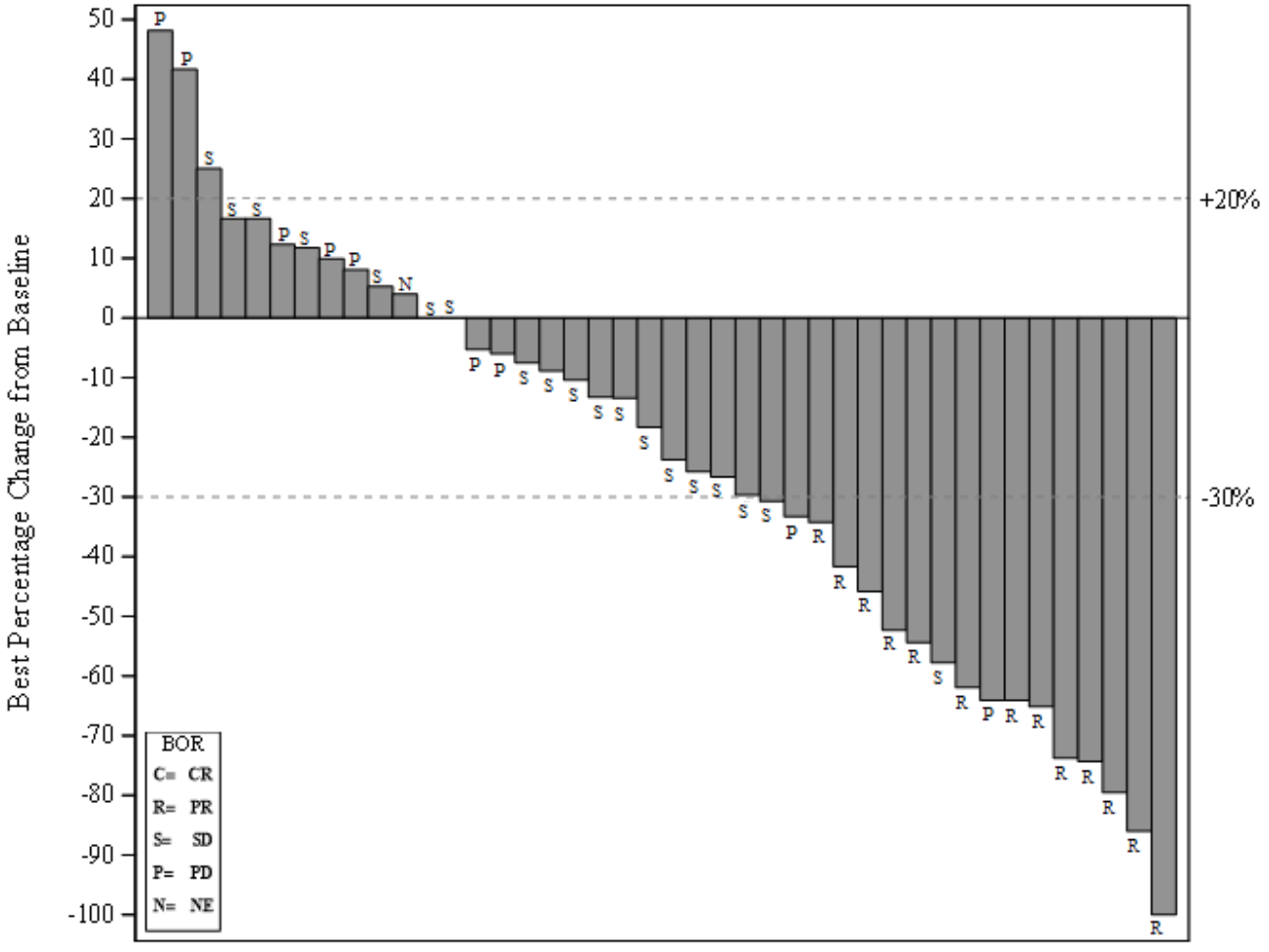


Figure 11. Best percentage changes in tumor diameter (target lesion)
(RECIST ver.1.1, QUADRA study, the main analysis set, assessed by investigators)

In the QUADRA study, the response rate [95% CI] in *tBRCA*-mutated and non-*tBRCA*-mutated patients with HRD-positive and platinum-sensitive ovarian cancer who had received 3 or more chemotherapy regimens and had not been previously treated with PARP inhibitors was 38.9% [17.3, 64.3] and 20.0% [8.4, 36.9],

50) Defined as the duration from the first response (CR or PR) to PD or death in patients with a confirmed response (CR or PR).

respectively. Meanwhile, the response rate [95% CI] in patients with HRD-negative and platinum-sensitive ovarian cancer was 2.4% [0.1, 12.9].

Besides, in Study 2002 targeting Japanese patients, the efficacy evaluation of niraparib yielded the response rate assessed by the investigators based on the RECIST ver. 1.1 [90% CI], the primary endpoint, of 35.0% [17.7, 55.8], with the lower limit of 90% CI above the prespecified threshold of 5% [see Section 7.1.1.3].

The treatment with niraparib of patients with recurrent ovarian cancer with homologous recombination deficiency who have received chemotherapies is described as follows in clinical practice guidelines and major textbooks of clinical oncology in and outside Japan.

- NCCN guidelines (v. 1.2020):
  In patients with recurrent ovarian cancer with homologous recombination deficiency who have received 3 or more chemotherapy regimens, niraparib therapy is recommended for (i) patients with deleterious or suspected deleterious *BRCA* mutation or (ii) platinum-sensitive patients with genomic instability.

In light of the response rates available from the QUADRA study, PMDA asked the applicant to explain the clinical significance of niraparib in the patients included in the primary analysis set of the QUADRA study.

The applicant's explanation:
In terms of the efficacy of currently available chemotherapies in patients with recurrent ovarian cancer receiving 3 or more prior chemotherapy regimens, there are only limited reports presenting results shown by determination method of homologous recombination deficiency or by platinum sensitivity. However, patients suffering recurrent ovarian cancer with a greater number of prior chemotherapy regimens tended to show a decreased response rate to chemotherapy, and the rate of response to chemotherapy in patients with recurrent ovarian cancer who had received 3 and 4 chemotherapy regimens was reported to be 11.9% and 2.9%, respectively (*Eur J Obstet Gynecol Reprod Biol*. 2013;166:94-8). In light of this observation, the data on the response rate available from the QUADRA study are of clinical significance.

Besides, no PARP inhibitors have been approved in Japan for patients with recurrent ovarian cancer who have received 3 or more chemotherapy regimens, and there are a certain number of patients who cannot receive currently available chemotherapy because of adverse events such as peripheral nerve disorders and hypersensitivity. Therefore, it is meaningful to offer niraparib as a therapeutic option for patients eligible for the QUADRA study.

The applicant's explanation about the clinical benefits of niraparib in patients with recurrent ovarian cancer receiving 3 or 4 previous chemotherapy regimens:
The results of the QUADRA study demonstrated clinical efficacy of niraparib in its primary analysis set, i.e., patients with HRD-positive and platinum-sensitive recurrent ovarian cancer who had received 3 or 4 chemotherapy regimens and had not been previously treated with PARP inhibitors [see Section 7.1.2.2].

The following subsections discuss treatment with niraparib in patients who were not included in the primary analysis set of the QUADRA study, i.e., (a) patients with platinum-insensitive ovarian cancer; (b) patients receiving 1 or 2 prior chemotherapy regimens; (c) patients with a histologic type or malignancy grade other than those for high-grade serous ovarian cancer; and (d) patients receiving treatment with PARP inhibitors.

(a) Patients with platinum-insensitive ovarian cancer:

In the QUADRA study, among the patients with HRD-positive ovarian cancer who had received 3 or more chemotherapy regimens and had not been previously treated with PARP inhibitors, the response rate [95% CI] was (i) 26.4% (14 of 53 patients) [15.3, 40.3] in patients with platinum-sensitive ovarian cancer,[33)] (ii) 13.8% (8 of 58 patients) [6.1, 25.4] in patients with platinum-resistant ovarian cancer,[51)] and (iii) 6.5% (4 of 62 patients) [1.8, 15.7] in patients with platinum-unresponsive ovarian cancer.[52)] The results suggest that niraparib is expected to have efficacy in patients with platinum-sensitive ovarian cancer.

In an exploratory analysis which was not prespecified, among patients with HRD-positive and *tBRCA*-mutated ovarian cancer who had received 3 or more chemotherapy regimens and had not been previously treated with PARP inhibitors, the response rate [95% CI] was (i) 38.9% (7 of 18 patients) [17.3, 64.3] in patients with platinum-sensitive ovarian cancer,[33)] (ii) 33.3% (7 of 21 patients) [14.6, 57.0] in patients with platinum-resistant ovarian cancer,[51)] and (iii) 18.8% (3 of 16 patients) [4.0, 45.6] in patients with platinum-unresponsive ovarian cancer.[52)] The response rate in patients with platinum-insensitive ovarian cancer was comparable to that in patients with platinum-sensitive ovarian cancer. Therefore, niraparib is expected to have efficacy in patients with *tBRCA*-mutated cancer with homologous recombination deficiency, regardless of their platinum sensitivity, and niraparib is recommendable for these patients.

Based on the above, the "Precautions Concerning Indications" section will include the following advice.

- Patients with HRD-positive *BRCA*-mutated cancer are all eligible regardless of their platinum sensitivity. Patients with HRD-positive non-*BRCA*-mutated cancer, in contrast, are eligible only if platinum-sensitive.

(b) Patients with 1 or 2 prior chemotherapy regimens:

The QUADRA study did not include patients with recurrent ovarian cancer who had received 1 or 2 previous chemotherapy regimens, and thus no clinical data of these patients are available. Therefore, niraparib is not recommendable for these patients. In the package insert, the "Clinical Studies" section will note that patients receiving 3 or 4 previous chemotherapy regimens were the population of the primary analysis set of the QUADRA study, and the "Precautions Concerning Indications" section will include the following advice.

- The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

[51)] PFI of >28 days and <180 days
[52)] PFI of ≤28 days

(c) Patients with a histologic type or malignancy grade other than those for high-grade serous ovarian cancer:
The QUADRA study included 2 patients with a histologic type or malignancy grade other than those for high-grade serous ovarian cancer. Niraparib did not demonstrate its efficacy in 1 patient evaluable for the efficacy. However, PARP inhibitors including niraparib have been reported to have therapeutic effect on ovarian cancer with a collapse of DNA repair mechanism mediated by homologous recombination repair, regardless of the histologic type or malignancy grade (*Clin Cancer Res.* 2014;20:764-75). These observations indicate that the use of niraparib is acceptable in patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency receiving 3 or 4 previous chemotherapy regimens, regardless of their histologic type or malignancy grade. Nevertheless, the fact that the QUADRA study targeted patients with high-grade serous ovarian cancer should be communicated to healthcare professionals and thus will be mentioned in the "Clinical Studies" section of the package insert.

(d) Patients with prior treatment with PARP inhibitors:
Patients who had been previously treated with PARP inhibitors were eligible for the QUADRA study, and 37 patients of this category were enrolled. The small number of patients enrolled allow limited efficacy evaluation of niraparib. However, given that 1 patient responded to niraparib, the use of niraparib in patients with prior treatment with PARP inhibitors is acceptable.

Accordingly, the indication of niraparib was proposed as "treatment of patients with advanced/recurrent ovarian cancer with homologous recombination deficiency (HRD)," along with information on prior treatment in patients enrolled in the QUADRA study to be presented in the "Clinical Studies" section and the following cautionary advice to be presented in the "Precautions Concerning Indications" section.

- Niraparib should be used for patients who have been treated with a platinum-based chemotherapy regimen.
- HRD-positive BRCA-mutated patients are eligible regardless of platinum sensitivity. HRD-positive non-BRCA-mutated patients are eligible only if platinum sensitive.
- The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

PMDA's view:
Extremely limited data are available in terms of the response rate to the approved chemotherapy regimens in patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency receiving 3 or 4 previous chemotherapy regimens, the population of the primary evaluation set of the QUADRA study. This precludes precise evaluation of the appropriateness of the threshold response rate specified in the study. However, given the applicant's explanation and the following observations, niraparib is of a certain clinical significance in patients, including Japanese individuals, with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency receiving 3 or 4 previous platinum-based chemotherapy regimens, who were included in the primary evaluation set in the QUADRA study.

- Niraparib demonstrated its efficacy in patients with platinum-sensitive recurrent ovarian cancer in the NOVA study [see Section 7.1.2.3].
- The response rate in Study 2002 in Japanese patients with HRD-positive and platinum-sensitive recurrent ovarian cancer receiving 3 or 4 previous chemotherapy regimens did not markedly differ from data from the QUADRA study.

Meanwhile, a non-prespecified exploratory analysis in the QUADRA study demonstrated the efficacy of niraparib in patients with homologous recombination deficiency to a certain extent in patients with *tBRCA*-mutated, platinum-insensitive recurrent ovarian cancer. However, because of the lack of confirmatory study data of niraparib in the patient population with recurrent ovarian cancer previously receiving chemotherapy that was eligible for the QUADRA study, no conclusion could be drawn on the clinical significance of niraparib in this patient population based on the exploratory analysis alone.

Accordingly, niraparib should be used in patients with platinum-sensitive ovarian cancer with homologous recombination deficiency, the patient population subjected to the primary analysis set, and this should be clearly stated in the "Indications" section.

Furthermore, the definitions for "platinum sensitivity" in the QUADRA study and Study 2002 to be mentioned in the "Indications" section [see Sections 7.1.2.2 and 7.1.1.3] as well as prior chemotherapy in patients enrolled in the clinical studies should be detailed in the "Clinical Studies" section of the package insert and also be advised in the "Precautions Concerning Indications" section.

In addition, in patients enrolled in the QUADRA study, the efficacy of niraparib was evaluated mainly based on the results of response rate, and data on survival effect were not available. This indicates that the use of treatment options other than niraparib should also be carefully considered. The appropriateness of the use of niraparib should be determined carefully after due consideration of other treatment options, and such advice should be given in the "Precautions Concerning Indications" section.

Based on the above, the indication of niraparib should be defined as "the treatment of patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency," along with the following advice provided in the "Precautions Concerning Indications" section of the package insert.

- Niraparib should be used for patients who have been treated with 3 or more prior chemotherapy regimens.
- The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about time from the completion of the platinum-based chemotherapy regimen to disease progression (PFI) and prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib as well as careful consideration of treatments other than with niraparib.

7.R.5.3 Tests for homologous recombination deficiency and patients eligible for treatment with niraparib

In the QUADRA study and Study 2002, tumor tissues were tested with Myriad myChoice HRD CDx, and the criterion of *tBRCA*-mutated or the GIS of ≥42 was used to determine the presence of HRD. PMDA asked the applicant to explain the appropriateness of the criterion for determination.

The applicant's explanation:
LOH, TAI, and LST, which compose GIS for the Myriad myChoice HRD CDx, were reported to have been detected in tumor cells with a defect of homologous recombination repair due to mutations in genes such as the *BRCA* gene related to the repair (*Br J Cancer*. 2012;107:1776-82; and *Cancer Discov*. 2012;2:366-75). Besides, the scores based on the LOH, TAI, and LST have been reported to be related to the functional defects of the *BRCA* protein (*Breast Cancer Res.* 2014;14:475-83). These findings suggest that the combined use of the results of *BRCA* genetic tests and the GIS will allow for highly accurate identification of patients with homologous recombination deficiency.

The applicant provided the following explanation about tests for homologous recombination deficiency used for the selection of patients to be treated with niraparib.

In the QUADRA study and Study 2002, the Myriad myChoice HRD CDx (Myriad Genetic Laboratories) was used for tests with tumor tissues in the central laboratory at enrollment. Niraparib has been demonstrated to have a certain extent of efficacy in patients tested HRD positive[36)] in the QUADRA study and Study 2002. Therefore, in the post- marketing use of niraparib, the Myriad myChoice HRD CDx (Myriad Genetic Laboratories) should be used for the selection of patients. The following advice will be given in the "Precautions Concerning Indications" section.

- Niraparib should be used for patients who have been confirmed to be HRD positive by tests using approved *in vitro* diagnostics.

PMDA's view:
The above applicant's explanation is acceptable. The "Precautions Concerning Indications" section should provide advice modified as follows:

- Niraparib should be used for patients who have homologous recombination deficiency confirmed by tests using approved *in vitro* diagnostics or medical devices.

7.R.6 Dosage and administration

The following dosage regimen of niraparib was proposed: "The usual adult dosage is 200 mg of niraparib administered orally once daily. For adult patients with a body weight of ≥77 kg and a platelet count of ≥150,000/μL at baseline, the recommended dose of niraparib is 300 mg administered orally once daily. The dose should be reduced, as appropriate, according to the patient's condition." After filing the application, the applicant explained that the following changes had been made to the statements in the "Precautions Concerning

Dosage and Administration" section about the duration of administration of niraparib as the maintenance treatment of patients with ovarian cancer after the initial chemotherapy.

For all indications:

- Guidelines for treatment interruption, dose reduction, treatment discontinuation for adverse reactions to niraparib
- The efficacy and safety of niraparib in combination with other antineoplastics have not been established.

For maintenance treatment of patients with ovarian cancer after the initial chemotherapy:

- The efficacy and safety of niraparib administered for >3 years have not been established.

As a result of its review presented in Sections "7.R.2 Safety," "7.R.3 Efficacy for maintenance treatment," and "7.R.5 Efficacy, clinical positioning, and indications of niraparib in patients with recurrent ovarian cancer with homologous recombination deficiency" and the sections below, PMDA has concluded that the dosage regimens of niraparib should be defined as proposed, along with the following cautionary statements presented in the "Precautions Concerning Dosage and Administration" section.

For all indications:

- Guidelines for treatment interruption, dose reduction, treatment discontinuation for adverse reactions to niraparib
- The efficacy and safety of niraparib in combination with other antineoplastics have not been established.

For maintenance treatment of patients with ovarian cancer after the initial chemotherapy:

- The efficacy and safety of niraparib administered for >3 years have not been established.

7.R.6.1 Dosage and administration of niraparib

The applicant's explanation about the dosage regimens of niraparib:

The MTD of niraparib was determined to be 300 mg QD in the foreign phase I study (Study PN001) and the Japanese phase I study (Study 1001) that enrolled patients with advanced solid cancer, and the dosage regimen was used in the foreign phase II study (QUADRA study), the foreign phase III study (NOVA study), and the Japanese phase II studies (Studies 2001 and 2002). The dosage regimen for the foreign phase III study (PRIMA study) was specified as 300 mg QD (fixed starting dose) in the study protocol version 1 (dated October 26, 2015). However, based on the results from the exploratory analysis of the NOVA study and for the reasons below, etc., the starting dose in the PRIMA study was changed to an individualized starting dose as follows: a 200 mg QD oral dose for patients with a body weight of <77 kg or a platelet count of <150,000/μL at baseline; and a 300 mg QD oral dose for patients with a body weight of ≥77 kg and a platelet count of ≥150,000/μL at baseline (protocol revision 2, dated November 16, 2017).

- The incidence of Grade 3 or 4 adverse events related to decreased platelets was (a) 34.6% and (b) 11.8% for (a) patients with a body weight of <77 kg or a platelet count of <150,000/μL at baseline and (b) patients with a body weight of ≥77 kg and a platelet count of ≥150,000/μL at baseline, respectively.

- The incidence of Grade 3 or 4 adverse events related to decreased platelets at 300 mg, 200 mg, and 100 mg was 33.2%, 5.9%, and 2.3%, respectively.
- In terms of efficacy, no marked differences in PFS were observed between patients who continued to receive niraparib 300 mg and patients whose dose was reduced to 200 mg 4 months after the start of treatment.[53)]

Accordingly, the PRIMA study was conducted and demonstrated the clinical benefit of niraparib, regardless of the starting dose [see Section 7.R.1]. The proposed dosage regimens of niraparib were defined based on the individualized starting dose in the PRIMA study.

The following observations indicate that the proposed dosage regimens are valid for use in patients eligible for the NOVA study and Study 2001 and those eligible for the QUADRA study and Study 2002.

- Despite differences in the number of prior regimens, the patients enrolled in the above studies had some common characteristics including their response to a platinum-based chemotherapy regimen.
- The sum of target lesion diameters remained stable in patients whose niraparib dose was reduced to 200 or 100 mg in the QUADRA study or Study 2002 even after the dose reduction.

Because of no clinical study data on the efficacy and safety of niraparib used in combination with other antineoplastics at present, such use of niraparib is not recommended.

The applicant's explanation about the duration of treatment with niraparib as maintenance treatment after the initial chemotherapy: In the PRIMA study, the treatment duration with niraparib was specified as 3 years, patients who had not presented with niraparib-associated disease progression were allowed to continue the receive niraparib beyond 3 years. Because the longest treatment duration was 29 months in the niraparib group in the PRIMA study, the efficacy or safety of niraparib administered for >3 years were not assessed. Therefore, it is difficult to strongly recommend to use niraparib for >3 years. Accordingly, the cautionary note will be presented in the "Precautions Concerning Indications" section.

- The efficacy and safety of niraparib administered for >3 years have not been established.

PMDA's view:
The applicant's explanation is generally acceptable. The dosage regimens of niraparib can be defined as "The usual adult dosage is 200 mg of niraparib administered orally once daily. For adult patients with a body weight of ≥77 kg and a platelet count of ≥150,000/μL at baseline, the recommended dose is 300 mg of niraparib administered orally once daily. The dose should be reduced, as appropriate, according to the patient's condition" as per the applicant's proposal. In terms of the duration of treatment with niraparib as maintenance treatment

[53)] Adverse events requiring the reduction of niraparib dose occurred in 73% of patients enrolled in the NOVA study, and the niraparib dose was adjusted before Month 4 of niraparib treatment in most of the patients. Thus the PFS analysis for individual dosages at Month 4 of treatment with niraparib was performed.

after the initial chemotherapy, the following cautionary note should be presented in the "Precautions for Dosage and Administration" section.

- The efficacy and safety of niraparib administered for >3 years have not been established.

7.R.6.2 Dose adjustment for niraparib

The applicant's explanation about the dose adjustment criteria for niraparib:
Criteria for treatment interruption, dose reduction, and treatment discontinuation were specified in the clinical studies including the PRIMA study, and the clinical benefits of niraparib were confirmed through the adherence to the criteria. The proposed dosage regimens for niraparib were the same as those for the individualized starting doses in the PRIMA, and the dose adjustment criteria for niraparib were defined according to those used in the PRIMA study in the "Precautions Concerning Dosage and Administration" section.

PMDA's view:
The applicant's explanation is generally acceptable. The criteria for treatment interruption, dose reduction, and treatment discontinuation for niraparib in case of any adverse reactions should be presented in the "Precautions Concerning Dosage and Administration" section. Measures taken in the clinical studies at the occurrence of decreased platelet count (e.g., blood transfusion) should be communicated via written materials.

- If any adverse reaction to niraparib occurs, treatment should be interrupted, continued at a reduced dose, or discontinued as per the following criteria.

Dosage for dose reduction/discontinuation

Starting dose level	200 mg	300 mg
First dose reduction	100 mg	200 mg
Second dose reduction	Discontinue treatment	100 mg
Third dose reduction		Discontinue treatment

Criteria for treatment interruption, dose reduction, and treatment discontinuation following adverse reaction

Adverse reactions	Severity*1	Actions	Dose for resumption
Platelet count decreased	Platelet count <100,000/μL	First episode: • Withhold niraparib for up to 28 days until platelet count returns to ≥100,000/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	• Same or reduced dose to the first dose reduction level. • Dose reduced to the first dose reduction level if the platelet count is <75,000/μL.
		Second episode: • Withhold niraparib for up to 28 days until platelet count returns to ≥100,000/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Neutrophil count decreased	Neutrophil count <1,000/μL	• Withhold niraparib for up to 28 days until neutrophil count returns to ≥1,500/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Anemia	Hemoglobin <8 g/dL	• Withhold niraparib for up to 28 days until hemoglobin returns to ≥9 g/dL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Adverse reactions other than the above*2	Grade ≥3	• Withhold niraparib for up to 28 days until recovery to baseline or ≤Grade 1. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction

*1, Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) ver.4.03.
*2, Adverse reaction persisting despite prevention or treatment

7.R.7 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan:
Post-marketing surveillance was planned as an all-case survey involving all patients treated with niraparib in post-marketing setting to investigate the safety, etc. of niraparib.

Bone marrow suppression, hypertension, secondary malignancy, embryo-fetal toxicity, and ILD were included in the safety specification of this surveillance based on the occurrence of these adverse events, etc. in the PRIMA study, NOVA study, Study 2001, the QUADRA study, and Study 2002.

The planned sample size was 300 patients (150 patients with ovarian cancer after the initial chemotherapy [maintenance treatment], 100 patients with platinum-sensitive recurrent ovarian cancer [maintenance treatment], and 50 patients with recurrent ovarian cancer with homologous recombination deficiency), which was determined based on the occurrence of the above-mentioned events in the surveillance safety specification in the clinical studies.

Because the majority of the events in the safety specification first occurred within a year after the start of treatment with niraparib in the above clinical studies, the observation period was specified as 1 year after the start of treatment with niraparib.

PMDA's view:
Given the limited safety data of niraparib administered in Japanese patients, the post-marketing surveillance is

essential and data obtained from the survey should be promptly provided to healthcare professionals. However, there is little need for the post-marketing surveillance to be an all-case survey, in light of no obvious differences in safety profiles between niraparib and similar drugs except for the occurrence of hypertension and posterior reversible encephalopathy syndrome, a certain level of clinical experience overseas, and no newly identified safety concerns except for posterior reversible encephalopathy syndrome.

Based on the review in Section "7.R.2 Safety," the safety specification of the surveillance should include bone marrow suppression, hypertension, ILD, posterior reversible encephalopathy syndrome, secondary malignancy, and thromboembolism.

Besides, the planned sample size and the observation period should be reviewed based on the occurrence of events in the surveillance safety specification.

7.3 Adverse events observed in clinical studies

Among the clinical study data submitted for safety evaluation, death-related data are summarized in Sections "7.1 Evaluation data" and "7.2 Reference data," and major adverse events other than deaths are described below.

7.3.1 Japanese phase I study (Study 1001)

All subjects experienced adverse events, and a causal relationship with niraparib could not be ruled out the events in all subjects. The following adverse events occurred at an incidence of ≥50% in each cohort: in the niraparib 200 mg cohort, vomiting in 2 subjects (66.7%), fatigue in 2 subjects (66.7%), and decreased appetite in 2 subjects (66.7%); in the niraparib 300 mg cohort, platelet count decreased in 5 subjects (83.3%), nausea in 4 subjects (66.7%), AST increased in 4 subjects (66.7%), increased blood ALP in 3 subjects (50.0%), and GGT increased in 3 subjects (50.0%).

A serious adverse event occurred in 1 of 6 subjects (16.7%) in the niraparib 300 mg cohort. The serious adverse event was pyelonephritis, and its causal relationship with niraparib was ruled out.

An adverse event led to discontinuation of the treatment with niraparib in 1 of 6 subjects (16.7%) in the niraparib 300 mg cohort. The event was malaise and its causal relationship with niraparib was not ruled out.

7.3.2 Japanese phase II study (Study 2001)

All subjects experienced adverse events, and all subjects experienced adverse events for which a causal relationship with niraparib could not be ruled out. The following adverse events occurred at an incidence of ≥20%: nausea in 13 subjects (68.4%), platelet count decreased in 12 subjects (63.2%), neutrophil count decreased in 9 subjects (47.4%), vomiting in 7 subjects (36.8%), decreased appetite in 7 subjects (36.8%), white blood cell count decreased in 6 subjects (31.6%), and headache in 6 subjects (31.6%).

A serious adverse event occurred in 1 of 19 subjects (5.3%). The serious adverse event was thrombocytopenia, and its causal relationship with niraparib was not ruled out.

No adverse events led to discontinuation of treatment with niraparib.

7.3.3 Japanese phase II study (Study 2002)

All subjects experienced any adverse events, and all subjects experienced adverse events for which a causal relationship with niraparib could not be ruled out. The following adverse events occurred at an incidence of ≥20%: anaemia in 14 subjects (70.0%), nausea in 12 subjects (60.0%), platelet count decreased in 11 subjects (55.0%), constipation in 7 subjects (35.0%), vomiting in 7 subjects (35.0%), malaise in 6 subjects (30.0%), neutrophil count decreased in 6 subjects (30.0%), headache in 6 subjects (30.0%), decreased appetite in 5 subjects (25.0%), palpitations in 4 subjects (20.0%), blood creatinine increased in 4 subjects (20.0%), and white blood cell count decreased in 4 subjects (20.0%).

Serious adverse events occurred in 4 of 20 subjects (20.0%). They were anaemia in 2 subjects (10.0%), platelet count decreased in 2 subjects (10.0%), ascites in 1 subject (5.0%), and dyspnoea in 1 subject (5.0%). Among these adverse events, a causal relationship with niraparib was not ruled out for anaemia in 2 subject, platelet count decreased in 2 subjects, and dyspnoea in 1 subject.

Adverse events led to discontinuation of treatment with niraparib in 1 of 20 subjects (5.0%). These event included neutrophil count decreased in 1 subject (5.0%), platelet count decreased in 1 subject (5.0%), and white blood cell count decreased in 1 subject (5.0%), and a causal relationship with niraparib was not ruled out for these events.

7.3.4 Foreign phase I study (Study PN001)

All subjects experienced any adverse events. A causal relationship with niraparib was not ruled for events in 5 of 6 subjects (83.3%) in the 30 mg cohort, 3 of 3 subjects (100%) in the 40 mg cohort, 7 of 7 subjects (100%) in the 60 mg cohort, 5 of 6 subjects (83.3%) in the 80 mg cohort, 2 of 5 subjects (40.0%) in the 110 mg cohort, 4 of 6 subjects (66.7%) in the 150 mg cohort, 6 of 6 subjects (100%) in the 210 mg cohort, 5 of 5 subjects (100%) in the 290 mg cohort, 51 of 54 subjects (94.4%) in the 300 mg cohort, and 6 of 6 subjects (100%) in the 400 mg cohort. The following adverse events occurred at an incidence of ≥50% in each cohort: diarrhoea, fatigue, and decreased appetite in 3 subjects (50.0%) each in the 30 mg cohort; diarrhoea, cough, and dyspnoea in 3 subjects (100%) each, and fatigue 2 subjects (66.7%) in the 40 mg cohort; anaemia in 4 subjects (57.1%) in the 60 mg cohort; fatigue in 3 subjects (50.0%) in the 80 mg cohort; fatigue in 3 subjects (60.0%) in the 110 mg cohort; nausea and vomiting in 4 subjects (66.7%) each, and constipation in 3 subjects (50.0%) in the 150 mg cohort; nausea in 5 subjects (83.3%), thrombocytopenia, dyspnoea in 4 subjects (66.7%) each, and decreased appetite in 3 subjects (50.0%) in the 210 mg cohort; fatigue in 5 subjects (100%), nausea in 4 subjects (80.0%), abdominal distension, constipation, vomiting, headache, and cough in 3 subjects (60.0%) each in the 290 mg cohort; nausea in 35 subjects (64.8%), anaemia in 34 subjects (63.0%), and fatigue in 32 subjects (59.3%) in the 300 mg cohort; anaemia in 6 subjects (100%), thrombocytopenia, nausea, and vomiting in 5

subjects (83.3%) each, neutropenia and fatigue in 4 subjects (66.7%) each, and decreased appetite in 3 subjects (50.0%) in the 400 mg cohort.

Serious adverse events occurred in 2 of 6 subjects (33.3%) in the 30 mg cohort, 4 of 7 subjects (57.1%) in the 60 mg cohort, 1 of 6 subjects (16.7%) in the 80 mg cohort, 2 of 6 subjects (33.3%) in the 150 mg cohort, 3 of 6 subjects (50.0%) in the 210 mg cohort, 3 of 5 subjects (60.0%) in the 290 mg cohort, 18 of 54 subjects (33.3%) in the 300 mg cohort, and 3 of 6 subjects (50.0%) in the 400 mg cohort, and no serious adverse events occurred in the 40 mg cohort or the 110 mg cohort. Serious adverse events occurring in ≥2 subjects in each cohort were anaemia in 2 subjects (28.6%) in the 60 mg cohort and thrombocytopenia in 2 subjects (3.7%) in the 300 mg cohort, and a causal relationship with niraparib was not ruled out for them.

Adverse events led to discontinuation of treatment with niraparib in 1 of 6 subjects (16.7%) in the 30 mg cohort, 1 of 7 subjects (14.3%) in the 60 mg cohort, 1 of 6 subjects (16.7%) in the 150 mg cohort, 4 of 54 subjects (7.4%) in the 300 mg cohort, and 2 of 6 subjects (33.3%) in the 400 mg cohort. No adverse events led to treatment discontinuation in the 40 mg cohort, the 80 mg cohort, the 110 mg cohort, the 210 mg cohort, or the 290 mg cohort. Adverse events leading to discontinuation of treatment with niraparib in ≥2 subjects in each cohort were electrocardiogram QT prolonged in 2 subjects (3.7%) in the 300 mg cohort and thrombocytopenia in 2 subjects (33.3%) in the 400 mg cohort, and a causal relationship with niraparib was not ruled out for fatigue 1 subject in the niraparib 30 mg cohort, pneumonitis in 1 subject in the niraparib 60 mg cohort, and electrocardiogram QT prolonged in 2 subjects in the niraparib 300 mg cohort.

7.3.5 Foreign phase II study (QUADRA study)

Adverse event occurred in 461 of 463 subjects (99.6%), and adverse events for which a causal relationship with niraparib was not ruled out were reported in 443 of 463 subjects (95.7%). Adverse events with an incidence of ≥20% are shown in Table 46.

Table 46. Adverse events with an incidence of ≥20%

SOC PT (MedDRA/J ver. 20.0)	Number of subjects (%) N = 463	
	All grades	Grade ≥3
All adverse events	461 (99.6)	338 (73.0)
Gastrointestinal disorders		
Nausea	312 (67.4)	45 (9.7)
Vomiting	205 (44.3)	37 (8.0)
Constipation	159 (34.3)	14 (3.0)
Abdominal pain	97 (21.0)	29 (6.3)
Blood and lymphatic system disorders		
Anaemia	229 (49.5)	122 (26.3)
Thrombocytopenia	159 (34.3)	95 (20.5)
General disorders and administration site conditions		
Fatigue	237 (51.2)	29 (6.3)
Laboratory test		
Platelet count decreased	101 (21.8)	42 (9.1)
Metabolism and nutrition disorders		
Decreased appetite	122 (26.3)	9 (1.9)
Psychiatric disorders		
Insomnia	98 (21.2)	5 (1.1)

Serious adverse events occurred in 197 of 463 subjects (42.5%). The serious adverse event occurred in ≥20 subjects were small intestinal obstruction in 34 subjects (7.3%), thrombocytopenia in 34 subjects (7.3%), vomiting in 27 subjects (5.8%), and nausea 21 subjects (4.5%). A causal relationship with niraparib was not ruled out for thrombocytopenia in 34 subjects, vomiting in 13 subjects, and nausea in 10 subjects.

Adverse events led to discontinuation of treatment with niraparib in 98 of 463 subjects (21.2%). The adverse events leading to discontinuation of treatment with niraparib in ≥5 subjects were vomiting in 18 subjects (3.9%), thrombocytopenia in 16 subjects (3.5%), nausea in 14 subjects (3.0%), small intestinal obstruction in 12 subjects (2.6%), and anaemia in 7 subjects (1.5%). A causal relationship with niraparib was not ruled out for thrombocytopenia in 15 subjects, nausea in 12 subjects, vomiting in 11 subjects, and anaemia in 7 subjects.

7.3.6 Foreign phase III study (NOVA study)

Adverse events occurred in 367 of 367 subjects (100%) in the niraparib group and 171 of 179 subjects (95.5%) in the placebo group. A causal relationship with the study drug could not be ruled out for events in 359 of 367 subjects (97.8%) in the niraparib group and 126 of 179 subjects (70.4%) in the placebo group. Adverse events with an incidence of ≥20% in either group are shown in Table 47.

Table 47. Adverse events with an incidence of ≥20% in either group

SOC PT (MedDRA/J ver. 18.0)	Number of subjects (%)			
	Niraparib n = 367		Placebo n = 179	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	367 (100)	278 (75.7)	171 (95.5)	42 (23.5)
Gastrointestinal disorders				
Nausea	272 (74.1)	12 (3.3)	64 (35.8)	2 (1.1)
Constipation	152 (41.4)	2 (0.5)	38 (21.2)	1 (0.6)
Vomiting	131 (35.7)	7 (1.9)	31 (17.3)	1 (0.6)
Abdominal pain	90 (24.5)	4 (1.1)	56 (31.3)	3 (1.7)
Diarrhoea	76 (20.7)	1 (0.3)	38 (21.2)	1 (0.6)
Blood and lymphatic system disorders				
Anaemia	181 (49.3)	92 (25.1)	12 (6.7)	0
Thrombocytopenia	170 (46.3)	106 (28.9)	6 (3.4)	1 (0.6)
General disorders and administration site conditions				
Fatigue	172 (46.9)	21 (5.7)	58 (32.4)	0
Laboratory test				
Platelet count decreased	77 (21.0)	27 (7.4)	3 (1.7)	0
Metabolism and nutrition disorders				
Decreased appetite	95 (25.9)	1 (0.3)	26 (14.5)	1 (0.6)
Nervous system disorders				
Headache	98 (26.7)	2 (0.5)	19 (10.6)	0
Psychiatric disorders				
Insomnia	91 (24.8)	1 (0.3)	15 (8.4)	0
Vascular disorders				
Hypertension	77 (21.0)	32 (8.7)	9 (5.0)	4 (2.2)

Serious adverse events occurred in 117 of 367 subjects (31.9%) in the niraparib group and 27 of 179 subjects (15.1%) in the placebo group. Serious adverse events occurring in ≥4 subjects in the respective groups were: in the niraparib group, thrombocytopenia in 40 subjects (10.9%), anaemia in 15 subjects (4.1%), small intestinal obstruction in 7 subjects (1.9%), and constipation in 4 subjects (1.1%); and in the placebo group,

small intestinal obstruction in 4 subjects (2.2%). A causal relationship with the study drug was not ruled out for thrombocytopenia in 40 subjects and anaemia in 14 subjects in the niraparib group.

Adverse events led to discontinuation of treatment with the study drug in 60 of 367 subjects (16.3%) in the niraparib group and 4 of 179 subjects (2.2%) in the placebo group. Serious adverse events leading to discontinuation of treatment with the study drug in ≥4 subjects in the respective groups were fatigue in 10 subjects (2.7%), thrombocytopenia in 7 subjects (1.9%), nausea in 6 subjects (1.6%), platelet count decreased in 6 subjects (1.6%), anaemia in 5 subjects (1.4%), and neutrophil count decreased 4 subjects (1.1%) in the niraparib group. A causal relationship with the study drug was not ruled out for all these events.

7.3.7 Foreign phase III study (PRIMA study)

Adverse events occurred in 478 of 484 subjects (98.8%) in the niraparib group and 224 of 244 subjects (91.8%) in the placebo group, and a causal relationship with the study drug was not ruled out in 466 of 484 subjects (96.3%) in the niraparib group and 168 of 244 subjects (68.9%) in the placebo group. Adverse events with an incidence of ≥20% in either group are shown in Table 48.

Table 48. Adverse events with an incidence of ≥20% in either group

SOC PT (MedDRA/J ver. 18.0)	Number of subjects (%)			
	Niraparib n = 484		Placebo n = 244	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	478 (98.8)	341 (70.5)	224 (91.8)	46 (18.9)
Gastrointestinal disorders				
Nausea	278 (57.4)	6 (1.2)	67 (27.5)	2 (0.8)
Constipation	189 (39.0)	1 (0.2)	46 (18.9)	0
Vomiting	108 (22.3)	4 (0.8)	29 (11.9)	2 (0.8)
Abdominal pain	106 (21.9)	7 (1.4)	75 (30.7)	1 (0.4)
Diarrhoea	91 (18.8)	3 (0.6)	55 (22.5)	1 (0.4)
Blood and lymphatic system disorders				
Anaemia	307 (63.4)	150 (31.0)	43 (17.6)	4 (1.6)
Thrombocytopenia	222 (45.9)	139 (28.7)	9 (3.7)	1 (0.4)
Neutropenia	128 (26.4)	62 (12.8)	16 (6.6)	3 (1.2)
General disorders and administration site conditions				
Fatigue	168 (34.7)	9 (1.9)	72 (29.5)	1 (0.4)
Laboratory test				
Platelet count decreased	133 (27.5)	63 (13.0)	3 (1.2)	0
Nervous system disorders				
Headache	126 (26.0)	2 (0.4)	36 (14.8)	0
Psychiatric disorders				
Insomnia	119 (24.6)	4 (0.8)	35 (14.3)	1 (0.4)

Serious adverse events occurred in 156 of 484 subjects (32.2%) in the niraparib group and 32 of 244 subjects (13.1%) in the placebo group. Serious adverse events occurring in ≥10 subjects were thrombocytopenia in 59 subjects (12.2%), anaemia in 27 subjects (5.6%), platelet count decreased in 20 subjects (4.1%), and small intestinal obstruction 14 subjects (2.9%) in the niraparib group. A causal relationship with the study drug was not ruled out for thrombocytopenia in 59 subjects and anaemia in 26 subjects.

Adverse events led to discontinuation of treatment with the study drug in 58 of 484 subjects (12.0%) in the niraparib group and 6 of 244 subjects (2.5%) in the placebo group. Adverse events leading to discontinuation

of treatment with the study drug occurring in ≥5 subjects were thrombocytopenia in 18 subjects (3.7%), anaemia in 9 subjects (1.9%), nausea in 6 subjects (1.2%), and neutropenia in 6 subjects (1.2%) in the niraparib group. A causal relationship with the study drug was not ruled out for all these events.

7.3.8 Foreign phase I study (Study 5015-C)

Adverse events occurred in 5 of 6 subjects (83.3%) in the run-in period Part 1, 6 of 6 subjects (100%) in the run-in period the Part 2 and 11 of 11 subjects (100%) in the continuous treatment period. A causal relationship with niraparib could not be ruled out in 4 of 6 subjects (66.7%) in the run-in period the Part 2 and in 11 of 11 subjects (100%) in the continuous treatment period (0 in the run-in period Part 1). The following adverse events occurred at an incidence of ≥30% in each part: abdominal pain, pyrexia, and anaemia in 3 subjects (33.3%) each in the run-in period Part 1; constipation, dyspepsia, and dermatitis acneiform in 2 subjects (33.3%) each in the run-in period the Part 2; and nausea in 9 subjects (81.8%), fatigue and anaemia in 7 subjects (63.6%) each, platelet count decreased in 6 subjects (54.5%), abdominal pain, and constipation in 5 subjects (45.5%) each, vomiting, weight loss, and decreased appetite in 4 subjects (36.4%) each in the continuous treatment period.

Serious adverse events occurred in 2 of 6 subjects (33.3%) in the run-in period Part 1 and 1 of 11 subjects (9.1%) in the continuous treatment period (0 in the run-in period the Part 2). The following serious adverse events occurred: ileus and anaemia in 1 subject (16.7%) each the run-in period Part 1; and sepsis 1 subjects (9.1%) in the continuous treatment period. A causal relationship with niraparib was ruled out for all events.

An adverse event led to discontinuation of treatment with niraparib in 1 of 11 subjects (9.1%) in the continuous treatment period (0 in the run-in period Part 1 or the run-in period the Part 2). The adverse event leading to discontinuation of treatment with niraparib was AST increased, for which a causal relationship with niraparib was ruled out.

7.3.9 Foreign phase I study (Study PN014)

Adverse events occurred in all subjects, and a causal relationship with the study drug was not ruled out in 6 of 6 subjects (100%) in the niraparib 30 mg group, 9 of 10 subjects (90.0%) in the niraparib 40 mg group, and 3 of 3 subjects (100%) in the niraparib 70 mg group. The following adverse events occurred at an incidence of ≥50% in the respective groups: anaemia and thrombocytopenia in 5 subjects (83.3%) each, constipation, nausea, fatigue in 4 subjects (66.7%) each, leukopenia, neutropenia, decreased appetite, and dyspnoea in 3 subjects (50.0%) each in the niraparib 30 mg group; fatigue and thrombocytopenia in 7 subjects (70.0%) each, anaemia and leukopenia in 6 subjects (60.0%) each in the niraparib 40 mg group; and anaemia, leukopenia, and neutropenia in 2 subjects (66.7%) each in the niraparib 70 mg group.

Serious adverse events occurred in 2 of 6 subjects (33.3%) in the niraparib 30 mg group, 2 of 10 subjects (20.0%) in the niraparib 40 mg group, and 2 of 3 subjects (66.7%) in the niraparib 70 mg group. These events included thrombocytopenia, constipation, and neoplasm progression in 1 subject (16.7%) each in the niraparib 30 mg group; pelvic fracture and neoplasm progression in 1 subject (10.0%) each in the niraparib 40 mg group;

and disease progression and neoplasm progression in 1 subject (33.3%) each in the niraparib 70 mg group. A causal relationship with the study drug was not ruled out for thrombocytopenia in 1 subject in the niraparib 30 mg group.

Adverse events led to discontinuation of treatment with the study drug in 2 of 10 subjects (20.0%) in the niraparib 40 mg group (0 in the niraparib 30 mg group or the niraparib 70 mg group). There events included thrombocytopenia, neutropenia in 2 subjects (20.0%) each, and leukopenia in 1 subject (10.0%). A causal relationship with the study drug was not ruled out for thrombocytopenia in 2 subjects, leukopenia in 1 subject, and neutropenia in 1 subject.

7.3.10 Foreign phase Ib study (Study PN008)

Adverse events occurred in all subjects. A causal relationship with the study drug was not ruled out in 2 of 3 subjects (66.7%) in the niraparib 40 mg group, 2 of 3 subjects (66.7%) in the niraparib 60 mg group, 3 of 3 subjects (100%) in the niraparib 80 mg group, and 2 of 3 subjects (66.7%) in the niraparib 110 mg group. The following adverse events occurred at an incidence of ≥50% in each group: neutropenia and constipation in 2 subjects (66.7%) each in the niraparib 40 mg group; diarrhoea in 3 subjects (100%), neutropenia, tachycardia, constipation, and fatigue in 2 subjects (66.7%) each in the niraparib 60 mg group; fatigue in 3 subjects (100%), anaemia, constipation, headache, and alopecia in 2 subjects (66.7%) each in the niraparib 80 mg group; and constipation, nausea, fatigue, and dyspnoea in 2 subjects (66.7%) each in the niraparib 110 mg group.

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the niraparib 40 mg group, 1 of 3 subjects (33.3%) in the niraparib 60 mg group, 1 of 3 subjects (33.3%) in the niraparib 80 mg group, and 1 of 3 subjects (33.3%) in the niraparib 110 mg group: The observed serious events were superior vena cava syndrome in 1 of 3 subjects (33.3%); electrocardiogram T wave inversion in 1 of 3 subjects (33.3%) in the niraparib 60 mg group; cellulitis in 1 of 3 subjects (33.3%) in the niraparib 80 mg group; and neoplasm malignant in 1 of 3 subjects (33.3%) in the niraparib 110 mg group. A causal relationship with the study drug was ruled out for all these events.

No adverse events led to discontinuation of treatment with the study drug.

7.3.11 Foreign phase Ib study (Study PN011)

Adverse events occurred in all subjects, and a causal relationship with the study drug was not ruled out in 2 of 3 subjects (66.7%) in the niraparib 30 mg group and 3 of 3 subjects (100%) in the niraparib 40 mg group. The following adverse events occurred at an incidence of ≥50% in each group: nausea and fatigue in 3 subjects (66.7%) each in the niraparib 30 mg group; anaemia, fatigue, headache in 3 subjects (100%) each, abdominal pain, stomatitis, and mucosal inflammation in 2 subjects (66.7%) each in the niraparib 40 mg group.

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the niraparib 30 mg group and 1 of 3 subjects (33.3%) in the niraparib 40 mg group: The observed serious events were neoplasm malignant in 1 subject (33.3%) in the niraparib 30 mg group and gastric ulcer and epistaxis in 1 subject (33.3%) each in the niraparib

40 mg group. A causal relationship with the study drug was not ruled out for epistaxis in 1 subject in the niraparib 40 mg group.

An adverse event led to discontinuation of treatment with the study drug in 1 of 3 subjects (33.3%) in the niraparib 30 mg group (0 in the niraparib 40 mg group). Neoplasm malignant led to discontinuation of treatment with the study drug in 1 subject, and a causal relationship with the study drug was ruled out for the event.

7.3.12 Foreign phase III study (Study 5011-C1)

Adverse events occurred in 24 of 26 subjects (92.3%), and their causal relationship with niraparib was not ruled out in 22 of 26 subjects (84.6%). The following adverse events occurred at an incidence of ≥30%: nausea in 15 subjects (57.7%), anaemia in 13 subjects (50.0%), thrombocytopenia in 13 subjects (50.0%), fatigue in 13 subjects (50.0%), vomiting in 10 subjects (38.5%), constipation in 9 subjects (34.6%), neutropenia in 9 subjects (34.6%), and abdominal pain in 8 subjects (30.8%).

Serious adverse events occurred in 11 of 26 subjects (42.3%). Serious adverse events occurring in ≥2 subjects were thrombocytopenia in 3 subjects (11.5%) and anaemia in 2 subjects (7.7%), and a causal relationship with niraparib was not ruled out for them.

Adverse events led to discontinuation of treatment with niraparib in 4 of 26 subjects (15.4%): thrombocytopenia in 1 subject (3.8%), nausea in 1 subject (3.8%), product difficult to swallow in 1 subject (3.8%), procedural complication in 1 subject (3.8%), and headache in 1 subject (3.8%). A causal relationship with niraparib was not ruled out for thrombocytopenia in 1 subject (3.8%), product difficult to swallow in 1 subject (3.8%), nausea in 1 subject (3.8%), and headache in 1 subject.

7.3.13 Foreign phase III study (Study 5011-C2)

7.3.13.1 Cross-over period

Adverse events occurred in 4 of 16 subjects (25.0%) receiving niraparib under fasted conditions and 6 of 16 subjects (37.5%) receiving niraparib under fed conditions. Their causal relationship with niraparib was not ruled out in 2 of 16 subjects (12.5%) receiving niraparib under fasted conditions and 3 of 16 subjects (18.8%) receiving niraparib under fed conditions. No adverse events occurred at an incidence of ≥10% in either treatment.

A serious urinary tract infection occurred in 1 of 16 subjects (6.3%) receiving niraparib under fasted conditions. Its causal relationship with niraparib was ruled out.

One adverse event, vomiting, led to discontinuation of treatment with niraparib 1 of 16 subjects (6.3%) receiving niraparib under fed conditions. A causal relationship with niraparib was ruled out for the event.

7.3.13.2 QD treatment period

Adverse events occurred in all subjects, and their causal relationship with niraparib was not ruled out in 12 of 15 subjects (80.0%). Adverse events occurring at an incidence of ≥20% included anaemia in 8 subjects (53.3%), decreased appetite in 7 subjects (46.7%), nausea in 5 subjects (33.3%), constipation in 4 subjects (26.7%), vomiting, thrombocytopenia, fatigue, and dyspnoea in 4 subjects (26.7%) each, gastrooesophageal reflux disease, neutropenia, asthenia, and productive cough in 3 subjects (20.0%) each.

Serious adverse events occurred in 5 of 15 subjects (33.3%), which included gastrooesophageal reflux disease, small intestinal obstruction, thrombocytopenia, cardiac arrest, disease progression, sepsis in 1 of 15 subjects (6.7%), and gastrointestinal carcinoma in 1 of 15 subjects (6.7%) each. A causal relationship with niraparib was not ruled out for thrombocytopenia in 1 subject.

Adverse events led to discontinuation of treatment with niraparib in 4 of 15 subjects (26.7%), which included abdominal pain, small intestinal obstruction, sepsis, and cancer pain in 1 subject (6.7%) each. A causal relationship with niraparib was ruled out for all these events.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-3 for maintenance treatment of patients with ovarian cancer and CTD 5.3.5.2-2 for treatment of patients with advanced or recurrent ovarian cancer) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that the product has been demonstrated to have efficacy in (a) the maintenance treatment of patients with ovarian cancer after the initial chemotherapy and (b) the maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer. The product has also been shown to have a certain level of efficacy in (c) the treatment of patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency. The safety of the product is acceptable in view of its benefits. The product is a low-molecular-weight compound that inhibits PARP. The product is a drug with a new active ingredient that blocks the binding of NDA to PARP and prevents the dissociation of PARP-DNA complexes, allowing for the accumulation of DNA damage that leads to apoptosis, and thereby exerting its

inhibitory effects on the proliferation of tumor cells. The product is expected to offer a therapeutic option for ovarian cancer, which is of clinical significance. The clinical positioning, indications, dosing regimens should be further discussed.

PMDA considers that the product may be approved if no particular issues are raised on the basis of the review by the Expert Discussion.

Review Report (2)

August 21, 2020

Product Submitted for Approval

Brand Name	Zejula Capsules 100 mg
Non-proprietary Name	Niraparib Tosilate Hydrate
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	February 28, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Safety

As a result of its review described in "Section 7.R.2 Safety" of Review Report (1), PMDA considers that adverse events including bone marrow suppression, hypertension, ILD, thromboembolism, secondary malignancy, and posterior reversible encephalopathy syndrome require special attention during treatment with niraparib. In the use of niraparib, caution should be used against these adverse events.

Besides the adverse events mentioned above, gastrointestinal disorders also deserve attention in the use of niraparib. Nevertheless, PMDA has concluded that niraparib is tolerable when appropriate measures e.g., monitoring and management of adverse events, dose reduction or treatment interruption of niraparib, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Efficacy, clinical positioning, and indications

As a result of its review described in Sections "7.R.3 efficacy for maintenance treatment," "7.R.4 Clinical positioning and indications for maintenance treatment," and "7.R.5 Efficacy, clinical positioning, and indications of niraparib in patients with recurrent ovarian cancer with homologous recombination deficiency recurrent ovarian cancer with homologous recombination deficiency" of Review Report (1), PMDA reached the following conclusions (a), (b), and (c) for efficacy, clinical positioning, and indications, respectively.

(a) In a foreign phase III study (PRIMA study) in patients with advanced ovarian cancer in response to first-line platinum-based chemotherapy, niraparib was shown to be superior to the placebo for the primary endpoint of PFS in the HRD-positive group (i.e., the primary analysis set) and in the overall study population. The results demonstrated the efficacy of niraparib as the maintenance treatment in patients eligible for the study.

(b) In a foreign phase III study (NOVA study) in patients with platinum-sensitive, relapsed, ovarian cancer in response to their last platinum-based chemotherapy, niraparib was shown to be superior to the placebo for the primary endpoint of PFS in the *gBRCA*-mutated cohort (i.e., the primary analysis set), the HRD-positive group in the non-gBRCA-mutated cohort, and the overall study population. The results demonstrated the efficacy of niraparib as the maintenance treatment in patients eligible for the study.

(c) In a foreign phase II study (QUADRA study) with the primary analysis set of patients with HRD-positive recurrent ovarian cancer who had received 3 or 4 chemotherapy regimens and responded to their last platinum-based chemotherapy. In a Japanese phase II study (Study 2002) targeting patients with the same eligibility, the primary endpoint of response rate was 27.7% [95% CI, 15.6 to 42.6] and 35.0% [90% CI, 17.7 to 55.8], respectively. The results demonstrated a certain extent of the clinical significance of niraparib in these population.

Based on the above review, the statements shown in the table below should be included in the sections Indication and Precautions Concerning Indications.

	Indications	Precautions Concerning Indications
(a)	Maintenance treatment of patients with ovarian cancer after the initial chemotherapy	• Niraparib should be used in patients with stage III or IV ovarian cancer diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) who are in response to first-line platinum-based chemotherapy. • The selection of patients to treat with niraparib should be based on knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.
(b)	Maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer	• Niraparib should be used for patients who are in response to the platinum-based chemotherapy regimen for recurrence. • The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about time from the completion of the platinum-based chemotherapy regimen to disease progression (PFI) and prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.
(c)	Treatment of patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency	• Niraparib should be used for patients who have been treated with 3 or more prior chemotherapy regimens. • Niraparib should be used for patients who have homologous recombination deficiency confirmed by tests using approved *in vitro* diagnostics or medical devices. • The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about time from the completion of the platinum-based chemotherapy regimen to disease progression (PFI) and the prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib as well as careful consideration of treatments other than with niraparib.

At the Expert Discussion, the expert advisors supported the conclusions made by PMDA for the indications described in the above (a) and (b). In terms of the indication in (c), i.e., the treatment of patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency, the expert advisors supported the PMDA's conclusion while raising the following comments on the clinical significance of niraparib.

- Among patients with platinum-sensitive recurrent ovarian cancer, there are a certain number of patients who cannot receive platinum agents due to decreased renal function or the occurrence of hypersensitivity. Therefore, the provision of niraparib is of clinical significance as a new therapeutic option for these patients.

The expert advisors further made the following comments for the indication in (c), the inclusion of patients with *tBRCA*-mutated and platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency.

- An exploratory analysis, although non-prespecified one, yielded a certain level of response rate also in patients with platinum-insensitive and *tBRCA*-mutated ovarian cancer who had received ≥3 chemotherapy regimens in the QUADRA study [see Section 7.R.5.2 of Review Report (1)]. Therefore, the use of niraparib in *tBRCA*-mutated patients, regardless of their platinum sensitivity may be another scope for consideration.
- Patients receiving olaparib, an approved PARP inhibitor, in the maintenance treatment after the initial chemotherapy are presumed to have been confirmed as *BRCA*-mutated. It is therefore of a certain clinical significance to have niraparib as a therapeutic option for patients receiving ≥2 chemotherapy regimens after the maintenance therapy with olaparib, regardless of their last platinum sensitivity. Meanwhile, the patients who were enrolled in the QUADRA study had no previous treatment with PARP inhibitors, and therefore it is unclear whether the efficacy observed in the QUADRA study can be demonstrated also in patients with *tBRCA*-mutated and platinum-insensitive ovarian cancer who have previously been treated with other PARP inhibitors.

PMDA's view:
In view of the discussion above and the following, PMDA has concluded that niraparib should be recommended for the patient population with eligibility for the primary analysis of the QUADRA study and that the indication of niraparib should be defined as "treatment of patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency."

- In the QUADRA study, although a certain level of response rate was shown in patients with platinum-insensitive and *tBRCA*-mutated ovarian cancer, it was a result of a non-prespecified exploratory analysis in a limited number of patients. Therefore, it was considered difficult to draw a conclusion on the efficacy of niraparib in these patients based on the analysis results.
- The efficacy of niraparib in patients with recurrent ovarian cancer was demonstrated in the NOVA study, which was conducted in patients with platinum-sensitive cancer, and no clinical study data are available for the efficacy of niraparib in patients with platinum-insensitive recurrent ovarian cancer. Given these, platinum sensitivity, for being one of predictors of the effectiveness of PARP inhibitors, should also be taken into consideration to identify patients to be treated with niraparib.

Based on the above, PMDA instructed the applicant to describe the "Indications and Precautions Concerning

Indications" section as above, and the applicant responded to follow the instructions.

1.3 Dosage and administration

The following dosing regimen was proposed for the dosage and administration of niraparib: "The usual adult dosage is 200 mg of niraparib administered orally once daily. For adult patients with a body weight of ≥77 kg and a platelet count of ≥150,000/μL before the first dose, the recommended dose is 300 mg of niraparib administered orally once daily. The dose should be reduced, as appropriate, according to the patient's condition." As a result of its review in Section "7.R.6 Dosage and administration" in the Review Report (1), PMDA has concluded that the dosage regimens of niraparib should be defined as proposed, along with the following cautionary advice in the "Precautions Concerning Dosage and Administration" section of the package insert.

Precautions Concerning Dosage and Administration

For all indications

- If any adverse reaction to niraparib occurs, treatment should be interrupted, continued at a reduced dose, or discontinued as per the following criteria.

Dosage for dose reduction/treatment discontinuation

Starting dose level	200 mg	300 mg
First dose reduction	100 mg	200 mg
Second dose reduction	Discontinue treatment	100 mg
Third dose reduction		Discontinue treatment

Criteria for treatment interruption, dose reduction, and treatment discontinuation following adverse reaction

Adverse reactions	Severity*1	Actions	Dose for resumption
Platelet count decreased	Platelet count <100,000/μL	First episode: • Withhold niraparib for up to 28 days until platelet count returns to ≥100,000/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	• Same or reduced dose to the first dose reduction level. • Dose reduced to the first dose reduction level if the platelet count is <75,000/μL.
		Second episode: • Withhold niraparib for up to 28 days until platelet count returns to ≥100,000/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Neutrophil count decreased	Neutrophil count <1,000/μL	• Withhold niraparib for up to 28 days until neutrophil count returns to ≥1,500/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Anemia	Hemoglobin <8 g/dL	• Withhold niraparib for up to 28 days until hemoglobin returns to ≥9 g/dL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Adverse events other than the above*2	Grade ≥3	• Withhold niraparib for up to 28 days until recovery to baseline or ≤Grade 1. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction

*1, Graded according to the NCI-CTCAE ver.4.03. *2, Adverse reaction persisting despite prevention or treatment.

- The efficacy and safety of niraparib in combination with other antineoplastics have not been established.

Maintenance treatment of patients with ovarian cancer after the initial chemotherapy

- The efficacy and safety of niraparib administered for >3 years have not been established.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to present the above statements in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections, and the applicant agreed.

1.4 Risk management plan (draft)

The applicant planned to conduct post-marketing surveillance with a 1-year observation period as all-case survey covering all patients treated with niraparib to investigate the safety, etc. of niraparib in the post-marketing setting. The planned sample size was 300 patients (150 with ovarian cancer after the initial chemotherapy [maintenance treatment], 100 with platinum-sensitive recurrent ovarian cancer [maintenance treatment], and 50 with recurrent ovarian cancer with homologous recombination deficiency).

As a result of its review in Section "7.R.7 Post-marketing investigations" of the Review Report (1), because of limited safety data of niraparib from Japanese patients, PMDA concluded that post-marketing surveillance is essential to obtain safety data that should be promptly provided to healthcare professionals. However, the safety profile of niraparib showed no clear differences from that of similar drugs, except for the occurrence of hypertension and posterior reversible encephalopathy syndrome, and some clinical experience overseas has revealed no new safety concerns except for posterior reversible encephalopathy syndrome. PMDA thus concluded that there was little need for the post-marketing surveillance as all-case survey.

Based on the review in Section "7.R.2 Safety," PMDA has concluded that bone marrow suppression, hypertension, ILD, posterior reversible encephalopathy syndrome, secondary malignancy, and thromboembolism should be included in the safety specification of the surveillance.

PMDA has concluded that the planned sample size and the observation period should be reviewed in consideration of the occurrence of events specified in the safety specification of the surveillance.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to re-examine the surveillance plan.

The applicant's answer:

- Bone marrow suppression, hypertension, ILD, posterior reversible encephalopathy syndrome, secondary malignancy, and thromboembolism are to be included in the safety specification of the surveillance.
- The planned sample size has been determined as 300 patients (150 with ovarian cancer after the initial chemotherapy [maintenance treatment], 120 with platinum-sensitive recurrent ovarian cancer [maintenance treatment], and 30 with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency). The observation period has been determined as 1 year, in consideration of the

occurrence of adverse events specified in the safety specification in the clinical studies as well as the expected number of cases collected for respective indications.

PMDA accepted the applicant's explanation.

In view of the discussion above, PMDA has concluded that the current risk management plan (draft) for niraparib should include the safety presented in Table 49, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 50 and 51.

Table 49. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Bone marrow suppression • Hypertension • ILD • Posterior reversible encephalopathy syndrome	• Secondary malignancy • Embryo-fetal toxicity • Thromboembolism	Not applicable
Efficacy specification		
Not applicable		

Table 50. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified drug use-results survey • Post-marketing clinical study (an extension from Studies 2001 and 2002)	Not applicable	• Information provision via the early post-marketing phase vigilance

Table51. Outline of the post-marketing surveillance plan (draft)

Objectives	To evaluate the safety, etc. of niraparib in post-marketing clinical use.
Surveillance method	Central registration
Population	Patients with ovarian cancer after the initial chemotherapy (maintenance treatment), patients with platinum-sensitive recurrent ovarian cancer (maintenance treatment), and patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency.
Observation period	1 year
Planned sample size	300 patients (150 with ovarian cancer after the initial chemotherapy [maintenance treatment], 120 with platinum-sensitive recurrent ovarian cancer [maintenance treatment], and 30 with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency)
Main surveillance items	Safety specification: Bone marrow suppression, hypertension, ILD, posterior reversible encephalopathy syndrome, secondary malignancy, and thromboembolism. Main surveillance items other than the above: Patient characteristics (e.g., sex, age, stage, histologic type, concurrent diseases, and history of prior treatment), status of treatment with niraparib, concomitant drugs, etc.

1.5 Others

1.5.1 Use of niraparib in patients with hepatic impairment

The applicant submitted additional data from the foreign phase I study (Study 003) for the evaluation of the PK of niraparib in patients with moderate hepatic impairment.

In Study 003, the effects of hepatic impairment on the PK of niraparib were evaluated in 9 patients with solid cancer and normal hepatic function[54] (9 patients in the PK analysis set) and 8 patients with solid cancer and moderate hepatic impairment[55] (8 patients in the PK analysis set). A single oral dose of niraparib 300 mg was administered.

The ratio of least squares geometric mean [90% CI] of C_{max} and AUC_{inf} of niraparib in patients with moderate hepatic impairment to that in patients with normal hepatic function was 0.931 [0.639, 1.36] and 1.56 [1.06, 2.30], respectively.

The applicant's explanation about treatment with niraparib in patients with hepatic impairment based on the above results:
The AUC_{inf} of niraparib increased in patients with moderate hepatic impairment as compared with patients with normal hepatic function. Therefore, in the use of niraparib in patients with moderate or severe hepatic impairment, physicians should consider the dose reduction and should monitor the patient's condition more carefully for the occurrence of any adverse events. This will be advised in the "Precautions concerning Patients with Specific Backgrounds" section of the package insert, along with a reminder that no clinical studies have been conducted in patients with severe hepatic impairment. In addition, results of the investigation of the effects of hepatic impairment on the PK of niraparib available from the foreign phase I study (Study 003) will be appropriately provided to healthcare professionals via the package insert, etc.

PMDA accepted the applicant's explanation.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage regimens modified as shown below, with the following condition. The approval however presupposes the appropriate provision of cautionary advice via the package insert and of information about the proper use of niraparib in the post-marketing setting, as well as strict adherence to the proper use of niraparib under the supervision of physicians with adequate knowledge and experience in the cancer chemotherapy and at medical institutions that are fully equipped for emergency care. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indications

Maintenance treatment of ovarian cancer after the initial chemotherapy
Maintenance treatment of platinum-sensitive recurrent ovarian cancer
Treatment of platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency

Dosage and Administration

[54] Total bilirubin and AST of at or below the upper limit of the reference range
[55] Total bilirubin of >1.5-fold and ≤3-fold the upper limit of the reference range and any AST increased

The usual adult dosage is 200 mg of niraparib administered orally once daily. For adult patients with a body weight of ≥77 kg and a platelet count of ≥150,000/μL before the first dose, the recommended dose is 300 mg of niraparib administered orally once daily. The dose should be reduced, as appropriate, according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warning

Niraparib should be given only to patients who are found to be eligible for the therapy by physicians with adequate knowledge and experience in cancer chemotherapy and at medical institutions that are fully capable of providing emergency care. Prior to the therapy, the patient or their family member must be well-explained about the efficacy and risk of the treatment and give consent.

Contraindication

Patients with a history of hypersensitivity to niraparib or any of the excipients.

Precautions Concerning Indications

Maintenance treatment of patients with ovarian cancer after the initial chemotherapy:

1. Niraparib should be used in patients with stage III or IV ovarian cancer diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) who are in response to first-line platinum-based chemotherapy.
2. The selection of patients to treat with niraparib should be based on knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

Maintenance treatment of patients with platinum-sensitive recurrent ovarian cancer:

3. Niraparib should be used for patients who are in response to the platinum-based chemotherapy regimen for recurrence.
4. The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about prior treatment of study participants, and with a full understanding of the efficacy and safety of niraparib.

Treatment of patients with platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency:

5. Niraparib should be used for patients who have been treated with 3 or more prior chemotherapy regimens.
6. Niraparib should be used for patients who have homologous recombination deficiency confirmed by tests using approved *in vitro* diagnostics or medical devices.
7. The selection of patients to treat with niraparib should be based on the knowledge from the "Clinical Studies" section, such as about time from the completion of the platinum-based chemotherapy regimen to disease progression (PFI) and prior treatment of study participants, and with a full understanding of

the efficacy and safety of niraparib as well as careful consideration of treatments other than with niraparib.

Precautions Concerning Dosage and Administration

For all indications

1. If any adverse reaction to niraparib occurs, treatment should be interrupted, continued at a reduced dose, or discontinued as per the following criteria.

Dosage for dose reduction/discontinuation

Starting dose level	200 mg	300 mg
First dose reduction	100 mg	200 mg
Second dose reduction	Discontinue treatment	100 mg
Third dose reduction		Discontinue treatment

Criteria for treatment interruption, dose reduction, and treatment discontinuation following adverse reaction

Adverse reactions	Severity*1	Actions	Dose for resumption
Platelet count decreased	Platelet count <100,000/μL	First episode: • Withhold niraparib for up to 28 days until platelet count returns to ≥100,000/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	• Same or reduced dose to the first dose reduction level. • Dose reduced to the first dose reduction level if the platelet count is <75,000/μL.
		Second episode: • Withhold niraparib for up to 28 days until platelet count returns to ≥100,000/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Neutrophil count decreased	Neutrophil count <1,000/μL	• Withhold niraparib for up to 28 days until neutrophil count returns to ≥1,500/μL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Anemia	Hemoglobin <8 g/dL	• Withhold niraparib for up to 28 days until hemoglobin returns to ≥9 g/dL. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction
Adverse events other than the above*2	Grade ≥3	• Withhold niraparib for up to 28 days until recovery to baseline or ≤Grade 1. • Discontinue niraparib in case of no recovery within 28 days of the dose interruption.	First dose reduction

*1, Graded according to the NCI-CTCAE ver.4.03; *2, Adverse reaction persisting despite prevention or treatment

2. The efficacy and safety of niraparib in combination with other antineoplastics have not been established.

Maintenance treatment of patients with ovarian cancer after the initial chemotherapy:

3. The efficacy and safety of niraparib administered for >3 years have not been established.

Appendix

List of Abbreviations

ADP	adenosine 5'-diphosphate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
application	Application for marketing approval
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
BCRP	breast cancer resistance protein
BICR	Blinded independent central review
BRCA gene	breast cancer susceptibility gene
BSEP	bile salt export pump
BV	bevacizumab (genetical recombination)
CA-125	cancer antigen-125
CES	carboxylesterase
CI	confidence interval
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D1	duration of zero order drug release
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DSB	double strand break
ECOG	Eastern Cooperative Oncology Group
efflux ratio	ratio of the permeation coefficient in the absorption direction to the permeation coefficient in the secretion direction
FIGO	International Federation of Gynecology and Obstetrics
Frel	relative bioavailability
ETP	etoposide
gBRCA mutation	germline *BRCA* mutation
GC	gas chromatography
GCIG	Gynecologic Cancer Intergroup
GGT	γ-glutamyltransferase
GIS	genomic instability score
HEPES	4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid
hERG	human *ether-a-go-go* related gene
HRD	homologous recombination deficiency/deficient
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q3A Guideline	Impurities in New Drug Substances (in Japan: Notification No.1216001, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare, dated December 16, 2002)
ICH Q1E Guideline	Evaluation of Stability Data (in Japan: Notification No.0603004, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare, dated June 3, 2003)

ILD	interstitial lung disease
IR	infrared absorption spectrum
ITT	intent-to-treat
Japanese guidelines for treatment	Guidelines for Treatment of Ovarian Cancer 2015, edited by the Japan Society of Gynecologic Oncology
LC	liquid chromatography
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
LOH	loss of heterozygosity
LST	large-scale state transitions
MATE	multidrug and toxin extrusion
MAO	monoamine oxidase
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MTD	maximum tolerated dose
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Ovarian Cancer
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	not evaluable
niraparib	niraparib tosilate hydrate
NMR	nuclear magnetic resonance spectrum
NOVA study	Study PR-30-5011-C
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
PAR	poly (ADP-ribose)
PARP	poly (ADP-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PFI	platinum-free interval: time from the last platinum-based anti-cancer therapy to the recurrence
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PRIMA study	Study PR-30-5017-C
PS	performance status
PT	preferred term
PTP	press through packaging
PTX	paclitaxel
QbD	quality by design
QD	quaque die
QTcF	QT interval corrected using Fridericia's formula
ΔQTcF	changes from baseline in QTcF
QUADRA study	Study PR-30-5020-C

RECIST	Response Evaluation Criteria in Solid Tumors
SCID mouse	severe combined immunodeficient mouse
SD	stable disease
shRNA	short hairpin RNA
SMQ	standardized MedDRA queries
SOC	system organ class
SSB	single strand break
Study 1001	Niraparib-1001 study
Study 2001	Niraparib-2001 study
Study 2002	Niraparib-2002 study
Study 003	Study 3000-01-003
Study 42	Study 42
Study 5011-C1	Study PR-30-5011-C1 (a food-effect substudy of NOVA study)
Study 5011-C2	Study PR-30-5011-C2 (a QTc substudy of NOVA study)
Study 5015-C	Study PR-30-5015-C
TAI	telomeric allelic imbalance
tBRCA mutation	*BRCA* mutation detected in tumor tissues
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
UVA	ultraviolet A
UVB	ultraviolet B
UVR	ultraviolet radiation
Vc/F	apparent distribution volume of central compartment
Vp2/F	apparent distribution volume of second peripheral compartment
5-HT	5-hydroxytryptamine
^{14}C-niraparib	^{14}C-labeled niraparib