Report on the Deliberation Results

November 29, 2023

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

Brand Name	Talzenna Capsules 0.1 mg, Talzenna Capsules 0.25 mg, Talzenna Capsules 1 mg
Non-proprietary Name	Talazoparib Tosilate (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	February 24, 2023

Results of Deliberation

In its meeting held on November 27, 2023, 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 classified as a powerful drug and a poisonous drug, respectively.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

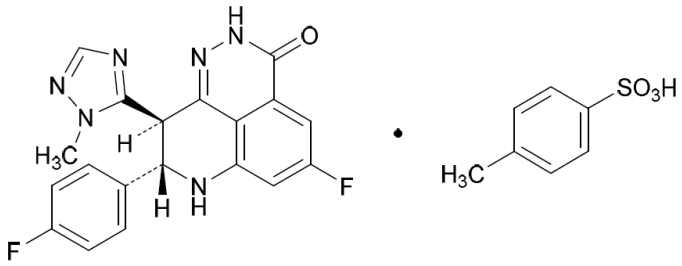
Review Report

November 15, 2023
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	(1) Talzenna Capsules 0.1 mg (2) Talzenna Capsules 0.25 mg (3) Talzenna Capsules 1 mg
Non-proprietary Name	Talazoparib Tosilate
Applicant	Pfizer Japan Inc.
Date of Application	February 24, 2023
Dosage Form/Strength	Capsules: Each capsule contains 0.145, 0.363, or 1.453 mg talazoparib tosilate (equivalent to 0.1, 0.25, or 1 mg talazoparib, respectively).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{19}H_{14}F_2N_6O \cdot C_7H_8O_3S$
Molecular weight: 552.55
Chemical name:
(8*S*,9*R*)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3*H*-pyrido[4,3,2-*de*]phthalazin-3-one mono(4-methylbenzenesulfonate)

Items Warranting Special Mention None
Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of "breast cancer susceptibility gene (*BRCA*)-mutated metastatic castration-resistant prostate cancer" and "*BRCA*-mutated human epidermal growth factor receptor 2 (HER2)-negative inoperable or recurrent breast cancer after prior chemotherapy," 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. A further investigation for myelosuppression, interstitial lung disease, thromboembolism, second primary malignancies, and use in patients with renal impairment via post-marketing surveillance is needed.

Indications

(1) *BRCA*-mutated metastatic castration-resistant prostate cancer
(2) *BRCA*-mutated metastatic castration-resistant prostate cancer
BRCA-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy
(3) *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy

Dosage and Administration

(1) The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition.
(2) [*BRCA*-mutated metastatic castration-resistant prostate cancer]
The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition.
[*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy]
The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.
(3) The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage 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)

October 16, 2023

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	(1) Talzenna Capsules 0.1 mg (2) Talzenna Capsules 0.25 mg (3) Talzenna Capsules 1 mg
Non-proprietary Name	Talazoparib Tosilate
Applicant	Pfizer Japan Inc.
Date of Application	February 24, 2023
Dosage Form/Strength	Capsules: Each capsule contains 0.145, 0.363, or 1.453 mg talazoparib tosilate (equivalent to 0.1, 0.25, or 1 mg talazoparib, respectively).

Proposed Indications

(1) Castration-resistant prostate cancer

(2) Castration-resistant prostate cancer
BRCA-mutated HER2-negative inoperable or recurrent breast cancer

(3) *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer

Proposed Dosage and Administration

(1) [Castration-resistant prostate cancer]
The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition.

(2) [Castration-resistant prostate cancer]
The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition.
[*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer]
The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

(3) [*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer]
The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage 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) enzymes play a role in DNA repair. PARP binds to the site of DNA single-strand breaks (SSBs) and synthesizes poly (ADP-ribose) (PAR) chains, which recruit DNA repair factors and contribute to SSB repair (*Nat Rev Mol Cell Biol*. 2006; 7: 517-28).

Talazoparib Tosilate (hereinafter referred to as "talazoparib") is a small molecule PARP inhibitor, discovered by BioMarin Pharmaceutical Inc. Talazoparib blocks SSB repair by inhibiting the binding of nicotinamide adenine dinucleotide (NAD) to PARP and prevents the dissociation of PARP-DNA complexes (*Sci Transl Med*. 2016; 8: 368er7, *Cancer Res*. 2012; 72: 5588-99, etc.), which give rise to double-strand breaks (DSBs) during DNA replication. In normal cells, these DSBs are repaired by homologous recombination mediated by homologous recombination repair (HRR) factors such as *BRCA* gene products (BRCA1 and BRCA2). On the other hand, in cancer cells that are defective in homologous recombination repair due to mutations in the HRR genes such as the *BRCA* genes, etc., treatment with talazoparib leads to the accumulation of unrepaired DSBs, resulting in cell death and tumor growth inhibition (*Nature*. 2012; 481: 287-94).

1.2 Development history, etc.

Outside Japan, BioMarin Pharmaceutical Inc. initiated a foreign phase I study in patients with advanced solid tumors (Study 007) in January 2011.

In the clinical development of talazoparib for breast cancer, Medivation Inc. initiated a foreign phase III study in patients with germline *BRCA* (g*BRCA*)-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy (the EMBRACA study) in October 2013.

In the clinical development of talazoparib for prostate cancer, Pfizer Inc. (the US) initiated a global phase III study in patients with metastatic castration-resistant prostate cancer (mCRPC) who had received no prior systemic therapy for mCRPC (the TALAPRO-2 study) in [redacted] 2017.

A US application was filed based mainly on the results from the EMBRACA study in April 2018. In October 2018, talazoparib was approved for the following indication: "TALZENNA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (*gBRCAm*) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA." Then, a supplemental new drug application for the combination of talazoparib and enzalutamide was filed based mainly on the results from the TALAPRO-2 study in December 2022. In June 2023, talazoparib was approved for the following additional indication: "TALZENNA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for: In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC)."

An EU application was filed based mainly on the results from the EMBRACA study in April 2018. In June 2019, talazoparib was approved for the following indication: "Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy." Then, a marketing authorization application for the combination of talazoparib and enzalutamide was submitted based mainly on the results from the TALAPRO-2 study in [redacted] 20[redacted] and is currently under review.

As of August 2023, talazoparib has been approved for the indication of *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer in ≥80 countries or regions and for the indication of mCRPC in 1 country.

In Japan, the applicant initiated a Japanese phase I study in patients with advanced solid tumors etc. (Study 030) in November 2017. Patient enrollment in the TALAPRO-2 study began in [redacted] 20[redacted].

The applicant has submitted a marketing application for talazoparib for (1) *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer and (2) mCRPC based mainly on the results from (1) Study 030 and the EMBRACA study and (2) the TALAPRO-2 study.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to yellow solid. Its appearance, solubility, hygroscopicity, melting point, acid dissociation constant, partition coefficient, and optical rotation have been determined.

Its chemical structure has been elucidated by infrared absorption spectroscopy (IR), nuclear magnetic resonance spectrometry (NMR) (^{1}H-, ^{13}C-, ^{15}N-, and ^{19}F-NMR), single-crystal X-ray crystallography, ultraviolet-visible spectroscopy (UV-VIS), mass spectrometry (MS), and elemental analysis.

2.1.2 Manufacturing process

The drug substance is synthesized using Starting Material A[1)] and Starting Material B.[2)]

A quality control strategy was developed based on the following etc. (Table 1).

- Identification of critical quality attributes (CQAs)
- (1) Identification of critical process parameters (CPPs) that impact CQAs and (2) determination of the proven acceptable ranges for manufacturing process parameters through quality risk assessment and design of experiments

1) [redacted]
2) [redacted]

Table 1. Overview of drug substance control strategy

CQA	Method of control
Content	Specification
Appearance	Specification
Identification	Specification
Related substances	Manufacturing process, Specification
Enantiomeric purity	Manufacturing process, Specification
Residual solvents	Manufacturing process, Specification
[redacted]	Manufacturing process
Particle size distribution	Manufacturing process, Specification
Residue on ignition	Specification
Water content	Manufacturing process, Specification
Tosic acid	Manufacturing process, Specification

Critical steps have been defined as Steps [redacted][3)], [redacted][4)], and [redacted]. Process control items and values have been established for Steps [redacted][5)], [redacted][6)], and [redacted]. [redacted], [redacted], and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identification (IR and liquid chromatography [LC]), purity (related substances [LC], enantiomeric purity [LC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, particle size, tosic acid (potentiometric titration), and assay (LC).

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2. The stability results indicated that the drug substance is stable. Photostability data showed that the drug substance is photosensitive.

Table 2. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25℃	60%RH	double low-density polyethylene bags + aluminum bag + high-density polyethylene drum	[redacted] months
Accelerated	3 commercial-scale batches	40℃	75%RH		6 months

On the basis of the above, a re-test period of [redacted] months was proposed for the drug substance when packaged in double low-density polyethylene bags within an aluminum bag to protect from light and stored in a high-density polyethylene drum at room temperature.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is presented as immediate-release hard capsules containing 0.145, 0.363, or 1.453 mg talazoparib tosilate (equivalent to 0.1, 0.25, or 1 mg talazoparib, respectively). It contains the excipient silicified microcrystalline cellulose.

3) [redacted]
4) [redacted]
5) [redacted]
6) [redacted]

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of screening, mixing 1 and 2, encapsulation, [redacted], and packaging/labeling/testing/storage.

A quality control strategy was developed based on the following etc. (Table 3).

- Identification of CQAs
- (1) Identification of material attributes and CPPs that impact CQAs and (2) determination of the proven acceptable ranges for manufacturing process parameters through quality risk assessment and design of experiments

Table 3. Overview of drug product control strategy

CQA	Method of control
Appearance	Manufacturing process, Specification
Identification	Manufacturing process, Specification
Assay	Manufacturing process, Specification
Degradation products	Manufacturing process, Specification
Uniformity of dosage units (Content uniformity of dosage units)	Manufacturing process, Specification
[redacted]	Manufacturing process
Dissolution	Manufacturing process, Specification
Water content	Manufacturing process, Specification
[redacted]	Manufacturing process

Critical steps have been defined as Steps [redacted], [redacted], and [redacted]. Process control items and values have been established for Step [redacted] and packaging/labeling/testing/storage.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identification (LC and UV-VIS), purity (degradation products [LC]), water content, uniformity of dosage units (content uniformity testing [LC]), dissolution (LC), and assay (LC).

2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 4. The stability results indicated that the drug product is stable. Bracketing was applied to the long-term testing of the 0.25-mg strength capsule. Photostability data showed that the drug product is photosensitive.

Table 4. Stability studies on drug product

Strength	Study	Primary batches	Temperature	Humidity	Storage package	Storage period
0.1 mg	Long-term	3 commercial-scale batches	25℃	60%RH	Blister pack (polyvinyl chloride/polyvinylidene chloride and an aluminum foil)	18 months
	Accelerated	3 commercial-scale batches	40℃	75%RH		6 months
0.25 mg	Long-term	1 commercial-scale batch	25℃	60%RH		18 months
		2 commercial-scale batches				12 months
	Accelerated	3 commercial-scale batches	40℃	75%RH		6 months
1 mg	Long-term	3 commercial-scale batches	25℃	60%RH		18 months
	Accelerated	3 commercial-scale batches	40℃	75%RH		6 months

On the basis of the above, a shelf-life of 24 months was proposed for the drug product when packaged in a blister pack (polyvinyl chloride/polyvinylidene chloride and an aluminum foil) and stored at room temperature, in accordance with the ICH Q1E guideline.

2.R Outline of the review conducted by PMDA

On the basis of 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

3.1 Primary pharmacodynamics

3.1.1 Inhibition of PARP (CTD 4.2.1.1.1, 4.2.1.1.4)

The inhibitory activities of talazoparib, olaparib, and niraparib were assessed with a panel of 13 PARP enzymes (recombinant proteins) using a biochemical assay that measured incorporation of biotin-NAD+. The IC_{50} values of talazoparib, olaparib, and niraparib for PARP inhibition are shown in Table 5.

Table 5. PARP inhibition by talazoparib, olaparib, and niraparib

	IC_{50} value (nmol/L)		
	Talazoparib	Olaparib	Niraparib
PARP-1	0.7	0.8	2.6
PARP-2	0.3	0.3	0.7
PARP-3	22.0	28.0	>10,000
PARP-5a	13.5	2,000	7,200
PARP-5b	4.7	446	1,100
PARP-6	574	482	>10,000
PARP-7	>10,000	2,400	>10,000
PARP-8	225	2,500	>10,000
PARP-10	>10,000	1,100	3,100
PARP-11	517	—	>10,000
PARP-12	9,600	3,700	>10,000
PARP-14	>10,000	>10,000	>10,000
PARP-15	>10,000	>10,000	>10,000

n = 1; —, Not calculable

Using 4 human breast cancer cell lines, the inhibitory activities of talazoparib, olaparib, and niraparib against PARP-1 were assessed based on PARylation, using an electrochemiluminescence assay. The IC_{50} values of talazoparib, olaparib, and niraparib are shown in Table 6.

Table 6. Inhibition of PARP-1 by talazoparib, olaparib, and niraparib

Cell line	IC_{50} value (nmol/L)		
	Talazoparib	Olaparib	Niraparib
MDA-MB-436	15 ± 6	21 ± 8	414 ± 199
HCC1954	6 ± 4	21 ± 17	270 ± 151
JIMT1	9 ± 3	10 ± 7	196 ± 166
HCC1143	9 ± 1	10 ± 2	312 ± 88

Mean ± SD, n = 3

Trapping of PARP-1-DNA complexes was assessed in a Western blotting assay of PARP-1 levels in the chromatin-bound fraction in 4 human breast cancer cell lines pre-treated with a DNA alkylating

agent, methyl methanesulfonate (MMS), followed by talazoparib, olaparib, or niraparib.[7)] PARP-1 trapping[8)] by talazoparib, olaparib, and niraparib is shown in Table 7.

Table 7. PARP-1 trapping by talazoparib, olaparib, and niraparib

Cell line	PARP-1 trapping (fold)		
	Talazoparib	Olaparib	Niraparib
MDA-MB-436	36	9	33
HCC1954	12	2	4
JIMT1	45	7	10
HCC1143	46	7	19

n = 1

3.1.2 Anti-proliferative activity against cancer cell lines

3.1.2.1 *In vitro* (CTD 4.2.1.1.2, 4.2.1.1.3, 4.2.1.1.4)

Talazoparib was assessed for cytotoxic activity in 9 human cancer cell lines based on adenosine triphosphate (ATP) content in viable cells. The IC_{50} values of talazoparib are shown in Table 8. The IC_{50} value of talazoparib for the normal human fetal lung (MRC-5) cell line (n = 1) was 306.0 nmol/L.

Table 8. Talazoparib cytotoxicity in human cancer cell lines

Cell line	Cancer type	HRR gene mutation	IC_{50} value (nmol/L)
CAPAN-1	Pancreatic	*BRCA2*/*ATM*/*FANCA*	5.0
MX-1	Breast	*BRCA1*	0.3
MDA-MB-468	Breast	*BRCA2*/*FANCA*/*PTEN*	3.7
LNCaP	Prostate	*BRCA2*/*ATM*/*ATR*/*CHEK2*/*FANCA*/*MLH-1*/*PTEN*	4.3
PC-3	Prostate	*PTEN*	4.4
HCT-116	Colorectal	*BRCA2*/*ATM*/*CDK12*/*CHEK2*/*FANCA*/*MLH-1*	10.6
MDA-MB-231	Breast	—	261.8
LoVo	Colorectal		257.7
A549	Lung		>1,000

n = 1; —, Not applicable

Talazoparib was assessed for cytotoxic activity in 5 human prostate cancer cell lines based on the ATP content in viable cells. The IC_{50} values of talazoparib are shown in Table 9.

Table 9. Talazoparib cytotoxicity in human prostate cancer cell lines

Cell line	HRR gene mutation	IC_{50} value (nmol/L)
LNCaP	*BRCA2*/*ATM*/*ATR*/*CHEK2*/*FANCA*/*MLH-1*/*PTEN*	<4.1
C4-2	*BRCA2*/*ATM*	<4.1
PC-3	*PTEN*	7.3
22RV1	*BRCA2*/*ATM*/*NBN*/*PALB2*	6.6
VCaP	—	268.5

n = 1; —, Not applicable

Talazoparib, olaparib, and niraparib were assessed for cytotoxic activity in 4 human breast cancer cell lines based on DNA content in viable cells. The IC_{50} values of talazoparib, olaparib, and niraparib are shown in Table 10.

[7)] Talazoparib, olaparib, and niraparib at the approximate IC_{90} concentrations for PARylation inhibition were administered (100 nmol/L, 1,100 nmol/L, and 550 nmol/L, respectively).

[8)] PARP-1 trapping (fold) = PARP-1 level in the PARP inhibitor (talazoparib, olaparib, or niraparib) + MMS group/PARP-1 level in the control (no drug) group

Table 10. Talazoparib cytotoxicity in human breast cancer cell lines

Cell line	*BRCA* mutation	IC_{50} value (nmol/L)		
		Talazoparib	Olaparib	Niraparib
MDA-MB-436	*BRCA1*	1	28	40
HCC1954		32	2,628	126
JIMT1	—	34	2,175	703
HCC1143		119	3,549	649

n = 1; —, Not applicable

3.1.2.2 *In vivo* (CTD 4.2.1.1.5, 4.2.1.1.6, 4.2.1.1.7, 4.2.1.1.8, 4.2.1.1.9, 4.2.1.1.10, 4.2.1.1.11)

The anti-tumor effect of talazoparib was evaluated in a subcutaneous patient-derived xenograft model of BR-05-0028 breast cancer harboring HRR gene mutations[9] in nude mice (7/group). The day when the mean tumor volume reached approximately 115 mm^3 was designated as Study Day 0. Talazoparib 0.3 mg/kg QD was administered orally for 68 days, or carboplatin 30 mg/kg QW was administered via intraperitoneal injection for 68 days, and tumor volumes were calculated. On Day 67, talazoparib and carboplatin achieved 108% and 67% tumor growth inhibition,[10] respectively. While talazoparib had statistically significant anti-tumor activity compared to control (0.5% carboxymethylcellulose [CMC]) (P = 0.031, Games-Howell test), carboplatin did not show statistically significant anti-tumor activity.

The anti-tumor effect of talazoparib was evaluated in nude mice subcutaneously xenografted with LNCaP cell line harboring HRR gene mutations[11] (6/group). The day when the mean tumor volume reached 217 to 221 mm^3 was designated as Study Day 0. Talazoparib 0.15 mg/kg BID was administered orally for 28 days, and tumor volumes were calculated. On Day 27, talazoparib had statistically significant anti-tumor activity compared to control (10% dimethylacetamide) (P = 0.017, Fisher's LSD test).

The anti-tumor effect of talazoparib was evaluated in subcutaneous patient-derived xenograft models of T168, HBCx-10, HBCx-6, HBCx-9, and HBCx-12B breast cancer in nude mice (8 or 10/group). The day when subcutaneous xenografts in nude mice reached a certain volume[12] was designated as Study Day 0. Talazoparib 0.07 or 0.15 mg/kg BID was administered orally from Day 1 through Day 34 (Day 33 for T168), and tumor volumes were calculated. The best T/C%[13] and the number of mice with complete tumor regression[14] in the talazoparib groups are shown in Table 11.

[9] *BRCA1*, *BRCA2*, *ATM*, *FANCA*, and *PALB2* mutations
[10] Tumor growth inhibition (%) = {1 − (change in the mean tumor volume of the talazoparib or carboplatin group/change in the mean tumor volume of the control [0.5% CMC] group)} × 100
[11] *BRCA2*, *ATR*, *PTEN*, *ATM*, *CHEK2*, *FANCA*, and *MLH-1* mutations
[12] T168, 62.5-288.0 mm^3; HBCx-10, 62.5-196.0 mm^3; HBCx-6, 75.0-126.0 mm^3; HBCx-9, 62.5-196.0 mm^3; HBCx-12B, 62.5-196.0 mm^3
[13] T/C% = {the mean tumor volume of the talazoparib group/the mean tumor volume of the control (0.5% CMC) group} × 100
The day of the best T/C% was Day 18 for T168, Day 24 for HBCx-10, Day 35 for HBCx-6, Day 25 for HBCx-9, and Day 31 for HBCx-12B.
[14] ≥80% tumor volume reduction relative to Day 0 at ≥3 consecutive measurements

Table 11. Talazoparib anti-tumor activity in subcutaneous patient-derived xenograft breast cancer models in nude mice

Model	*BRCA* mutation	Talazoparib (mg/kg)	T/C%	Complete regression (n/N)
T168	*BRCA1*	0.07	1.26[*1]	10/10
		0.15	0.39[*1]	10/10
HBCx-10	*BRCA2*	0.07	34.3[*1]	0/10
		0.15	3.48[*1]	6/10
HBCx-6	—	0.07	1.63[*1]	2/10
		0.15	0.32[*1]	8/10
HBCx-9	—	0.07	73.8	0/10
		0.15	46.3[*2]	0/10
HBCx-12B	—	0.07	44.4[*3]	0/8
		0.15	26.6[*2]	0/8

Mean; —, Not applicable; *1 $P < 0.001$ (Mann-Whitney test); *2 $P < 0.01$ (Mann-Whitney test); *3 $P < 0.05$ (Mann-Whitney test)

3.2 Secondary pharmacodynamics (CTD 4.2.1.2.1, 4.2.1.2.2)

Talazoparib at 10 µmol/L was assessed for inhibitory activity against 72 receptors, enzymes, and ion channels. Less than 50% inhibition of binding or enzyme activity was observed against all targets.

3.3 Safety pharmacology

3.3.1 Effect on CNS (CTD 4.2.1.3.2)

Rats (6/group) received a single oral dose of talazoparib 0.3, 1.0, or 3.0 mg/kg, and the effect of talazoparib on the central nervous system was evaluated using the modified Irwin's test. There were no talazoparib-related effects.

3.3.2 Effects on cardiovascular system

3.3.2.1 Effect on hERG potassium current (CTD 4.2.1.3.1)

Using the human embryonic kidney HEK293 cell line transfected with human *ether-a-go-go* related gene (hERG), the effect of talazoparib 10, 30, and 100 µmol/L on the hERG potassium current was evaluated. Talazoparib at 10, 30, and 100 µmol/L inhibited the hERG potassium current by 6.7 ± 1.9%, 14.2 ± 0.7%, and 33.4 ± 2.9%, respectively (mean ± standard deviation [SD], n = 3 or 4). Statistically significant inhibition occurred in all of the talazoparib groups compared with the control (0.3% dimethyl sulfoxide [DMSO]) group ($P < 0.05$, Dunnett's multiple comparison test).

3.3.2.2 Effect on ECG

In (1) 5-day, (2) 28-day, and (3) 13-week oral toxicity studies in dogs (14/group) [see Section 5.2], (1) talazoparib 0.003, 0.01, 0.03, or 0.1 mg/kg QD, (2) talazoparib 0.0005, 0.0015, 0.005, or 0.01 mg/kg QD, and (3) talazoparib 0.0015, 0.005, or 0.01 mg/kg QD were administered, and the effect of talazoparib on the ECG was assessed. There were no talazoparib-related effects.

3.3.3 Effect on respiratory system (CTD 4.2.1.3.3)

Rats (8/group) received a single oral dose of talazoparib 0.3, 1.0, or 3.0 mg/kg, and the effect of talazoparib on tidal volume, respiration rate, and minute volume was evaluated. A statistically significant decrease in tidal volume was noted in all talazoparib dose groups ($P < 0.05$, Dunnett's multiple comparison test).

The applicant's explanation:
Given that the unbound plasma C_{max} for talazoparib (12.3 ng/mL) at 0.3 mg/kg in a 5-day repeated oral dose toxicity study in rats (n = 24) [see Section 5.2] was higher than the human unbound plasma C_{max} (5.46 ng/mL[15)]), etc., the above finding is unlikely to become a safety problem in the clinical use of talazoparib.

3.R Outline of the review conducted by PMDA

On the basis of the submitted data and the considerations in the following section, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of talazoparib is acceptable.

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

The applicant's explanation about the mechanism of action of talazoparib and its efficacy in the treatment of breast cancer and prostate cancer:
PARP enzymes play a role in DNA repair. PARP binds to the site of DNA SSBs and synthesizes PAR chains, which recruit DNA repair factors and contribute to SSB repair (*Nat Rev Mol Cell Biol*. 2006; 7: 517-28).

Talazoparib is a small molecule PARP inhibitor. Talazoparib blocks SSB repair by inhibiting the binding of NAD to PARP [see Section 3.1.1] and prevents the dissociation of PARP-DNA complexes (*Sci Transl Med*. 2016; 8: 368er7, *Cancer Res*. 2012; 72: 5588-99, etc.), which give rise to DSBs during DNA replication. In normal cells, these DSBs are repaired by homologous recombination mediated by HRR factors such as *BRCA* gene products (BRCA1 and BRCA2). On the other hand, in cancer cells that are defective in homologous recombination repair due to mutations in the HRR genes such as the *BRCA* genes, etc., treatment with talazoparib leads to the accumulation of unrepaired DSBs, resulting in cell death and tumor growth inhibition (*Nature*. 2012; 481: 287-94).

Actually, the anti-tumor activity of talazoparib was observed in subcutaneous patient-derived xenograft models of *BRCA*-mutated breast cancer in nude mice and nude mice subcutaneously xenografted with a *BRCA2*-mutated human prostate cancer cell line [see Section 3.1.2]. Taking also account of this finding, the efficacy of talazoparib is expected in the treatment of *BRCA*-mutated breast cancer and prostate cancer.

Talazoparib caused cytotoxicity in human cancer cell lines harboring mutations in the non-*BRCA* HRR genes [see Section 3.1.2], and non-BRCA factors (ATM, CHEK, etc.) involved in the homologous recombination DNA repair pathway have been reported (*Nat Rev Mol Cell Biol*. 2021; 22: 796-814, *Int J Mol Sci*. 2021; 23: 348, etc.). Given these points etc., the efficacy of talazoparib is expected in the treatment of tumors harboring mutations in the non-*BRCA* HRR genes as well as *BRCA*-mutated tumors.

Furthermore, though there are no non-clinical study data on the use of talazoparib/enzalutamide in the treatment of non-HRR-deficient prostate cancer, the efficacy of talazoparib/enzalutamide is expected in the

[15)] Calculated based on the C_{max} of talazoparib (21 ng/mL) on Day 35 following oral administration of talazoparib 1 mg QD in patients with solid tumors in Study 007 [see Section 6.2.3.1] and the unbound fraction in human (0.260) [see Section 4.2.2].

treatment of prostate cancer, regardless of HRR gene mutation status, based on the following mechanisms of action (1) and (2).

(1) Since a PARP inhibitor, veliparib (unapproved in Japan) suppressed the transcription of androgen receptor (AR) target genes such as *KLK3* in human prostate cancer cell lines (*Cancer Discov*. 2012; 2: 1134-49), PARP inhibition by talazoparib should also result in decreased AR target gene transcription and suppressed prostate cancer growth.

(2) Given that the combination of a PARP inhibitor, olaparib, and enzalutamide downregulated HRR factors including BRCA1 in human prostate cancer cell lines without HRR gene mutations (*Sci Signal*. 2017; 10: eaam7479), etc., enzalutamide suppresses the expression of HRR factors, thus inducing homologous recombination deficiency and suppressing prostate cancer growth.

There are the following differences in the pharmacological properties between talazoparib and other PARP inhibitors approved in Japan, olaparib and niraparib. The impact of the potency to trap PARP-DNA complexes on the clinical efficacy of talazoparib etc. is not fully understood.

- All of talazoparib, olaparib, and niraparib inhibit PARP-1 and PARP-2. Talazoparib inhibits PARP-5a and PARP-5b as well [see Section 3.1.1].
- Talazoparib is more potent at trapping PARP-1-DNA complexes compared to olaparib and niraparib [see Section 3.1.1].
- Talazoparib has been reported to be more potent at trapping PARP-2-DNA complexes than olaparib (*Mol Cancer Ther*. 2014; 13: 433-43).

PMDA's discussion:

PMDA accepted the applicant's explanation about the efficacy of talazoparib in the treatment of *BRCA*-mutated breast cancer and prostate cancer. On the other hand, given that the degrees of contribution of non-BRCA factors involved in DNA repair to homologous recombination repair are unknown etc., whether the efficacy of talazoparib is expected also in the treatment of tumors with mutations in the non-BRCA genes involved in DNA repair, like *BRCA*-mutated tumors, is unknown at present.

With regard to the applicant's explanation about the primary mechanism of action of talazoparib/enzalutamide against tumors without HRR gene mutations, the primary mechanism of action of talazoparib/enzalutamide against HRR gene-mutated tumors is different. On the basis of the following points, it is difficult to conclude that the mechanisms of action independent of HRR gene mutation status are supported by non-clinical studies etc.

- As to the above mechanism of action (1), whether talazoparib is expected to have an add-on effect to enzalutamide by suppressing PARP-dependent AR target gene transcription in non-HRR-deficient patients, is unknown.
- As to the above mechanism of action (2), given that the differences in the degree of contribution to the homologous recombination repair mechanism between the suppression of the expression of HRR genes by AR inhibition and the presence of HRR gene mutations are unknown, whether AR inhibition induces

homologous recombination deficiency and suppresses tumor growth to a similar extent as HRR gene mutations is unknown.

The efficacy of talazoparib/enzalutamide in the treatment of tumors without HRR gene mutations should be evaluated, including clinical study results. Thus, this point is discussed in Sections "7.2.R.2.1 Study population" and "7.2.R.2.4 Results of efficacy assessment."

The knowledge of the pharmacological properties of talazoparib, including the differences between talazoparib and olaparib/niraparib, may be important in terms of predicting efficacy and selecting eligible patients in the clinical use of talazoparib. Thus, an investigation should be continued, and any new finding should be provided appropriately to healthcare professionals in clinical practice.

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

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

The non-clinical pharmacokinetics (PK) of talazoparib were characterized in rats and dogs. Studies on the plasma protein binding, drug metabolizing enzymes, transporters, etc. of talazoparib were conducted using human or animal biomaterials.

Talazoparib in dog plasma was quantitated by LC-MS/MS (lower limit of quantitation [LLOQ] = 5 pg/mL). Radioactivity in rat tissues was quantitated using quantitative whole-body autoradiography (LLOQ = 0.0306 μg Eq./g).

4.1 Absorption

4.1.1 Single-dose studies

Following a single intravenous dose of 0.025 mg/kg of talazoparib or a single oral dose of 0.0015, 0.01, or 0.1 mg/kg of talazoparib in male and female dogs, plasma talazoparib concentrations were determined (Table 12).

Table 12. PK parameters of talazoparib (male and female dogs, single intravenous or oral administration)

Route of administration	Dose (mg/kg)	Sex	C_{max} *1 (ng/mL)	t_{max} *2 (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	F*3 (%)
IV	0.025	M	20.4 ± 1.29	—	289 ± 106	45.7 ± 2.6	—
		F	20.6 ± 5.14	—	260 ± 29.5	51.3 ± 10.1	—
Oral	0.0015	M	0.182 ± 0.067	1 (0.25, 2)	10.3 ± 1.37	72.9 ± 9.4	59.6
		F	0.227 ± 0.069	1 (0.5, 2)	13.5 ± 6.66	89.3 ± 29.1	86.7
	0.01	M	2.51 ± 0.949	0.5 (0.25, 1)	72.0 ± 6.15	69.7 ± 3.9	62.4
		F	2.21 ± 0.612	1 (0.5, 1)	68.7 ± 7.70	65.2 ± 7.6	66.1
	0.1	M	54.9 ± 6.63	3 (3, 4)	590 ± 51.6	54.5 ± 6.7	51.1
		F	76.0 ± 2.88	3 (2, 4)	746 ± 86.1	58.0 ± 22.9	71.8

Mean ± SD; n = 3; *1 Concentration at 5 minutes after intravenous administration; *2 Median (Min., Max.); *3 Calculated based on the mean AUC_{inf}.

4.1.2 Repeated-dose studies

Talazoparib 0.0015, 0.005, or 0.01 mg/kg QD was administered orally for 13 weeks in male and female dogs, and plasma talazoparib concentrations were determined (Table 13). There were no clear sex differences in

talazoparib exposure. Talazoparib exposure increased approximately dose-proportionally, and talazoparib exposure tended to increase after multiple dosing.

Table 13. PK parameters of talazoparib (male and female dogs, 13-week oral administration)

Sampling day (Day)	Dose (mg/kg)	C_{max} (pg/mL)		t_{max}* (h)		AUC_{24h} (pg·h/mL)	
		M	F	M	F	M	F
1	0.0015	102 ± 38	75 ± 19	1 (0.25, 6)	4 (1, 18)	1,470 ± 247	1,360 ± 233
	0.005	402 ± 220	624 ± 450	4 (1, 6)	2 (0.25, 4)	5,840 ± 1,420	6,860 ± 2,120
	0.01	820 ± 465	1,680 ± 1,060	4 (0.25, 8)	2 (0.25, 6)	11,700 ± 2,920	19,600 ± 5,730
29	0.0015	314 ± 150	317 ± 127	1 (1, 6)	6 (0.25, 24)	5,550 ± 1,400	6,420 ± 2,660
	0.005	970 ± 229	1,260 ± 414	2 (0.5, 6)	4 (0, 12)	14,300 ± 3,820	24,500 ± 8,790
	0.01	1,830 ± 455	2,630 ± 746	2 (0, 4)	1 (1, 18)	28,000 ± 7,260	41,900 ± 5,700
91	0.0015	278 ± 50	323 ± 117	24 (1, 24)	24 (2, 24)	5,560 ± 1,340	5,750 ± 2,060
	0.005	1,110 ± 172	1,190 ± 513	2 (1, 24)	2 (0.25, 12)	19,600 ± 2,530	23,500 ± 11,300
	0.01	2,010 ± 365	2,900 ± 1,180	2 (0.5, 24)	2 (1, 8)	36,200 ± 8,380	49,900 ± 24,900

Mean ± SD; n = 7; * Median (Min., Max.)

4.1.3 *In vitro* cell permeability

The cell permeability of talazoparib was evaluated using the human colon carcinoma Caco-2 cell line. The apparent permeability in apical to basal direction ($P_{app\ A\rightarrow B}$) of talazoparib 10 μmol/L was 2.49×10^{-6} cm/sec. The applicant explained that talazoparib permeability was determined to be moderate as its $P_{app\ A\rightarrow B}$ value was higher than the $P_{app\ A\rightarrow B}$ value of digoxin (2.01×10^{-6} cm/sec).

4.2 Distribution

4.2.1 Tissue distribution

Following a single oral dose of ^{14}C-talazoparib 3 mg/kg in male pigmented and albino rats, the tissue distribution of radioactivity was determined. In male pigmented and albino rats, radioactivity was widely distributed to tissues, and the C_{max} in most tissues occurred at 4 hours post-dose in pigmented rats and at 1 hour post-dose in albino rats. In pigmented rats, the maximum concentrations of radioactivity in the uveal tract, liver, kidney medulla, kidney, and arterial wall (1,830, 1,820, 1,140, 1,060, and 1,060 ng Eq./g, respectively) were particularly higher than the maximum concentration of radioactivity in blood (439 ng Eq./g). In albino rats, the maximum concentrations of radioactivity in the liver, kidney medulla, kidney, and kidney cortex (2,690, 1,470, 1,370, and 1,360 ng Eq./g, respectively) were particularly higher than the maximum concentration of radioactivity in blood (438 ng Eq./g).

Radioactivity was below the LLOQ in the skin and uveal tract at 24 hours post-dose in albino rats, whereas radioactivity was detected in the pigmented skin and uveal tract up to 72 hours post-dose in pigmented rats.

The applicant's explanation:
Radioactivity was detected in the uveal tract for long hours after dosing in pigmented rats, suggestive of the binding of talazoparib and its metabolites to melanin. Meanwhile, there were no talazoparib-related cutaneous reactions or ocular findings in a phototoxicity study in pigmented rats [see Section 5.6.1], and clinical studies raised no safety concerns specific to the skin or eyes.

4.2.2 Plasma protein binding

Mouse, rat, dog, monkey, or human plasma was incubated with talazoparib (0.01-1 μmol/L) at 37℃ for 4 hours, and the plasma protein binding of talazoparib was determined using an equilibrium dialysis method. The unbound fractions of talazoparib in (1) mouse, (2) rat, (3) dog, (4) monkey, and (5) human plasma were (1) 4.16% to 4.70%, (2) 10.0% to 10.3%, (3) 35.9% to 37.2%, (4) 31.4% to 34.0%, and (5) 25.5% to 26.7%.

4.2.3 Distribution in blood cells

Using the whole blood collected following oral administration of ^{14}C-talazoparib in rats, dogs, and humans, the distribution of talazoparib in blood cells was determined. The blood to plasma concentration ratios of talazoparib in rats, dogs, and humans were 0.572, 0.924, and 1.05, respectively. On the basis of the above, the applicant explained that talazoparib was shown to be evenly distributed between red blood cells and plasma in human whole blood.

4.2.4 Placental transfer to fetus

Placental and fetal transfer of talazoparib was not studied. The applicant explained that given that fetal death and teratogenicity were observed in an embryo-fetal development study in rats [see Section 5.5], talazoparib may cross the placenta into the fetus.

4.3 Metabolism

4.3.1 *In vitro*

Rat, dog, and human liver microsomes were incubated with ^{14}C-talazoparib (1 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37℃ for 2 hours, and the metabolites of talazoparib were identified. Talazoparib underwent minimal metabolism.

Mouse, rat, dog, and human hepatocytes were incubated with ^{14}C-talazoparib (1 or 10 μmol/L) at 37℃ for 4 hours, and the metabolites of talazoparib were identified. No metabolites of talazoparib were detected in human hepatocytes. There was negligible metabolism of talazoparib also in mouse, rat and dog hepatocytes.

4.3.2 *In vivo*

Following a single oral dose of ^{14}C-talazoparib 3 mg/kg in male and female rats, its metabolites in plasma, urine, and feces were identified. The results are shown below.

- In the plasma collected at 12 to 24 hours post-dose, the unchanged drug was mainly detected (accounting for 95.1% in males and 96.1% in females of the total radioactivity in plasma). (1) M2 (the monoxide metabolite) was detected in both males and females, and (2) M1 (the dehydrogenated metabolite) was detected in males only (accounting for (1) 2.31% in males and 2.34% in females and (2) 0.70% of the total radioactivity in plasma).
- In the urine collected up to 24 hours post-dose, the unchanged drug was mainly detected (representing 16.5% in males and 24.3% in females of the administered radioactivity). The M1 metabolite was detected in males (representing 1.33% of the administered radioactivity).

- In the feces collected up to 24 hours post-dose, the unchanged drug was mainly detected (representing 64.2% in males and 65.6% in females of the administered radioactivity). As metabolites, (1) M1 and (2) M2 were detected (representing (1) 3.47% in males and 0.44% in females and (2) 1.07% in males and 1.16% in females of the administered radioactivity).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

The applicant explained that the following study results etc. indicated that fecal excretion is the major route of elimination of talazoparib and its metabolites.

- Following a single oral dose of ^{14}C-talazoparib 3 mg/kg in bile duct-intact male and female rats, 19.5% in males and 25.8% in females of the administered radioactivity were recovered in the urine, and 73.6% in males and 70.9% in females of the administered radioactivity were recovered in the feces, over 240 hours.
- Following a single oral dose of ^{14}C-talazoparib 3 mg/kg in bile duct-cannulated male rats, 24.2%, 64.1%, and 3.37% of the administered radioactivity were recovered in the urine, feces, and bile, respectively, over 120 hours.

4.4.2 Excretion into milk

Milk excretion of talazoparib was not studied. The applicant explained that talazoparib may be excreted in milk, considering its physicochemical properties (a molecular weight of 380.35, a logP value of 1.6).

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about pharmacokinetic interactions via the inhibition of metabolizing enzymes by talazoparib:

Given the following study results, talazoparib is unlikely to cause pharmacokinetic interactions via the inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1), UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15 in clinical use.

- Human liver microsomes were incubated with talazoparib (0.01-10 μmol/L) and the substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A)[16)] in the presence of NADPH, and the ability of talazoparib to inhibit CYP isoforms was evaluated. Talazoparib did not cause evident inhibition of the metabolism of the substrates for CYP isoforms tested.
- Human liver microsomes were preincubated with talazoparib (0.01-10 μmol/L) in the presence of NADPH and then incubated with the substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A),[16)] and talazoparib was evaluated as a time-dependent inhibitor of these CYP isoforms. Talazoparib did not show evident time-dependent inhibition of the metabolism of the substrates for CYP isoforms tested.

[16)] Phenacetin, efavirenz, amodiaquine, diclofenac, *S*-mephenytoin, and dextromethorphan were used as the substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, respectively, and midazolam and testosterone were used as CYP3A substrates.

- Human liver microsomes were incubated with talazoparib (0.1-10 μmol/L) and the substrates for UGT isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15)[17] in the presence of uridine diphosphate glucuronic acid (UDPGA) and 2% bovine serum albumin, and the potential of talazoparib to inhibit UGT isoforms was evaluated. Talazoparib did not cause evident inhibition of the metabolism of the substrates for UGT isoforms tested.

4.5.2 Enzyme induction

Primary human hepatocytes were incubated with talazoparib (0.003-10 μmol/L) for 3 days, and the mRNA expression levels of CYP isoforms (CYP1A2, CYP2B6, CYP3A4) were determined. The increase in the mRNA expression of CYP3A4 induced by talazoparib was 90.1%-243% of the response of vehicle control and ≤15.7% of the response of the positive control.[18] The increase in the mRNA expression of CYP3A4 induced by talazoparib (1 μmol/L) was 97% of the response of vehicle control. On the other hand, talazoparib did not cause evident induction of the mRNA expression of CYP1A2 or CYP2B6.

The applicant's explanation:
Given the above study results and the unbound plasma C_{max} of talazoparib (0.014 μmol/L) following oral administration of talazoparib 1 mg QD, talazoparib is unlikely to cause pharmacokinetic interactions via the induction of CYP1A2, CYP2B6, or CYP3A in clinical use.

4.5.3 Transporters

The applicant's explanation about transporter-mediated pharmacokinetic interactions of talazoparib:
The following study results showed that talazoparib is not a substrate of organic cation transporter 1 (OCT1), organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, organic anion transporter 1 (OAT1), OAT3, OCT2, multidrug and toxin extrusion 1 (MATE1), MATE-2K, or bile salt export pump (BSEP), but is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). P-gp- and BCRP-mediated pharmacokinetic interactions of talazoparib are described in Section "6.R.4 P-gp-mediated pharmacokinetic interactions" and Section "4.R.1 Pharmacokinetic interactions," respectively.

- P-gp-mediated transport of talazoparib (1 μmol/L) was investigated using the canine kidney MDCK cell line expressing human P-gp. The ratio of the efflux ratios from the P-gp-expressing cell line to the parental cell line was 7.40.
- BCRP-mediated transport of talazoparib (0.01-1 μmol/L) was investigated using the Caco-2 cell line. The efflux ratio of talazoparib was 2.59 to 2.87.
- Using MDCKII cells expressing human OCT1, OATP1B1, or OATP1B3, each transporter-mediated transport of talazoparib (0.01-1 μmol/L) was investigated. The ratios of the uptake of talazoparib in the transporter-expressing cell lines to the parental cell line were all <2.

[17] β-estradiol, trifluoroperazine, 5-hydroxytryptophol, propofol, zidovudine, and *S*-oxazepam were used as the substrates of UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, respectively.
[18] Rifampicin (20 μmol/L) was used as the positive control for CYP3A4.

- Using the MDCKII cell line expressing human OAT1, OAT3, OCT2, MATE1, or MATE-2K, each transporter-mediated transport of talazoparib (0.01-1 μmol/L) was investigated. The ratios of the uptake of talazoparib in the transporter-expressing cell lines to the parental cell line were all <2.
- Using the membrane vesicles from the insect ovarian Sf9 cell line expressing human BSEP, BSEP-mediated transport of talazoparib (0.01-1 μmol/L) was investigated. The ratio of the uptake of talazoparib in the presence of ATP relative to the absence of ATP was <2.

Given the following study results, talazoparib is unlikely to cause pharmacokinetic interactions via the inhibition of transporters in clinical use.

- Using the MDCK cell line expressing human P-gp, the HEK293 cell line expressing human BCRP, the membrane vesicles from the Sf9 cell line expressing BSEP, and the MDCKII cell line expressing human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K, the potential of talazoparib (0.014-30 μmol/L[19)]) to inhibit each transporter-mediated transport of their substrates[20)] was evaluated. Talazoparib did not cause evident inhibition of the transport of the substrates of these transporters.

4.R Outline of the review conducted by PMDA

On the basis of the submitted data and the considerations in the following section, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of talazoparib is acceptable.

4.R.1 Pharmacokinetic interactions

The applicant's explanation about BCRP-mediated pharmacokinetic interactions of talazoparib:

Since an *in vitro* study suggested that talazoparib is a substrate of BCRP [see Section 4.5.3], caution should be exercised when coadministering talazoparib with a strong BCRP inhibitor, and the relevant precautionary statement will be included in the package insert. The ABRAZO and EMBRACA studies[21)] raised no particular safety concerns about coadministration of talazoparib with a BCRP inhibitor.

PMDA's discussion:

Given that there were no safety concerns associated with pharmacokinetic interactions in patients who received talazoparib plus a BCRP inhibitor in the ABRAZO and EMBRACA studies, etc., at present, there is little need to include a precautionary statement regarding coadministration of talazoparib with BCRP inhibitors in the package insert. However, as the information on BCRP-mediated pharmacokinetic interactions of talazoparib is important for the proper use of talazoparib, it is necessary to continue to collect relevant information and appropriately provide any useful information to healthcare professionals in clinical practice.

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19) The concentrations tested for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, and BSEP were 1 μmol/L.

20) ^{3}H-digoxin (10 μmol/L), rosuvastatin (0.2 μmol/L), ^{3}H-*p*-aminohippuric acid (2 μmol/L), ^{3}H-*p*-aminohippuric acid (10 μmol/L), ^{3}H-estradiol-17β-glucuronide (2 μmol/L), ^{3}H-cholecystokinin-8 (10 μmol/L), ^{14}C-1-methyl-4-phenylpyridinium (10 μmol/L), and ^{3}H-taurocholic acid (1 μmol/L) were used the substrates of P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and BSEP, respectively. ^{14}C-metformin (10 μmol/L) was used as a substrate of OCT2, MATE1, and MATE2-K.

21) There were subjects who received talazoparib plus a BCRP inhibitor in the ABRAZO and EMBRACA studies among the clinical studies of talazoparib monotherapy at the proposed dosing regimen (Study 030, ABRAZO study, EMBRACA study).

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and other studies (photosafety studies, mechanistic investigation of bone marrow suppression).

5.1 Single-dose toxicity

No single-dose toxicity studies were conducted with talazoparib. The approximate lethal dose and acute toxicity of talazoparib were assessed based on the results from 5-day repeated oral dose toxicity studies in rats (CTD 4.2.3.2.3) and dogs (CTD 4.2.3.2.6). Talazoparib caused mortality at 1 mg/kg in rats and at ≥0.1 mg/kg in dogs, and the approximate lethal dose of talazoparib was determined to be 1 mg/kg in rats and 0.1 mg/kg in dogs. No acute symptoms were observed following a single dose administration.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in rats and dogs (5 days, 4 and 13 weeks) were conducted (Table 14). The main toxicity findings observed in both rats and dogs at subtherapeutic exposures[22)] were decreases in red blood cell (RBC) and white blood cell (WBC) parameters, bone marrow hypocellularity, depletion of lymphoid tissue, and gastrointestinal mucosal injury. In rats, bacterial infection associated with immunosuppression due to decreases in WBC parameters, abnormal liver function parameters, and hepatocyte necrosis were observed.

The applicant's explanation:
The changes in body weight and RBC parameters, depletion of lymphoid tissue, and changes in urinalysis parameters observed in rats and dogs after repeated dosing at or below the no observed adverse effect level (NOAEL) were nonadverse because those changes were minimal. With respect to the effects of talazoparib on the liver, gastrointestinal tract, and hematolymphopoietic system observed in the repeated-dose toxicity studies, though a certain proportion of subjects experienced adverse events related to those toxicity findings in clinical studies, such events are manageable and tolerable in the clinical use of talazoparib.

PMDA's conclusion on the effects of talazoparib on the hematolymphopoietic system, the primary target organs for the toxicity of talazoparib, is described in Section "7.R.1.1 Myelosuppression," taking account of the safety results from clinical studies.

[22)] Talazoparib exposures (AUC_{24}) at the NOAELs in rats and dogs (0.015 mg/kg/day and 0.005 mg/kg/day, respectively) were 8.43 ng·h/mL (males and females combined) and 7.86 ng·h/mL (males and females combined), respectively, which were both 0.2-fold the steady-state human exposure (AUC_{24} = 52.5 ng·h/mL) at 1 mg QD.

Table 14. Repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Major findings[*3]	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral gavage	5 days (QD) + 4-week recovery period	0,[*1] 0.3, 1, 3	≥0.3: decreased food consumption, apoptosis in the stomach/duodenum/small intestine/large intestine (male and female) ≥1: rough haircoat (male), follicular atresia (female) Mortality during the recovery period 1: 12 of 12 animals (male and female) 3: 12 of 12 animals (male and female) decreased food consumption, thin appearance, hunched posture, pale, hypoactivity, porphyrin eye/nasal discharge, rough/stained haircoat, squinted eyes, swelling of the head/ventral neck, irritability, liquid feces, inflammation/bacterial infection in the mandibular lymph node/ salivary gland/lung/kidney, cerebral hemorrhage/bacterial infection	—	4.2.3.2.3
Male and female rats (Sprague Dawley)	Oral gavage	4 weeks (QD) + 4-week recovery period	0,[*1] 0.005, 0.015, 0.05	≥0.005: higher blood urea nitrogen (female), sperm granulomas of the epididymis (male) ≥0.015: lower neutrophil count[*4]/blood globulin, higher A/G ratio/chloride, sternal bone marrow hypocellularity (female) 0.05: red stained haircoat in the back and neck/nose, decreases in RBC count/hemoglobin/hematocrit/reticulocyte count[*4]/WBC count[*5]/monocyte count/eosinophil count[*6]/basophil count[*5]/large unstained cell count,[*7] increases in platelet count/blood glucose/γ-GTP/potassium, femoral bone marrow hypocellularity, increased apoptosis in the glandular stomach/duodenum, hepatocyte necrosis in the liver, lymphocyte depletion in the mandibular lymph node germinal center/mesenteric lymph node germinal center/marginal zone of the spleen/thymus (male and female), decreases in neutrophil count[*8]/lymphocyte count/fibrinogen[*9]/blood globulin/blood ALP, increases in MCV/MCH/A/G ratio/inorganic phosphate/chloride, decreases in the testis/thymus weights, focal tan discoloration of the epididymis, sternal bone marrow hypocellularity, atrophy/degeneration of the testes (male), lower lymphocyte count[*4] (female) These findings were reversible.	—	4.2.3.2.4
Male and female rats (Sprague Dawley)	Oral gavage	13 weeks (QD) + 4-week recovery period	0,[*1] 0.005, 0.015, 0.05/0.04[*2]	Mortality[*10] 0.05/0.04: 4 of 18 animals (male), 1 of 18 animals (female) pale eyes/ears/feet, decreased body weight, hypoactivity, decreases in RBC count/hemoglobin/hematocrit/reticulocyte count/WBC count/neutrophil count/lymphocyte count/basophil count/large unstained cell count, bone marrow hypocellularity Surviving animals ≥0.015: lower RBC count, higher MCV/MCH,[*11] decreased lymphocytes in the mesenteric lymph node (male and female), decreased body weight gain (male), increased urine volume, decreased urine specific gravity (female) 0.05/0.04: pale eyes/feet, decreases in hemoglobin/hematocrit/reticulocyte count/WBC count/lymphocyte count/monocyte count/basophil count/large unstained cell count, higher platelet count, hypocellularity/increased M/E ratio/mast cell infiltrate in the femoral/sternal bone marrow, increased extramedullary hematopoiesis in the spleen, decreased lymphocytes in the thymus (male and female), pale ears, increased spleen weight, decreases in testis/epididymis weights, luminal cell debris/reduced sperm/epithelial vacuolation in the epididymis, degeneration/atrophy of the testis (male), higher MCV/MCH, decreased thymus weight (female) 0.015: decreased food consumption (male) These findings were reversible.	0.015	4.2.3.2.5
Male and female dogs (Beagle)	Oral gavage	5 days (QD) + 4-week recovery period	0,[*1] 0.003, 0.01, 0.03, 0.1	≥0.01: increased apoptosis in the duodenum/small intestine/large intestine Mortality during the recovery period 0.1: 3 of 3 animals (male), 3 of 3 animals (female) hypoactivity, salivation, liquid/mucoid/red or orange discolored/nonformed feces, increased body temperature, decreases in body weight/food consumption	—	4.2.3.2.6

Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Major findings[*3]	NOAEL (mg/kg/day)	Attached document CTD
Male and female dogs (Beagle)	Oral gavage	4 weeks (QD) + 29-day recovery period	0,[*1] 0.0005, 0.0015, 0.005, 0.01	≥0.005: decreases in hematocrit/basophil count, lymphocyte depletion in the GALT in the ileum/mandibular lymph node germinal center/mesenteric lymph node germinal center/splenic germinal center (male and female), decreases in lymphocyte count/large unstained cell count (male), lower monocyte count (female) 0.01: decreases in RBC count/hemoglobin/reticulocyte count/platelet count/WBC count/neutrophil count/monocyte count/large unstained cell count, increased apoptosis in the duodenum, sternal bone marrow hypocellularity (male and female), lower lymphocyte count, lymphocyte depletion in the GALT in the cecum/colon, femoral bone marrow hypocellularity (female) 0.005: lymphocyte depletion in the GALT in the cecum (male), decreases in WBC/neutrophil counts[*4] (female) These findings were reversible.	0.005	4.2.3.2.7
Male and female dogs (Beagle)	Oral gavage	13 weeks (QD) + 4-week recovery period	0,[*1] 0.0015, 0.005, 0.01	≥0.005: lower RBC count (male) 0.01: decreases in hemoglobin/hematocrit/MCHC/reticulocyte count/platelet count/basophil count, higher MCV, increased M/E ratio in the sternal bone marrow (male and female), decreases in WBC count/neutrophil count/lymphocyte count/monocyte count/large unstained cell count, decreased testicular weight, luminal cell debris/reduced sperm in the epididymis, increased M/E ratio in the femoral bone marrow (male), lower RBC count (female) Recovery period[*12] degeneration/atrophy in the seminiferous epithelium in the testis	0.005	4.2.3.2.8

*1 0.5 % CMC; *2 Animals had a dosing holiday from Day 50 to Day 63 due to pale feet and eyes, and dosing was resumed on Day 64 at a reduced dose of 0.04 mg/kg/day; *3 Five-day repeated dose toxicity studies in rats and dogs: acute toxicities and the findings observed in this study only or the findings unique to this study are listed; *4 Day 8; *5 Excluding females on Day 29; *6 Day 15; *7 Excluding males on Day 22; *8 Excluding Days 22 and 29; *9 Day 29; *10 The main toxicity findings related to talazoparib only are listed; *11 Males on Day 85 and females on Day 92; *12 New findings observed during the recovery period

5.3 Genotoxicity

A bacterial reverse mutation assay (Ames assay), a chromosomal aberration assay in human peripheral blood lymphocytes, and a micronucleus assay in rats were conducted (Table 15). Since talazoparib was clastogenic in the chromosomal aberration assay in human peripheral blood lymphocytes and induced micronuclei in the micronucleus assay in rats, the applicant explained that talazoparib is clastogenic.

Table 15. Genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment time)	Concentrations or doses	Test result	Attached document CTD
In vitro	Ames assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A	S9−/+	0,[*1] 100, 333, 1,000, 3,333, 5,000 μg/plate	Negative	4.2.3.3.1.1
	Chromosomal aberration assay	Human peripheral blood lymphocytes	S9− (4 hours)	0,[*1] 50, 100, 200 μg/mL	Positive (Structural chromosome aberrations)	4.2.3.3.1.2
			S9+ (4 hours)	0,[*1] 50, 100, 125 μg/mL		
			S9− (20 hours)	0,[*1] 0.5, 1.0, 2.5 μg/mL		
In vivo	Micronucleus assay	Rat (Sprague Dawley), bone marrow, single oral doses		0,[*2] 150, 300, 600 mg/kg (24 hours post-dose)	Positive	4.2.3.3.2.1
				0,[*2] 600 mg/kg (48 hours post-dose)		

*1 DMSO; *2 0.5% CMC

5.4 Carcinogenicity

No carcinogenicity studies were conducted because talazoparib is an anti-neoplastic drug intended to treat patients with advanced cancer.

5.5 Reproductive and developmental toxicity

The effects of talazoparib on the male and female reproductive organs were evaluated in repeated-dose toxicity studies. Following repeated dosing in rats and dogs, abnormal findings in the epididymis related to seminiferous tubule degeneration in the testis were observed. Following repeated dosing in rats, follicular atresia of the ovary was noted [see Section 5.2].

An embryo-fetal development study in pregnant rats was conducted (Table 16). The main toxicity findings in the embryos/fetuses were embryo-fetal death, decreased fetal weights, external and skeletal malformations, and skeletal variations, and the NOAEL for embryo-fetal development was <0.015 mg/kg/day.[23)]

The applicant's explanation about the use of talazoparib in pregnant women or women who may be pregnant:
Genotoxicity [see Section 5.3] and reproductive and development studies suggested the genotoxic potential of talazoparib and its effects on embryo-fetal development. Thus, the results from these studies will be provided appropriately to healthcare professionals in clinical practice, using the package insert etc., and the package insert will advise that (1) administration of talazoparib to pregnant women or women who may be pregnant is not recommended, and (2) women of reproductive potential should be advised to use effective contraception during treatment with talazoparib and for 7 months after the last dose,[24)] and male patients with female partners of reproductive potential or pregnant partners should be advised to use effective contraception during treatment with talazoparib and for 4 months after the last dose.[24)]

[23)] Talazoparib exposure (AUC_{24}) at 0.015 mg/kg/day in pregnant female rats was 4.97 ng·h/mL, which was 0.09-fold the steady-state human exposure (AUC_{24} = 52.5 ng·h/mL) at 1 mg QD.

[24)] On the basis of "Guidance on the need for contraception related to the use of pharmaceuticals" (PSEHB/PED Notification No. 0216-1 and PSEHB/PSD Notification No.0216-1, dated February 16, 2023), a contraception period of 5 half-lives (the half-life of talazoparib in humans is 50.7-89.8 hours) [see Section 6.2.1.1] plus 6 months after cessation of therapy for women of reproductive potential and a contraception period of 5 half-lives plus 3 months after cessation of therapy for men were recommended.

Table 16. Reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development	Female rats (Sprague Dawley)	Oral gavage	Gestation days 6-17 (QD)	0,[*1] 0.015, 0.05, 0.15	Dams: Mortality 0.15: 8 of 25 animals dehydration, hunched posture, cold to touch, hypoactivity, thin appearance, partially closed eyes, pale eyes, decreased food consumption Surviving animals ≥0.015: red vaginal discharge, decreases in body weight gain/food consumption ≥0.05: dehydration, hunched posture 0.15: pale skin, decreases in RBC count/hemoglobin/hematocrit, decreases in reticulocyte count/WBC count/monocyte count/neutrophil count/eosinophil count, increases in blood AST/ALT/γ-GTP/glucose, decreased blood cholesterol Embryos/fetuses ≥0.05: complete litter loss 0.015: fetal resorption, decreased fetal weights, depressed eye bulge,[*2] small eye,[*2] misshapen zygomatic arch,[*3] incompletely ossified [*3]/split[*2]/misshapen[*3] sternebrae, supernumerary rib,[*3] incompletely ossified[*3]/fused[*2]/misshapen[*3] cervical vertebral arch	Maternal toxicity:<0.015 Embryo-fetal developmental toxicity: <0.015	4.2.3.5.2.1

*1 0.5% CMC; *2 Malformation; *3 Variation

5.6 Other toxicity studies

5.6.1 Photosafety

The neutral red uptake phototoxicity assay of talazoparib in mouse fibroblasts and a phototoxicity study in pigmented rats were conducted (Table 17). Although the *in vitro* phototoxicity assay suggested the phototoxic potential of talazoparib, as the *in vivo* phototoxicity study in pigmented rats showed no findings indicative of phototoxicity, the applicant explained that talazoparib has little phototoxic potential.

Table 17. Photosafety studies

Test system	Test method	Major findings	Attached document CTD
Mouse fibroblasts (Balb/c 3T3)	0,[*1] 0.6, 1.0, 1.8, 3.2, 5.7, 10.1, 17.9, and 31.9 μg/mL UVA (5 J/cm^2) and UVB (20.2-20.4 J/cm^2) radiation	Assay 1 IC_{50} = 9.389 μg/mL (PIF >3.408, MPE = 0.345) Assay 2 IC_{50} = 9.015 μg/mL (PIF >3.540, MPE = 0.275) Phototoxic	4.2.3.7.7.1
Rat (Long Evans)	After talazoparib was administered by oral gavage at 0,[*2] 0.015, or 0.05 mg/kg/day for 3 days, rats were exposed to UVA (10.29 mJ/cm^2) and UVB (145 mJ/cm^2).	No findings	4.2.3.7.7.4

*1 DMSO; *2 0.5% CMC

5.6.2 Mechanistic investigation of bone marrow suppression

Studies were conducted to characterize the mechanism by which talazoparib alone or in combination with a DNA alkylating agent, temozolomide, induces bone marrow suppression (Table 18). Talazoparib was cytotoxic to bone marrow-derived cells, and talazoparib in combination with temozolomide induced apoptosis. The applicant explained that the above results suggested the following possibilities: the talazoparib-induced

hematological toxicities are due to inhibition of cell proliferation in bone marrow cells, and induction of apoptosis in bone marrow-derived cells is potentiated with talazoparib plus temozolomide.

Table 18. Mechanistic investigation of bone marrow suppression

Test system	Test method	Test results	Attached document CTD
Peripheral blood mononuclear cells (PBMCs)/bone marrow-derived mononuclear cells (BMMNCs) (a heterogeneous population), CD34+ bone marrow cells	The effects of talazoparib alone or in combination with temozolomide on cell viability, apoptosis, and double-strand DNA breaks and the effects of talazoparib on cell differentiation/proliferation in bone marrow cells were evaluated.	[PBMCs] Decreased cell viability was observed with talazoparib ≥10 μmol/L in combination with temozolomide ≥30 μmol/L. Talazoparib alone did not impact cell viability. [BMMNCs] Talazoparib in combination with temozolomide induced apoptosis (double-strand DNA breaks). Talazoparib alone did not induce apoptosis. IC_{50} values for cytotoxicity in rat, mouse, and human BMMNCs (nmol/L) 2.9 for rat, 5.4 for mouse, 6.9 for human [CD34+ cells] Talazoparib had no lineage-specific effects on cell differentiation/proliferation in different bone marrow cell lineages (erythroid, myeloid, megakaryocytic). IC_{50} values for bone marrow cell lineages (nmol/L) 8.7 for erythroid, 18.7 for myeloid, 10.0 for megakaryocytic	4.2.3.7.7.2 Reference data

5.6.3 Safety assessment of impurities

The applicant's explanation:

The impurities present in the drug substance (Impurity A and Impurity B) were not evaluated for mutagenicity. When the drug substance containing Impurity A and Impurity B at the upper specification limit is administered at the maximum daily dose of 1.45 mg, the exposure to these impurities (4.4 μg/day) is lower than the threshold of toxicological concern (TTC)-based acceptable daily intake for treatment duration of 1 to 10 years (10 μg/day) defined in the ICH-M7 (R1) guideline. Thus, there is little risk of mutagenicity.

5.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the toxicity of talazoparib is acceptable.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

As the oral formulations of talazoparib, the oral solution and capsules are available, and the PK etc. of talazoparib were studied using these formulations (Table 19). The capsule formulations used in the EMBRACA study, i.e., DP Gen2.0 and DP Gen3.1, differ in formulation. The proposed commercial drug product and the capsule formulation used in the EMBRACA and TALAPRO-2 studies (DP Gen3.1) are identical except for the differences in capsule shell color and printing.

Table 19. Oral formulations used in clinical studies

Formulation	Study ID
Oral solution containing ^{14}C-talazoparib	Foreign phase I study (Study 003)
0.025-, 0.05-, and 0.25-mg capsules (DP Gen1.0)	Foreign phase I studies (Study 007, Study 022)
0.1- and 0.25-mg capsules (DP Gen2.0)[*1]	Foreign phase I studies (Study 007, Study 023), foreign phase II study (ABRAZO study), foreign phase III study (EMBRACA study)
0.1-, 0.25-, and 1-mg capsules (DP Gen3.1)[*2]	Japanese phase I study (Study 030), foreign phase I studies (Study 001, Study 002, Study 004, Study 005), foreign phase II studies (ABRAZO study, Study 020, TALAPRO-1 study, Study 010), foreign phase III study (EMBRACA study), global phase III study (TALAPRO-2 study)

*1 The 0.1-mg capsule (DP Gen2.0) was used in the EMBRACA study only. At the beginning of the EMBRACA study, a fourth dose reduction to 0.1 mg was included, and the 0.1-mg capsule (DP Gen2.0) was used in 1 subject, but this option was omitted during the study (Protocol Version 2 [dated [redacted], 20[redacted]]); *2 The 0.1-mg capsule (DP Gen3.1) was used in the TALAPRO-2 study only, and the 1-mg capsule (DP Gen3.1) was used in Study 004, Study 005, ABRAZO study, Study 020, TALAPRO-1 study, Study 010, and EMBRACA study.

Talazoparib in human plasma was quantified by LC-MS/MS (LLOQ, 5 or 25 pg/mL[25)]).

6.1.1 Foreign study

6.1.1.1 Foreign phase I study (CTD 5.3.1.1.1, Study 023 [February to [redacted] 2013])

A 2-treatment, 2-period crossover study was conducted in 18 healthy volunteers (18 included in the PK analysis) to assess the effect of food on the PK of talazoparib.

A single oral dose of talazoparib 0.5 mg was to be administered under fasting conditions[26)] or after a high-fat meal,[27)] and a 21-day washout period was included between the treatment periods.

The talazoparib C_{max} and AUC_{inf} geometric mean ratios for a high-fat meal vs. fasted [90% confidence interval (CI)] were 0.539 [0.481, 0.603] and 0.976 [0.925, 1.03], respectively, and the median t_{max} of talazoparib was 1 hour in the fasted condition and 4 hours in the fed condition.

The applicant's explanation about the effect of food on the PK of talazoparib:
In Study 023, the C_{max} of talazoparib was lower and the t_{max} was delayed after a high-fat meal compared to fasting conditions, which was considered attributable to the decreased rate of talazoparib absorption by food intake. Food had no clear impact on the AUC_{inf} of talazoparib in Study 023, and based on this finding and the following points etc., talazoparib may be taken with or without food.

- Given the following point, the differences between the 0.25-mg capsule (DP Gen2.0) used in Study 023 and the 0.25-mg capsule (DP Gen3.1) used in the EMBRACA and TALAPRO-2 studies etc. have limited effects on the absorption of talazoparib under fasted and fed conditions. The effect of food on the PK of talazoparib administered using the proposed commercial drug product can be discussed based on the results of Study 023.
  - In the dissolution test using pH 1.2, pH 5.0, and pH 6.8 buffers as dissolution media, the average dissolution rates of the 0.25-mg capsule (DP Gen2.0) and the 0.25-mg capsule (DP Gen3.1) met the acceptance criterion provided in "Guideline for Bioequivalence Studies for Formulation Changes of

[25)] Plasma samples from Study 007, EMBRACA study, Study 022, and Study 023 were analyzed with a LLOQ of 5 pg/mL. Plasma samples from Study 001, Study 002, Study 003, Study 004, Study 005, TALAPRO-1 study, ABRAZO study, EMBRACA study, TALAPRO-2 study, and Study 030 were analyzed with a LLOQ of 25 pg/mL.
[26)] Subjects were to be fasted for ≥10 hours pre-dose and for 4 hours post-dose.
[27)] Consisting of 827 kcal with 57% fat

Oral Solid Dosage Forms" (PMSB/ELD Notification No.67 dated February 14, 2000) under all test conditions,[28] etc. Thus, the dissolution profiles of the two capsule formulations are similar.

- Talazoparib was administered without regard to food intake in the EMBRACA and TALAPRO-2 studies, which demonstrated the efficacy and tolerable safety of talazoparib.

6.1.2 Effect of gastric pH on PK of talazoparib

The applicant's explanation:

The solubility of talazoparib is [redacted] μg/mL over the pH range of 1.2 to 6.8, and the highest dose of 1 mg of talazoparib should dissolve in 250 mL of water. Thus, an increase in gastric pH following administration of proton pump inhibitors etc. is unlikely to impact the PK of talazoparib.

6.2 Clinical pharmacology

The PK of talazoparib when used alone or with enzalutamide, itraconazole, or rifampicin were studied in healthy volunteers and patients with cancer.

6.2.1 Japanese study

6.2.1.1 Japanese phase I study (CTD 5.3.5.2.4.BC: Study 030 [November 2017 to January 2021])

An open-label, uncontrolled study was conducted in 9 patients with advanced solid tumors (9 included in the PK analysis) to evaluate the PK etc. of talazoparib.[29]

Patients were to receive a single oral dose of talazoparib 0.75 or 1 mg on Day 1 followed by continuous daily dosing from Day 8, and plasma talazoparib concentrations were determined.

The PK parameters of talazoparib are shown in Table 20. The accumulation ratio of talazoparib[30] following oral administration of talazoparib 1 mg QD was 2.87.

Table 20. PK parameters of talazoparib

Dose (mg)	Sampling day	N	C_{max} (ng/mL)	t_{max} *1 (h)	AUC_{tau} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
0.75	1	3	7.52 ± 2.58	0.983 (0.750, 1.92)	47.1 ± 8.97	108 ± 13.0	56.6 ± 17.9
	29	3	14.8 ± 3.95	1.02 (0.967, 1.87)	127 ± 8.02	—	—
1	1	6	14.2 ± 3.62	0.967 (0.467, 1.98)	90.8 ± 29.4	200 ± 17.7*2	50.7 ± 10.1*2
	29	6	33.1 ± 5.16	1.03 (0.733, 1.92)	249 ± 49.6	—	—

Mean ± SD; *1 Median (Min., Max.); *2 N = 4; —, Not calculated

[28] The acceptance criterion was not met when using water as dissolution medium.
[29] In Study 030, the expansion part in patients with g*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy was also conducted.
[30] The ratio of AUC_{tau} on Day 29 to AUC_{tau} on Day 1

6.2.2 Global study

6.2.2.1 Global phase III study (CTD5.3.5.1.1.CRPC: TALAPRO-2 study [ongoing since ■ 2017 (data cutoff date on August 16, 2022)])

In 421 patients with mCRPC who had received no prior systemic therapy for mCRPC (414 included in the PK analysis), an open-label, uncontrolled study to evaluate the PK of talazoparib in combination with enzalutamide (Part 1) and a randomized, double-blind study (Part 2 [Cohort 1]) were conducted.

Talazoparib 0.5 or 1 mg QD was to be administered orally, in combination with enzalutamide 160 mg, and plasma concentrations of talazoparib and enzalutamide were determined.

Table 21 shows the PK parameters of talazoparib and enzalutamide in Part 1. In Part 2 (Cohort 1), when talazoparib 0.5 mg QD was administered orally in combination with enzalutamide 160 mg, the geometric mean C_{trough} of talazoparib at Week 9 was 3.68 ng/mL.

Table 21. PK parameters of talazoparib and enzalutamide

Analyte	Dose of talazoparib (mg)	Sampling day	N	C_{max} (ng/mL[*1])	t_{max}[*2] (h)	AUC_{tau} (ng·h/mL[*3])
Talazoparib	0.5	Day 1	6	1.65 ± 0.474	1.51 (1.0, 4.0)	18.3 ± 4.63
		Week 9[*4]	5	8.95 ± 2.27	1.95 (1.0, 4.0)	137 ± 32.9
	1	Day 1	13	3.78 ± 1.86	2.10 (1.0, 24.0)	48.9 ± 14.5[*5]
		Week 9[*4]	3	16.5 ± 6.13	5.05 (4.0, 5.5)	302 ± 151
Enzalutamide	0.5	Day 1	6	3.88 ± 1.54	1.00 (1.0, 2.0)	33.2 ± 10.4
		Week 9[*4]	6	12.0 ± 3.23	1.00 (0.9, 2.0)	215 ± 41.4
	1	Day 1	13	3.69 ± 0.999	1.00 (1.0, 2.0)	34.9 ± 11.4[*6]
		Week 9[*4]	6	12.3 ± 1.98	1.05 (1.0, 2.0)	253 ± 32.3

Mean ± SD; *1 μg/mL for enzalutamide; *2 Median (Min., Max.); *3 μg·h/mL for enzalutamide; *4 Measured at visit; *5 N = 12; *6 N = 11

The applicant's explanation about the above results:

In Part 1 of the TALAPRO-2 study, talazoparib exposure (AUC_{tau}) following administration of talazoparib 1 mg QD in combination with enzalutamide was higher than talazoparib exposure (AUC_{tau}) following administration of talazoparib 1 mg QD alone [see Section 6.2.10], suggesting that coadministration with enzalutamide increases talazoparib exposure. Since P-gp is involved in the clearance of talazoparib [see Section 4.5.3], and enzalutamide has been reported to inhibit P-gp (see "Review Report on Xtandi Capsules 40 mg dated January 15, 2014"), the increase in talazoparib exposure following coadministration with enzalutamide was due to the inhibition of P-gp by enzalutamide.

6.2.3 Foreign studies

6.2.3.1 Foreign phase I study (CTD 5.3.5.2.1.BC: Study 007 [January 2011 to March 2015])

An open-label, uncontrolled study was conducted in 39 patients with advanced solid tumors (39 included in the PK analysis) to evaluate the PK etc. of talazoparib.

Patients were to receive single oral doses of talazoparib 0.025 to 1.1 mg on Day 1 followed by continuous daily dosing from Day 8. Plasma talazoparib concentrations were determined.

The PK parameters of talazoparib are shown in Table 22.

Table 22. PK parameters of talazoparib

Dose (mg)	Sampling day	N	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{0-24} (ng·h/mL)	Accumulation ratio*2
0.025	1	3	0.0600 ± 0.0159	7.92 (1.95, 9.95)	0.952 ± 0.386	—
	35	3	0.300 ± 0.0788	1.02 (0.580, 3.98)	3.42, 4.50*3	3.97, 6.73*3
0.05	1	3	0.0797 ± 0.00750	1.00 (0.800, 1.02)	1.16 ± 0.166	—
	35	2	0.562, 0.667	0.770, 10.1	8.04, 11.5	6.23, 9.42
0.1	1	3	0.214 ± 0.0509	1.02 (1.00, 3.98)	3.16 ± 1.27	—
	35	2	1.64, 2.11	0.750, 0.820	26.9, 33.2	8.68, 15.8
0.2	1	3	0.788 ± 0.369	1.03 (1.00, 2.32)	9.13 ± 3.54	—
	35	3	5.62 ± 3.53	1.97 (1.00, 3.02)	83.1 ± 49.3	9.14 ± 4.57
0.4	1	3	1.83 ± 0.699	2.03 (0.750, 2.95)	13.5 ± 5.20	—
	35	3	6.56 ± 1.50	0.980 (0.750, 2.00)	67.3 ± 22.6	5.62 ± 3.36
0.6	1	6	4.10 ± 1.40	0.835 (0.750, 1.95)	37.9 ± 12.9	—
	35	6	11.3 ± 3.23	1.04 (0.730, 5.98)	119 ± 19.9	3.32 ± 0.806
0.9	1	6	6.10 ± 3.06	2.00 (1.02, 9.98)	58.2 ± 24.3	—
	35	5	15.4 ± 1.54	1.02 (0.970, 2.07)	157 ± 24.5	3.70 ± 2.43
1.0	1	5	10.6 ± 4.22	1.03 (0.730, 2.07)	85.1 ± 29.1	—
	35	6	21.0 ± 7.99	1.02 (0.750, 2.00)	202 ± 54	2.31 ± 0.353
1.1	1	7	13.2 ± 3.22	1.00 (0.730, 2.05)	91.6 ± 31.8	—
	35	4	23.4 ± 4.81	1.48 (0.980, 2.00)	188 ± 29.2	2.51 ± 0.498

Mean ± SD (Individual values are listed for N = 2); —, Not calculated
*1 Median (Min., Max.); *2 The ratio of AUC_{0-24} on Day 35 to AUC_{0-24} on Day 1; *3 N = 2

6.2.3.2 Foreign phase I study (CTD 5.3.3.2.1, Study 003 [September 2016 to June 2017])

An open-label, uncontrolled study was conducted in 6 patients with advanced solid tumors (6 included in the PK analysis) to evaluate the mass balance of talazoparib.

A single oral dose of ^{14}C-talazoparib 1 mg was to be administered, and radioactivity concentrations in plasma, urine, feces, etc., were determined.

Over 504 hours, 68.7% and 19.7% of the administered radioactive dose were recovered in the urine and feces, respectively. The unchanged drug was mainly detected in the urine and feces collected up to 504 hours post-dose (representing 54.6% and 13.6% of the administered radioactive dose, respectively).

In the plasma collected up to 504 hours post-dose, the unchanged drug only was detected.

6.2.4 Drug-drug interaction study

6.2.4.1 Drug-drug interaction study with itraconazole and rifampicin (CTD 5.3.3.4.1, Study 004 [November 2016 to January 2018])

An open-label, uncontrolled study was conducted in 36 patients with advanced solid tumors (36 included in the PK analysis) to evaluate the effect of itraconazole (a P-gp inhibitor) and rifampicin (a P-gp inducer) on the PK of talazoparib.

The dosing regimens are shown below.

Part 1: Two single oral doses of talazoparib 0.5 mg on Days 1 and 23 with multiple oral doses of itraconazole 100 mg BID on Days 16 to 36

Part 2: Two single oral doses of talazoparib 1 mg on Days 1 and 25 with multiple oral doses of rifampicin 600 mg QD on Days 16 to 38

The geometric least-square mean ratios of the C_{max} and AUC_{inf} of talazoparib for (1) talazoparib + itraconazole and (2) talazoparib + rifampicin vs. talazoparib alone [90% CI] were (1) 1.40 [1.13, 1.73] and 1.56 [1.38, 1.77], respectively, and (2) 1.37 [1.03, 1.81] and 1.02 [0.940, 1.11], respectively.

The applicant's explanation:
Since the above results indicated that coadministration with a P-gp inducer is unlikely to decrease talazoparib exposure, a precautionary statement regarding coadministration with P-gp inducers is unnecessary.

Coadministration with P-gp inhibitors is described in Section "6.R.4 P-gp-mediated pharmacokinetic interactions."

6.2.5 Foreign phase I study to assess the effect of hepatic impairment on PK of talazoparib (CTD 5.3.3.3.2, Study 002 [September 2016 to February 2020])

An open-label study was conducted in 7 patients with advanced solid tumors and normal hepatic function (7 included in the PK analysis) and 31 patients with advanced solid tumors and mild, moderate, or severe hepatic impairment[31)] (10 patients with mild hepatic impairment, 5 patients with moderate hepatic impairment, 16 patients with severe hepatic impairment [8 patients with mild hepatic impairment, 5 patients with moderate hepatic impairment, and 13 patients with severe hepatic impairment included in the PK analysis) to assess the effect of hepatic impairment on the PK of talazoparib.

Talazoparib 0.5 mg QD was to be administered orally, and plasma talazoparib concentrations were determined.

Table 23 shows the PK parameters of unbound talazoparib.

[31)] Classified by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

Table 23. PK parameters of unbound talazoparib by severity of hepatic impairment

Severity of hepatic impairment	N	C_{max} (ng/mL)	AUC_{24} (ng·h/mL)	Geometric mean ratio [90% CI] (Patients with hepatic impairment/Patients with normal hepatic function)	
				C_{max}	AUC_{24}
Day 1					
Normal	7	1.13 ± 1.05	6.81 ± 2.52	—	—
Mild	8	0.872 ± 0.251	7.97 ± 2.71	0.946 [0.567, 1.58]	1.18 [0.838, 1.67]
Moderate	5	0.865 ± 0.352	6.98 ± 1.01	0.922 [0.517, 1.64]	1.08 [0.733, 1.60]
Severe	13	0.916 ± 0.599	8.35 ± 4.01*	0.844 [0.531, 1.34]	1.18 [0.853, 1.63]*
Day 22					
Normal	6	2.86 ± 0.765	30.3 ± 3.30	—	—
Mild	6	3.60 ± 2.01	55.9 ± 40.2	1.15 [0.780, 1.71]	1.49 [0.915, 2.44]
Moderate	3	3.77 ± 1.09	34.8 ± 12.3	1.32 [0.819, 2.14]	1.11 [0.609, 2.02]
Severe	2	3.79, 5.24	60.2, 69.8	—	—

Mean ± SD (Individual values are listed for N = 2); —, Not calculated; *N = 11

The applicant's explanation:

Given the above results and the following points, no dose adjustment is required for patients with hepatic impairment.

- The results of a foreign phase I study (Study 003) suggested that renal excretion of talazoparib is the major route of elimination [see Section 6.2.3.2].
- The EMBRACA and TALAPRO-2 studies showed no clear differences in the incidence of adverse events between patients with normal hepatic function[32)] and patients with hepatic impairment.

6.2.6 Foreign phase I study to assess the effect of renal impairment on PK of talazoparib (CTD 5.3.3.3.1, Study 001 [February 2017 to January 2019])

An open-label study was conducted in 9 patients with advanced solid tumors and normal renal function (9 included in the PK analysis) and 25 patients with advanced solid tumors and mild, moderate, or severe renal impairment[33)] (9 patients with mild renal impairment, 8 patients with moderate renal impairment, 8 patients with severe renal impairment [9 patients with mild renal impairment, 8 patients with moderate renal impairment, and 8 patients with severe renal impairment included in the PK analysis) to assess the effect of renal impairment on the PK of talazoparib.

Talazoparib 0.5 mg QD was to be administered orally, and plasma talazoparib concentrations were determined.

Table 24 shows the PK parameters of unbound talazoparib.

[32)] Normal hepatic function was defined as total bilirubin and AST at or below the upper limit of normal, and hepatic impairment was defined as total bilirubin or AST exceeding the upper limit of normal.

[33)] eGFR (mL/min/1.73m^2) ≥90 was classified as normal renal function, eGFR ≥60 and <90 was classified as mild renal impairment, eGFR ≥30 and <60 was classified as moderate renal impairment, and eGFR ≥15 and <30 with no dialysis was classified as severe renal impairment.

Table 24. PK parameters of unbound talazoparib by severity of renal impairment

Severity of renal impairment	N	C_{max} (ng/mL)	AUC_{24} (ng·h/mL)	Geometric mean ratio [90% CI] (Patients with renal impairment/Patients with normal renal function)	
				C_{max}	AUC_{24}
Day 1					
Normal	6	0.793 ± 0.504	6.45 ± 2.76	—	—
Mild	7	0.947 ± 0.599	8.35 ± 2.77	1.21 [0.701, 2.07]	1.43 [0.931, 2.20]
Moderate	8	0.974 ± 0.588	6.62 ± 2.22*	1.22 [0.718, 2.06]	1.13 [0.733, 1.73]
Severe	6	1.11 ± 0.517	11.3 ± 3.10	1.52 [0.868, 2.67]	1.97 [1.26, 3.08]
Day 22					
Normal	6	2.74 ± 1.05	29.6 ± 9.95	—	—
Mild	7	3.35 ± 2.02	35.1 ± 12.8	1.17 [0.797, 1.73]	1.19 [0.839, 1.68]
Moderate	8	3.60 ± 1.66	43.2 ± 20.3	1.28 [0.881, 1.87]	1.39 [0.995, 1.95)]
Severe	7	5.51 ± 1.75	85.3 ± 27.7	2.06 [1.40, 3.04]	2.87 [2.03, 4.05]

Mean ± SD; —, Not calculated; *N = 7

The applicant's explanation:
Since the above results showed that mild renal impairment had no clear impact on talazoparib exposure, no dose adjustment is required for patients with mild renal impairment.

The use of talazoparib in patients with moderate or severe renal impairment is described in Section "6.R.3 Use of talazoparib in patients with renal impairment."

6.2.7 Relationship between exposure and change in QT/QTc interval

On the basis of the data from a foreign phase I study (Study 005), the relationship between plasma talazoparib concentrations and ΔQTcF was analyzed using a linear mixed-effects model. There was no clear relationship between plasma talazoparib concentrations and ΔQTcF. At the mean steady-state C_{max} (17.2 ng/mL), the upper bound of the 90% confidence interval for the predicted ΔQTcF was below 5 ms.

The applicant's explanation:
On the basis of the above results, talazoparib is unlikely to cause QT/QTc prolongation in clinical use.

6.2.8 PPK analysis

On the basis of talazoparib PK data (490 patients, 6,207 PK observations)[34)] obtained from a global phase III study (the EMBRACA study), foreign phase I studies (Studies 022 and 007), and a foreign phase II study (the ABRAZO study), a PPK analysis was performed by non-linear mixed effects modeling (software, NONMEM Version 7.3). The PK of talazoparib were described by a 2-compartment model with first-order absorption.

In the analysis, (1) age, race, and baseline creatinine clearance (CLcr), (2) body weight, and (3) acid-reducing agents, BCRP inhibitors, food, formulation strength, proton pump inhibitors, H_2 receptor antagonists, other

34) For the patients included in the analysis, patient demographics [median (min., max.)] or the number of patients or PK observations in each category are shown below.
Age, 49 (18, 88) years; race, 361 Caucasian patients, 16 Black patients, 41 Asian patients, 9 patients with other race, 63 patients with unknown race; CLcr, 105 (26.0, 362) mL/min; body weight, 67.0 (35.7, 162) kg; coadministration of acid-reducing agents, 190 patients (158 patients [proton pump inhibitors], 20 patients [H_2 receptor antagonists], 48 patients [other acid-reducing agents]); coadministration of BCRP inhibitors, 3 patients; coadministration of P-gp inhibitors, 56 patients; coadministration of P-gp inducers, 1 patient; food, 3,713 PK observations (fasted), 1,889 PK observations (fed), 605 PK observations (unknown); formulation strength, 1-mg capsule (269 patients), 0.25-mg capsule (252 patients), 0.05-mg capsule (2 patients), 0.25- and 0.05-mg capsules (45 patients)

acid-reducing agents, P-gp inhibitors, and P-gp inducers were tested as potential covariates on (1) CL/F, (2) V_2/F, and (3) ka and F1. (i) Age, race, and baseline CLcr, (ii) body weight, (iii) food and formulation strength, and (iv) P-gp inhibitors were identified as significant covariates on (i) CL/F, (ii) V_2/F, (iii) ka, and (iv) F1.

The applicant's explanation:
Since age, race, and body weight had limited impacts on talazoparib exposure,[35)] no dose adjustment based on these covariates is required.

The effects of renal function at baseline, food, formulation, and P-gp inhibitors on talazoparib exposure are described in Sections "6.R.3 Use of talazoparib in patients with renal impairment," "6.1.1.1 Foreign phase I study," "6.R.1 Bioequivalence among talazoparib capsules used in the EMBRACA study," and "6.R.4 P-gp-mediated pharmacokinetic interactions," respectively.

6.2.9 Exposure-efficacy/safety relationship

6.2.9.1 Exposure-efficacy relationship

On the basis of the data from (1) the EMBRACA study and (2) the TALAPRO-2 study, the relationship between the $C_{avg,t}$ of talazoparib and (1) progression-free survival (PFS) or (2) radiographic progression-free survival (rPFS) was characterized. (1) PFS and (2) rPFS tended to increase with increasing $C_{avg,t}$ of talazoparib.

6.2.9.2 Exposure-safety relationship

On the basis of the data from (1) the ABRAZO and EMBRACA studies and (2) Part 1 and Part 2 Cohort 1 of the TALAPRO-2 study, the relationship between the $C_{avg,t}$ of talazoparib and Grade ≥3 anaemia, neutropenia, and thrombocytopenia was characterized. According to the analysis based on the data from (1), although the incidences of Grade ≥3 anaemia and thrombocytopenia tended to increase with increasing $C_{avg,t}$ of talazoparib, there was no clear relationship between the $C_{avg,t}$ of talazoparib and Grade ≥3 neutropenia. According to the analysis based on the data from (2), the incidences of Grade ≥3 anaemia, neutropenia, and thrombocytopenia tended to increase with increasing $C_{avg,t}$ of talazoparib.

6.2.10 Differences in PK between Japanese and non-Japanese populations

The applicant explained that given the following points, there were no clear differences in the PK of talazoparib between the Japanese and non-Japanese populations.

- Although the steady-state C_{max} and AUC_{tau} of talazoparib following administration of talazoparib 1 mg QD tended to be higher in Japanese patients than in non-Japanese patients (Table 25), the limited number of patients was evaluated, and the C_{trough} was similar between Japanese and non-Japanese patients (Table 26).

[35)] The ratios of CL/F between the 10th or 90th percentile and median age were 1.02 and 0.975, respectively, and the ratios of V_2/F between the 10th or 90th percentile and median body weight were 0.753 and 1.50, respectively. As to race, the ratio of CL/F in Asian patients versus non-Asian patients was 1.24.

Table 25. C_{max} and AUC of talazoparib

Study	Study population	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)
Dose-escalation part of Study 030	Japanese patients	6	32.8 (14)	245 (21)
Dose-escalation part of Study 007	Non-Japanese patients	6	19.8 (39)	196 (27)

Geometric mean (Geometric coefficient of variation %)

Table 26. C_{trough} of talazoparib

Study	Study population	N	C_{trough} (ng/mL)
Expansion part of Study 030	Japanese patients	17	3.35 (39)
ABRAZO	Non-Japanese patients	47	3.61 (66)
EMBRACA	Non-Japanese patients	175	3.53 (61)
005	Non-Japanese patients	27	4.95 (56)

Geometric mean (Geometric coefficient of variation %)

- In Part 2 (Cohort 1) of the TALAPRO-2 study, the steady-state C_{trough} values of talazoparib [geometric mean (geometric coefficient of variation %)] following administration of talazoparib 0.5 mg QD in combination with enzalutamide in Japanese patients (N = 51) and non-Japanese patients (N = 259) were 3.44 (43) and 3.08 (47) ng/mL, respectively, showing no clear differences between Japanese and non-Japanese patients.

6.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the clinical pharmacology etc. of talazoparib is acceptable, except for the considerations in the following sections.

6.R.1 Bioequivalence among talazoparib capsules used in the EMBRACA study

Talazoparib 1 mg QD was to be administered in the EMBRACA study, and the 0.25-mg capsule (DP Gen2.0), the 0.25-mg capsule (DP Gen3.1), or the 1-mg capsule (DP Gen3.1) was used.

The applicant's explanation about the bioequivalence among the talazoparib capsules used in the EMBRACA study:

On the basis of “Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms” (PMSB/ELD Notification No. 64 dated February 14, 2000) and "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No.67 dated February 14, 2000), dissolution tests were performed, which failed to demonstrate the bioequivalence between the 0.25-mg capsule (DP Gen3.1) and the 1-mg capsule (DP Gen3.1) or between the 0.25-mg capsule (DP Gen2.0) and the 0.25-mg capsule (DP Gen3.1). Although the above guidelines state that if the comparability of the dissolution profiles of the test and reference products is not demonstrated, a human bioequivalence study should be conducted, it is difficult to conduct the study for the following reason.

- Given the intra-individual variability in talazoparib exposure etc., 178 subjects each are required to conduct bioequivalence studies of the 0.25-mg capsule (DP Gen3.1) vs. the 1-mg capsule (DP Gen3.1) and of the 0.25-mg capsule (DP Gen2.0) and the 0.25-mg capsule (DP Gen3.1), and a long period of time will be needed to enroll the required number of subjects.

However, given the following point etc., when the 0.25-mg capsule (DP Gen2.0), the 0.25-mg capsule (DP Gen3.1), or the 1-mg capsule (DP Gen3.1) is used to administer a 1 mg dose of talazoparib, these talazoparib capsules should result in comparable exposure.

- In the ABRAZO and EMBRACA studies in which the above talazoparib capsules were used, the geometric mean C_{trough} values (geometric coefficient of variation %, number of subjects) on Day 1 of Cycle 2 following administration of talazoparib 1 mg using (1) the 0.25-mg capsule (DP Gen2.0), (2) the 0.25-mg capsule (DP Gen3.1), and (3) the 1-mg capsule (DP Gen3.1) were (1) 2,760 (96.6, N = 43), (2) 4,900 (92.5, N = 5), and (3) 3,610 (65.0, N = 126) pg/mL, and the distributions of individual values overlapped (Figure 1).

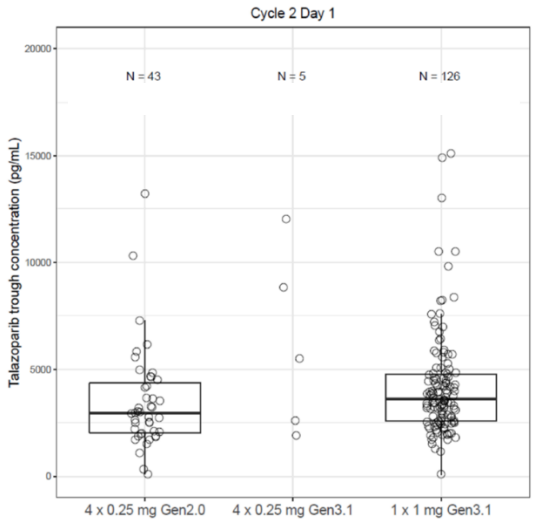

Figure 1. C_{trough} values by talazoparib capsule on Day 1 of Cycle 2 in the ABRAZO and EMBRACA studies

PMDA's discussion:

Given the absence of data demonstrating the bioequivalence among the talazoparib capsules used in the EMBRACA study and the following points, it is difficult to conclude that administration of talazoparib 1 mg using the 0.25-mg capsule (DP Gen2.0), the 0.25-mg capsule (DP Gen3.1), or the 1-mg capsule (DP Gen3.1) results in comparable exposure.

- In the above 2 studies, the limited number of patients received 4 × 0.25-mg capsules (DP Gen3.1), and assessment of talazoparib exposure following administration of 4 × 0.25-mg capsules (DP Gen3.1) has limitations.
- Given the distribution of exposure levels and the geometric mean values, it cannot be concluded from the above results that there are no differences in talazoparib exposure among the talazoparib capsules.

The capsules from different formulations were used in the EMBRACA study. Its impact on the assessment of the efficacy and safety of talazoparib in patients with breast cancer is described in Section "7.1.R.1 Review strategy."

6.R.2 Bioequivalence among different strengths of proposed commercial drug product

The present application was submitted for the 0.25- and 1-mg capsules for breast cancer and the 0.1- and 0.25-mg capsules for CRPC.

The applicant's explanation about the bioequivalence among the different strengths of the proposed commercial drug product:

On the basis of “Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms” (PMSB/ELD Notification No. 64 dated February 14, 2000), dissolution tests were performed, which failed to demonstrate the bioequivalence between the 0.25-mg capsule (DP Gen3.1) and the 1-mg capsule (DP Gen3.1) or between the 0.1-mg capsule (DP Gen3.1) and the 0.25-mg capsule (DP Gen3.1). For the reason presented in Section "6.R.1 Bioequivalence among talazoparib capsules used in the EMBRACA study," it is difficult to conduct a human bioequivalence study.

PMDA asked the applicant to explain the need for the 0.25-mg capsule in the clinical use of talazoparib for patients with breast cancer and the need for the 0.1-mg capsule in the clinical use of talazoparib for patients with CRPC.

The applicant's response:

In the expansion part of Study 030 and the EMBRACA study, the 0.25-mg capsule was to be used to administer talazoparib 0.25 to 0.75 mg QD for dose reductions due to adverse events, and 54.2% of patients had adverse events leading to dose reduction of talazoparib. In the TALAPRO-2 study, the 0.1-mg capsule was to be used to administer talazoparib 0.1 to 3.5 mg QD for dose reductions due to adverse events, and 57.8% of patients had adverse events leading to dose reduction of talazoparib.

Given the above situation, a reduced dose of talazoparib should be used to manage adverse events etc. also in the clinical use of talazoparib in patients with breast cancer or CRPC. Thus, the need for the 0.25-mg capsule for patients with breast cancer and the need for the 0.1-mg capsule for patients with CRPC are high.

The applicant's explanation about (1) the interchangeability between the 0.25-mg and 1-mg capsules in patients with breast cancer and (2) the interchangeability between the 0.1-mg and 0.25-mg capsules in patients with CRPC:

- The interchangeability between the 0.25-mg and 1-mg capsules in patients with breast cancer
  Though the bioequivalence between the 0.25-mg and 1-mg capsules has not been demonstrated, as the EMBRACA study showed no clear differences in the PK etc. of talazoparib between patients who used the 1-mg capsule (DP Gen3.1) and patients who used the 0.25-mg capsule (DP Gen3.1) [see Section 6.R.1], the 0.25-mg capsule is interchangeable with the 1-mg capsule.
- The interchangeability between the 0.1-mg and 0.25-mg capsules in patients with CRPC
  Since the bioequivalence between the 0.1-mg and 0.25-mg capsules has not been demonstrated, and the 0.1-mg capsule (DP Gen3.1) was to be used to support dose reductions only in the TALAPRO-2 study, the 0.1-mg capsule should be used for dose reductions only. Thus, "Do not use the 0.1-mg capsule to

administer a 0.5 mg dose of talazoparib in patients with CRPC" will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert [see Section 7.2.R.5].

PMDA's discussion:
Given the following points, the use of the 0.25-mg capsule interchangeably with the 1-mg capsule in patients with breast cancer is not recommended. Thus, "Do not use the 0.25-mg capsule to administer a 1 mg dose of talazoparib" should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert.

- The bioequivalence between the 1-mg and 0.25-mg capsules has not been demonstrated.
- The limited number of patients received talazoparib 1 mg using the 0.25-mg capsule (DP Gen3.1) in the EMBRACA study. It cannot be concluded that there are no clear differences in the PK of talazoparib between patients who used the 1-mg capsule (DP Gen3.1) and patients who used the 0.25-mg capsule (DP Gen3.1), and the efficacy and safety of 4 × 0.25-mg capsules (DP Gen3.1) are unclear.

PMDA accepted the applicant's explanation about the interchangeability between the 0.1-mg and 0.25-mg capsules in patients with CRPC.

6.R.3 Use of talazoparib in patients with renal impairment

The applicant's explanation about the use of talazoparib in patients with moderate or severe renal impairment:
Given the following points etc., the starting dose of talazoparib needs to be reduced in patients with moderate or severe renal impairment, and a linear regression model analysis showed the highest correlation between CLcr and the predicted talazoparib exposure by degree of renal function. Thus, the severity of renal impairment should be defined by CLcr, and then the recommended dosage for patients with renal impairment should be included in the package insert as shown in Table 27.

Table 27. Recommended dosage for patients with renal impairment

CLcr (mL/min)	Starting dose (CRPC)	Starting dose (Breast cancer)
≥60	0.5 mg	1 mg
≥30 and <60	0.35 mg	0.75 mg
≥15 and <30	0.25 mg	0.5 mg

[Breast cancer]

- In the EMBRACA study in which talazoparib 1 mg was administered regardless of renal function, the incidences of Grade ≥3 adverse events and serious adverse events tended to be higher in patients with moderate renal impairment (CLcr ≥30 mL/min and <60 mL/min) than in patients with normal renal function (CLcr ≥90 mL/min) or mild renal impairment (CLcr ≥60 mL/min and <90 mL/min) (Table 28).
- Given the extent of increase in talazoparib exposure in patients with moderate or severe renal impairment [see Section 6.2.6], talazoparib exposure at 0.75 mg in patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) and talazoparib exposure at 0.5 mg in patients with severe renal impairment (eGFR ≥15 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2) are expected to be similar to

talazoparib exposure at 1 mg in patients with normal renal function. Thus, there should be no efficacy or safety concerns.

Table 28. Summary of safety data by renal function (EMBRACA study)

	n (%)		
	Patients with normal renal function[*1] N = 194	Patients with mild renal impairment[*2] N = 79	Patients with moderate renal impairment[*3] N = 12
All adverse events	190 (97.9)	79 (100)	12 (100)
Grade ≥3 adverse events	134 (69.1)	55 (69.6)	11 (91.7)
Adverse events leading to death	5 (2.6)	1 (1.3)	0
Serious adverse events	63 (32.5)	31 (39.2)	9 (75.0)

*1 CLcr ≥90 mL/min; *2 CLcr ≥60 mL/min and <90 mL/min; *3 CLcr ≥30 mL/min and <60 mL/min

[CRPC]

- In the TALAPRO-2 study, patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) were to receive a talazoparib starting dose of 0.35 mg QD orally, and the steady-state C_{trough} at 0.35 mg in patients with moderate renal impairment was similar to that at 0.5 mg in patients with normal renal function or mild renal impairment (Table 29).

Table 29. C_{trough} of talazoparib

Severity of renal impairment	Dose	N	C_{trough} (ng/mL)
Normal	0.5 mg	66	3.10 (45)
Mild	0.5 mg	52	3.61 (52)
Moderate	0.35 mg	9	4.06 (37)

Geometric mean (Geometric coefficient of variation %)

- In the TALAPRO-2 study, the hazard ratios of rPFS and overall survival (OS) [95% CI] for the talazoparib group vs. the placebo group in patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) were 0.86 [0.45, 1.66] and 0.96 [0.54, 1.71], respectively. However, the following analyses etc. suggested the effect of imbalances in patient characteristics between the treatment groups. On the basis of the results of analyses adjusted for the imbalances, the efficacy of talazoparib is expected.
  - There were ≥10% differences in the following patient characteristics between the talazoparib and placebo groups: (1) circulating tumor cell (CTC) count (cells/7.5 mL blood) (<5, ≥5) and (2) type of progression (radiographic progression, prostate-specific antigen [PSA] progression)
  - The above (1)- and (2)-adjusted hazard ratios of rPFS for the talazoparib group vs. the placebo group [95% CI] were (1) 0.76 [0.38, 1.54] and (2) 0.88 [0.45, 1.73], and the OS hazard ratios [95% CI] were (1) 0.78 [0.41, 1.77] and (2) 0.91 [0.50, 1.67].
- In the TALAPRO-2 study, there were no clear differences in the safety of talazoparib between patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) who received talazoparib 0.35 mg and patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2) or mild renal impairment (eGFR ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2) who received talazoparib 0.5 mg (Table 30).

Table 30. Summary of safety data by renal function (Part 2 [Cohort 1] of TALAPRO-2 study)

	n (%)		
	Patients with normal renal function[*1] N = 163	Patients with mild renal impairment[*2] N = 177	Patients with moderate renal impairment[*3] N = 42
All adverse events	158 (96.9)	177 (100)	41 (97.6)
Grade ≥3 adverse events	113 (69.3)	140 (79.1)	33 (78.6)
Adverse events leading to death	5 (3.1)	5 (2.8)	3 (7.1)
Serious adverse events	51 (31.3)	77 (43.5)	20 (47.6)

*1 eGFR ≥90 mL/min/1.73 m^2 (talazoparib 0.5 mg dose)
*2 eGFR ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2 (talazoparib 0.5 mg dose)
*3 eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2 (talazoparib 0.35 mg dose)

- Given the extent of increase in talazoparib exposure in patients with severe renal impairment [see Section 6.2.6], talazoparib exposure at 0.25 mg in patients with severe renal impairment (eGFR ≥15 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2) is expected to be similar to talazoparib exposure at 0.5 mg in patients with normal renal function. Thus, there should be no efficacy or safety concerns.

PMDA's discussion:
Starting dose of talazoparib in patients with breast cancer and moderate renal impairment
Given the results of Study 001, the applicant's explanation (Talazoparib exposure at 0.75 mg in patients with moderate renal impairment is similar to that at 1 mg in patients with normal renal function, and there should be no efficacy or safety concerns) is understandable. In addition, taking also account of the safety risk associated with an increase in talazoparib exposure in patients with breast cancer and moderate renal impairment without dose reduction of talazoparib, it is understandable to a certain extent to recommend a reduced starting dose of 0.75 mg in these patients in the package insert.

PMDA accepted the applicant's explanation about the recommended starting dose of talazoparib for patients with CRPC and moderate renal impairment.

However, given the following points etc., the appropriateness of dose adjustment of talazoparib according to the severity of renal impairment based on CLcr is unknown. Thus, the severity of renal impairment should be defined by eGFR to select a starting dose of talazoparib for patients with moderate renal impairment in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section [see Sections 7.1.R.5 and 7.2.R.5].

- In the TALAPRO-2 study, the starting dose of talazoparib was adjusted based on eGFR.
- In Study 001, the severity of renal impairment was defined by eGFR to assess the effect of renal impairment on talazoparib exposure.

With respect to the use of talazoparib in patients with breast cancer or CRPC and severe renal impairment, given a 2.87-fold increase in unbound talazoparib exposure (AUC_{24}) in patients with severe renal impairment compared with patients with normal renal function [see Section 6.2.6], the appropriateness of halving the starting dose of talazoparib is unknown. Thus, administration of talazoparib in patients with severe renal impairment should be avoided wherever possible, and if administration of talazoparib in patients with

severe renal impairment cannot be avoided, the patient's condition should be closely monitored, and adequate attention should be paid to the possible occurrence of adverse events. The PK results obtained from Study 001 should be appropriately provided to healthcare professionals in clinical practice using the package insert etc., and then the following statement for patients with severe renal impairment should be included in the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section of the package insert.

- Avoid administration of talazoparib wherever possible. If administration of talazoparib cannot be avoided, the patient's condition should be closely monitored, and adequate attention should be paid to the possible occurrence of adverse events. Adverse reactions may be enhanced due to increased blood concentrations of talazoparib.

6.R.4 P-gp-mediated pharmacokinetic interactions

The applicant's explanation about coadministration of talazoparib with P-gp inhibitors:

Since the geometric mean ratios of the C_{max} and AUC_{inf} of talazoparib for talazoparib + itraconazole vs. talazoparib alone were 1.40 and 1.56, respectively, in a foreign phase I study (Study 004) [see Section 6.2.4.1], coadministration with P-gp inhibitors may increase talazoparib exposure. Thus, concomitant use of P-gp inhibitors during talazoparib monotherapy should be avoided. Given the following point, the package insert should advise that if coadministration of talazoparib with P-gp inhibitors cannot be avoided, the dose of talazoparib should be reduced to the next lower dose (0.75 mg).

- Given the extent of increase in talazoparib exposure following coadministration with itraconazole, talazoparib exposure at the next lower dose of talazoparib (0.75 mg) when coadministered with a P-gp inhibitor is expected to be similar to talazoparib exposure at the recommended dose of 1.0 mg of talazoparib as monotherapy in patients with breast cancer. Thus, there should be no efficacy or safety concerns.

The effect of coadministration of P-gp inhibitors on the PK of talazoparib when talazoparib was taken in combination with enzalutamide has not been studied in any clinical study, etc. Thus, the package insert should advise that concomitant use of P-gp inhibitors during treatment with talazoparib/enzalutamide should be avoided, and that if coadministration with P-gp inhibitors cannot be avoided, the patient's condition should be closely monitored, and adequate attention should be paid to the possible occurrence of adverse events.

PMDA's discussion:

Given that coadministration with a P-pg inhibitor increased talazoparib exposure in Study 004, the applicant's explanation that the package insert will advise that concomitant use of P-gp inhibitors during talazoparib monotherapy should be avoided wherever possible is understandable to a certain extent. However, as the efficacy and safety of talazoparib at the next lower dose when coadministered with a P-gp inhibitor have not been studied in any clinical study, the appropriateness of recommending dose reduction to the next lower dose is unknown at present. Thus, the PK results from Study 004 should be provided appropriately to healthcare professionals in clinical practice, using the package insert etc., and then the

following precautionary statement regarding coadministration with P-gp inhibitors should be included in the package insert.

- Avoid coadministration of talazoparib with P-gp inhibitors wherever possible. If coadministration of talazoparib with P-gp inhibitors cannot be avoided, the patient's condition should be closely monitored, and adequate attention should be paid to the possible occurrence of adverse events.

PMDA accepted the applicant's explanation about concomitant use of P-gp inhibitors during treatment with talazoparib/enzalutamide.

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

7.1 Data for breast cancer and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from 1 Japanese phase I study, 1 foreign phase I study, 1 foreign phase II study, and 1 foreign phase III study presented in Table 31. The applicant also submitted the results from a total of 9 studies (7 foreign phase I studies, 1 foreign phase II study, 1 foreign extension study) as reference data.

Table 31. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Japan	030	I	[Dose-escalation part] Patients with advanced solid tumors [Expansion part] Patients with g*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy	[Dose-escalation part] 9 [Expansion part] 19	[Dose-escalation part] Talazoparib 0.75 or 1 mg QD orally [Expansion part] Talazoparib 1 mg QD orally	Efficacy Tolerability Safety PK
	Foreign	007	I	Patients with advanced solid tumors	[Dose-escalation part] 39 [Expansion part] 74	[Dose-escalation part] Talazoparib 0.025, 0.05, 0.1, 0.2, 0.4, 0.6, 0.9, 1, or 1.1 mg QD orally [Expansion part] Talazoparib 1 mg QD orally	Tolerability Safety PK
		ABRAZO	II	Patients with g*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy	84	Talazoparib 1 mg QD orally	Efficacy Safety PK
		EMBRACA	III	Patients with g*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy	431 (1) 287 (2) 144	(1) Talazoparib 1 mg QD orally (2) Chemotherapy group: one of the following single-agent chemotherapies ● Capecitabine[*1] ● Eribulin[*2] ● Gemcitabine[*3] ● Vinorelbine[*4]	Efficacy Safety
Reference	Foreign	001	I	Patients with advanced solid tumors	34	Talazoparib 0.5 mg QD orally	Tolerability Safety PK
		002	I	Patients with advanced solid tumors	38	Talazoparib 0.5 mg QD orally	Tolerability Safety PK
		003	I	Patients with advanced solid tumors	6	A single oral dose of ^{14}C-talazoparib 1 mg	PK
		004	I	Patients with advanced solid tumors	[Group A] 19 [Group B] 17	[Group A] A single oral dose of talazoparib 0.5 mg under fasted conditions with or without itraconazole [Group B] A single oral dose of talazoparib 1 mg under fasted conditions with or without rifampicin	Tolerability Safety PK
		005	I	Patients with advanced solid tumors	38	Talazoparib 1 mg QD orally	Tolerability Safety
		022	I	Patients with relapsed or refractory AML, MDS, CLL, or MCL	[Arm 1] 25 [Arm 2] 8	[Arm 1] Talazoparib 0.1, 0.2, 0.3, 0.45, 0.9, 1.35, or 2 mg QD orally [Arm 2] Talazoparib 0.1 or 0.9 mg QD orally	Tolerability Safety PK
		023	I	Healthy volunteers	18	A single oral dose of talazoparib 0.5 mg under fasted or fed conditions	Tolerability Safety PK
		020	II	Patients with g*BRCA* mutated HER2-negative breast cancer who were suitable for neoadjuvant therapy	61	Talazoparib 1 mg QD orally	Efficacy Safety PK
		010	Extension	Patients with advanced solid tumors	120[*5]	Talazoparib 0.25, 0.5, 0.75, or 1 mg QD orally	Safety

*1 1,250 mg/m^2 BID orally from Day 1 through 14 of 3-week cycles; *2 1.4 mg/m^2 infusion on Days 1 and 8 of 3-week cycles; *3 1,250 mg/m^2 infusion on Days 1 and 8 of 3-week cycles; *4 30 mg/m^2 infusion on Days 1, 8, and 15 of 3-week cycles; *5 Includes patients who completed Studies 001, 002, 004, or 005.

The clinical studies are summarized below. The main adverse events other than deaths observed in the clinical studies are described in Section "7.3 Adverse events etc. observed in clinical studies."

7.1.1 Evaluation data

7.1.1.1 Japanese study

7.1.1.1.1 Japanese phase I study (CTD 5.3.5.2.4.BC: Study 030 [November 2017 to January 2021])

An open-label, uncontrolled study was conducted at 7 sites in Japan to evaluate the efficacy, tolerability, safety, etc. of talazoparib in patients with g*BRCA*-mutated[36] HER2-negative inoperable or recurrent breast cancer, etc.[37] after prior chemotherapy[38] (target sample size, up to 18 subjects in the dose-escalation part, 17 subjects in the expansion part[39]).

The dosing regimens are shown below. Treatment was to continue until disease progression or any withdrawal criterion was met.

[Dose-escalation part]

(1) Talazoparib 0.75 mg QD orally

(2) Talazoparib 1 mg QD orally

[Expansion part]

(3) Talazoparib 1 mg QD orally[40]

All of 28 subjects enrolled in the study [(1) 3, (2) 6, (3) 19] received study drug and were included in the safety population. The 19 subjects enrolled in the expansion part were included in the efficacy population.

In the dose-escalation part, DLT was assessed during Cycle 1 (until Day 28). No DLTs were reported. Thus, talazoparib 1 mg QD orally was selected as the recommended phase 2 dose (RP2D).

The primary endpoint of the expansion part of the study was the objective response rate (ORR) as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1.

The results of the final analysis of the primary efficacy endpoint of the objective response rate (data cutoff date on January 11, 2021) are shown in Table 32, and the lower limit of the 90% confidence interval exceeded the pre-defined null proportion of 18.4%.

[36] Patients with deleterious or suspected deleterious g*BRCA* mutations confirmed by BRACAnalysis CDx (Myriad Genetics, Inc.) were eligible for the study.

[37] Patients with advanced solid tumors were enrolled in the dose-escalation part.

[38] Patients who had received prior treatment with an anthracycline and/or a taxane in the neo-adjuvant, adjuvant, locally advanced, or metastatic setting, unless medically contraindicated, and ≤3 prior chemotherapy-inclusive regimens were eligible for the study.

[39] Assuming a talazoparib objective response rate of 50% based on clinical meaningfulness etc. and a null proportion of 18.4% based on the observed objective response rate in the chemotherapy group of the EMBRACA study, 17 patients are needed to preserve an 80% probability of the lower limit of the 90% confidence interval of the objective response rate exceeding the null proportion of 18.4%.

[40] The starting dose was reduced to 0.75 mg QD in patients with moderate renal impairment (CLcr = 30-59 mL/min).

Table 32. Best overall response and objective response rate
(RECIST ver.1.1, Investigator assessment, Efficacy population, Data cutoff date on January 11, 2021)

Best overall response	n (%)
	Total N = 19
CR	0
PR	11 (57.9)
SD	7 (36.8)
PD	1 (5.3)
NE	0
OR (CR + PR) (ORR [90% CI*] (%))	11 (57.9 [36.8, 77.0])

* Clopper-Pearson method

Regarding safety, there were no deaths during the study treatment period or within 30 days after the last dose of study drug.

7.1.1.2 Foreign studies

7.1.1.2.1 Foreign phase I study (CTD 5.3.5.2.1.BC: Study 007 [January 2011 to March 2015])

An open-label, uncontrolled study was conducted at 6 sites overseas to evaluate the tolerability, safety, etc. of talazoparib in patients with advanced solid tumors.

The dosing regimens are shown below. Treatment was to continue until disease progression or any withdrawal criterion was met.

[Dose-escalation part]

- Talazoparib 0.025, 0.05, 0.1, 0.2, 0.4, 0.6, 0.9, 1, or 1.1 mg QD orally

[Expansion part]

- Talazoparib 1 mg QD orally

Among 113 subjects enrolled in the study (39 in the dose-escalation part, 74 in the expansion part), 110 subjects (39 in the dose-escalation part, 71 in the expansion part) received talazoparib and were included in the safety population.

In the dose-escalation part, DLT was assessed during Cycle 1 (until Day 28). DLTs were observed in 1 of 6 subjects in the 0.9 mg group (Grade 3 thrombocytopenia) and 2 of 6 subjects in the 1.1 mg group (Grade 3 thrombocytopenia; and Grade 4 thrombocytopenia [1 subject each]). Thus, talazoparib 1 mg QD orally was selected as the RP2D.

Regarding safety, 1 of 6 subjects (16.7%) in the 1.1 mg group in the dose-escalation part and 5 of 71 subjects (7.0%) in the expansion part died during the talazoparib treatment period or within 30 days after the last dose of talazoparib. The causes of deaths other than disease progression (0 subjects in the dose-escalation part, 1 subject in the expansion part) were metastases to central nervous system (1 subject) in the dose-escalation part and dyspnoea; respiratory failure; hypoxia; and lung infection (1 subject each) in the expansion part, and a causal relationship to study drug was denied for all those cases.

7.1.1.2.2 Foreign phase II study (CTD 5.3.5.2.2.BC: ABRAZO study [May 2014 to September 2016])

An open-label, uncontrolled study was conducted at 34 sites overseas to evaluate the efficacy, safety, etc. of talazoparib in patients with g*BRCA*-mutated[36] HER2-negative inoperable or recurrent breast cancer after prior chemotherapy[41] (target sample size, 70 in Cohort 1, 70 in Cohort 2).

Talazoparib 1 mg QD was to be administered orally, and treatment was to continue until disease progression or any withdrawal criterion was met.

Among 84 subjects enrolled in the study (49 in Cohort 1, 35 in Cohort 2), 83 subjects (48 in Cohort 1, 35 in Cohort 2) received talazoparib and were included in the efficacy and safety populations.

The primary endpoint was the confirmed objective response rate as assessed by the independent radiology facility (IRF) per RECIST ver.1.1, and the study was planned following a Simon's 2-stage design.[42]

Regarding efficacy, among 35 subjects enrolled in Stage I into each of 2 cohorts, ≥5 subjects each had objective responses. However, enrollment was terminated prior to completion due to overlapping enrollment criteria with the EMBRACA study, etc.

Regarding safety, 4 of 48 subjects (8.3%) in Cohort 1 and 1 of 35 subjects (2.9%) in Cohort 2 died during the talazoparib treatment period or within 30 days after the last dose of talazoparib, and the causes of deaths were all disease progression.

7.1.1.2.3 Foreign phase III study (CTD 5.3.5.1.1.BC: EMBRACA study [October 2013 to September 2017])

A randomized, open-label study was conducted at 145 sites in 16 countries or regions to compare the efficacy and safety of talazoparib with physician's choice of chemotherapy in patients with g*BRCA*-mutated[36] HER2-negative inoperable or recurrent breast cancer after prior chemotherapy[38] (target sample size, up to 429 subjects[43]).

In the talazoparib group, talazoparib 1 mg QD was to be administered orally. Subjects in the chemotherapy group were to receive (1) capecitabine 1,250 mg/m^2 BID orally from Day 1 through 14 of 3-week cycles, (2) eribulin 1.4 mg/m^2 infusion on Days 1 and 8 of 3-week cycles, (3) gemcitabine 1,250 mg/m^2

[41] The following patients were eligible for the study.
Cohort 1: Patients with a CR or PR to a previous platinum-containing regimen, with no disease progression within 8 weeks of the last dose of platinum therapy
Cohort 2: Patients who had received ≥3 previous cytotoxic chemotherapy regimens and no previous platinum therapy

[42] If five or more responses were observed for 35 patients in the first stage of each cohort, enrollment of an additional 35 patients into each cohort was to occur in the second stage, for a total of 70 treated patients per cohort. Talazoparib would be considered effective as a single agent if at least 16 patients in a cohort had an objective response.

[43] For the primary endpoint of PFS as assessed by IRF per RECIST ver.1.1, based on 2:1 randomization allocation ratio between the talazoparib and chemotherapy groups, a total of 288 PFS events were considered necessary to provide 90% power at a 2-sided significance level of 0.05 to detect a hazard ratio of 0.67. Considering the duration of follow-up etc., a target sample size of 429 subjects was chosen.

infusion on Days 1 and 8 of 3-week cycles, or (4) vinorelbine 30 mg/m^2 infusion on Days 1, 8, and 15 of 3-week cycles. Treatment was to continue until disease progression or any withdrawal criterion was met.

All of 431 subjects who were enrolled in the study and randomized (287 in the talazoparib group, 144 in the chemotherapy group) were included in the intention-to-treat (ITT) population, which was used for efficacy analyses. Among the ITT population, 412 subjects (286 in the talazoparib group, 126 in the chemotherapy group) after excluding 19 subjects who did not receive study drug (1 in the talazoparib group, 18 in the chemotherapy group) were included in the safety population.

The primary endpoint was PFS as assessed by the IRF per RECIST ver.1.1. In order to demonstrate the superiority of talazoparib to chemotherapy in improving PFS, the analysis was to be conducted when 288 PFS events had been observed.

The results of the primary analysis of the primary efficacy endpoint of PFS as assessed by the IRF per RECIST ver.1.1 (data cutoff date on September 15, 2017[44)]) and the Kaplan-Meier curves are shown in Table 33 and Figure 2, respectively. The superiority of talazoparib to chemotherapy was demonstrated.

Table 33. Results of primary analysis of PFS (IRF assessment, ITT, Data cutoff date on September 15, 2017)

	Talazoparib	Chemotherapy
N	287	144
No. of events (%)	186 (64.8)	83 (57.6)
Median [95% CI] (months)	8.6 [7.2, 9.3]	5.6 [4.2, 6.7]
Hazard ratio [95% CI][*1]	0.54 [0.41, 0.71]	
P-value (two-sided)[*2]	<0.0001	

*1 A Cox proportional-hazards model stratified by the number of previous cytotoxic chemotherapy regimens for inoperable or recurrent breast cancer (0, 1/2/3), HR status (positive, negative), and history of CNS metastasis (yes, no); *2 A stratified log-rank test (the same stratification factors as were used for the stratified Cox proportional-hazards model), a significance level (two-sided) of 0.05

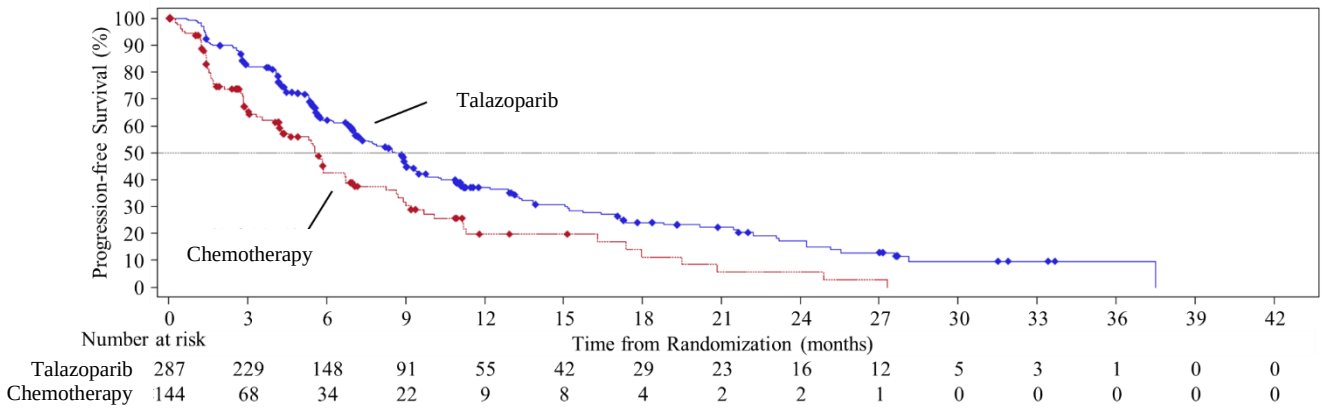

Figure 2. Kaplan-Meier curves of PFS at primary analysis (IRF assessment, ITT, data cutoff date on September 15, 2017)

[44)] In a phase III study of olaparib (NCT02000622) with similar enrollment criteria as the EMBRACA study, PFS was statistically significantly longer in the olaparib group based on 234 events, and the median PFS in the control group was 4.2 months, which was shorter than the expected PFS in the EMBRACA study. On the basis of this result, September 15, 2017 was selected as the data cutoff date because it was estimated that 95% of the total anticipated PFS events (288 events) would have occurred, and this would be sufficient to inform the primary analysis.

Regarding safety, 10 of 286 subjects (3.5%) in the talazoparib group and 5 of 126 subjects (4.0%) in the chemotherapy group died during the study treatment period or within 30 days after the last dose of study drug. The causes of deaths other than disease progression (7 in the talazoparib group, 4 in the chemotherapy group) were neurological symptom; venoocclusive liver disease; and cerebral haemorrhage (1 subject each) in the talazoparib group and sepsis (1 subject) in the chemotherapy group. A causal relationship to study drug could not be ruled out for venoocclusive liver disease (1 subject) in the talazoparib group and sepsis (1 subject) in the chemotherapy group.

7.1.2 Reference data

7.1.2.1 Clinical pharmacology studies

The applicant submitted the results from the following 6 clinical pharmacology studies in healthy volunteers or patients with advanced solid tumors [see Sections 6.1 and 6.2], and 1 of 34 subjects in Study 001, 5 of 38 subjects in Study 002, and 1 of 36 subjects in Study 004 died during the study treatment period or follow-up period.[45)] The causes of deaths other than disease progression (3 subjects in Study 002) were condition aggravated (1 subject) in Study 001, neoplasm progression; and cardio-respiratory arrest (1 subject each) in Study 002, and neoplasm progression (1 subject) in Study 004, and a causal relationship to study drug was denied for all those cases. No deaths occurred during the study treatment period or follow-up period [45)] in Studies 003, 005, and 023.

7.1.2.1.1 Foreign phase I study (CTD 5.3.3.3.1, Study 001 [February 2017 to January 2019])

7.1.2.1.2 Foreign phase I study (CTD 5.3.3.3.2, Study 002 [September 2016 to February 2020])

7.1.2.1.3 Foreign phase I study (CTD 5.3.3.2.1, Study 003 [September 2016 to June 2017])

7.1.2.1.4 Foreign phase I study (CTD 5.3.3.4.1, Study 004 [November 2016 to January 2018])

7.1.2.1.5 Foreign phase I study (CTD 5.3.4.2.1, Study 005 [October 2016 to May 2017])

7.1.2.1.6 Foreign phase I study (CTD 5.3.1.1.1, Study 023 [February to [redacted] 2013])

7.1.2.2 Foreign studies

7.1.2.2.1 Foreign phase I study (CTD 5.3.5.4.2.BC: Study 022 [[redacted] 2011 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 7 sites overseas to evaluate the tolerability, safety, etc. of talazoparib in patients with relapsed or refractory hematologic malignancies.[46)]

The dosing regimens are shown below. Treatment was to continue until disease progression or any withdrawal criterion was met.

[Arm 1]

- Talazoparib 0.1, 0.2, 0.3, 0.45, 0.9, 1.35, or 2.0 mg QD orally

[45)] The follow-up period was 30 days after the last dose of study drug in Studies 001, 002, 003, 004, and 005 and 28 days after the last dose of study drug in Study 023.

[46)] The following patients were eligible for the study.
Arm 1: Patients with AML or MDS who had failed, were ineligible for, or declined standard-of-care therapy
Arm 2: Patients with CLL or MCL who had failed, were ineligible for, or declined standard-of-care therapy

[Arm 2]

- Talazoparib 0.1 or 0.9 mg QD orally

All of 33 subjects who were enrolled in the study and received study drug (25 in Arm 1, 8 in Arm 2) were included in the safety population.

Regarding safety, 12 of 33 subjects (36.4%) died during the study treatment period or within 30 days after the last dose of study drug (11 of 25 subjects [44.0%] in Arm 1, 1 of 8 subjects [12.5%] in Arm 2). The causes of deaths other than disease progression (2 subjects in Arm 1) were AML; and pneumonia (2 subjects each); and malignant neoplasm progression; neutropenic sepsis; cardio-respiratory arrest; lung infection; and leukaemic infiltration (1 subject each) in Arm 1 and renal dysfunction (1 subject) in Arm 2, and a causal relationship to study drug could not be ruled out for neutropenic sepsis (1 subject) in Arm 1.

7.1.2.2.2 Foreign phase IIb study (CTD 5.3.5.2.3.BC: Study 020 [August 2018 to September 2020])

An open-label, uncontrolled study was conducted at 18 sites overseas to evaluate the efficacy, safety, etc. of talazoparib in patients with g*BRCA*-mutated HER2-negative operable breast cancer (target sample size, 60 subjects).

Talazoparib 1 mg QD was to be administered orally for 24 weeks.

All of 61 subjects who were enrolled in the study and received study drug were included in the safety population.

Regarding safety, there were no deaths during the study treatment period or within 28 days after the last dose of study drug.

7.1.2.2.3 Foreign extension study (CTD 5.3.5.4.1.BC: Study 010 [November 2016 to July 2021])

An open-label, uncontrolled study was conducted at 23 sites overseas to evaluate the safety etc. of talazoparib in patients who had completed the planned treatment period in Studies 001, 002, 004, or 005.

Talazoparib (1) 0.25, (2) 0.5, (3) 0.75, or (4) 1 mg QD was to be administered orally. Treatment was to continue until disease progression or any withdrawal criterion was met.

Among 120 subjects enrolled in the study, 118 subjects who received study drug [(1) 2, (2) 61, (3) 3, (4) 52] were included in the safety population.

Regarding safety, 14 of 118 subjects (11.9%) [(2) 6 of 61 subjects (9.8%), (4) 8 of 52 subjects (15.4%)] died during the talazoparib treatment period or within 30 days after the last dose of talazoparib. The causes of deaths other than disease progression [(2) 3 subjects] were (2) respiratory failure; death; and sepsis (1 subject each) and (4) ovarian cancer (3 subjects); breast cancer (2 subjects); and bacterial endocarditis; cerebrovascular

accident; and failure to thrive (1 subject each), and a causal relationship to study drug was denied for all those cases.

7.1.R Outline of the review conducted by PMDA

7.1.R.1 Review strategy

PMDA review strategy:

Among the evaluation data submitted, the pivotal clinical study to evaluate the efficacy and safety of talazoparib is a foreign phase III study to evaluate the efficacy and safety of talazoparib in patients with g*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy (the EMBRACA study). PMDA decided to focus its review on this study.

The efficacy and safety of talazoparib in Japanese patients are evaluated, focusing on the expansion part of a Japanese phase I study (Study 030) with similar enrollment criteria with the EMBRACA study.

The bioequivalence among the 0.25-mg capsule (DP Gen2.0) and the 0.25- and 1-mg capsules (DP Gen3.1) used in the EMBRACA study was not demonstrated [see Section 6.R.1]. PMDA asked the applicant to explain the possible impact of the use of the talazoparib capsules that have not been demonstrated to be bioequivalent in the EMBRACA study on the assessment of the efficacy and safety of talazoparib.

The applicant's response:

In the EMBRACA study, PFS in (1) patients who started treatment with talazoparib using the 0.25-mg capsule (DP Gen2.0) in the talazoparib group (N = 69) and PFS in (2) patients who started treatment with talazoparib using the 1.0-mg capsule (DP Gen3.1) in the talazoparib group (N = 217) were compared with PFS in their respective groups of patients enrolled contemporaneously in the chemotherapy group. On the basis of a multivariate Cox proportional-hazards model with the prognostic factors for PFS[47] identified in the overall population of the EMBRACA study as covariates, the PFS hazard ratios in (1) and (2) [95% CI] were 0.54 [0.37, 0.80] and 0.53 [0.40, 0.72], respectively. The incidences of adverse events in (1) and (2) are shown in Table 34.

Table 34. Summary of safety data by talazoparib capsule used at the start of treatment (EMBRACA study, talazoparib group)

	n (%)	
	(1) N = 69	(2) N = 217
All adverse events	68 (98.6)	214 (98.6)
Grade ≥3 adverse events	47 (68.1)	154 (71.0)
Adverse events leading to death	3 (4.3)	3 (1.4)
Serious adverse events	23 (33.3)	80 (36.9)
Adverse events leading to treatment discontinuation	4 (5.8)	11 (5.1)
Adverse events leading to dose interruption	44 (63.8)	148 (68.2)
Adverse events leading to dose reduction	14 (20.3)	44 (20.3)

[47] As the prognostic factors for PFS, *BRCA1* mutation status (positive, negative), prior endocrine therapy (yes, no), visceral disease (yes, no), and disease-free interval (<12 months, ≥12 months) were identified.

On the basis of the above, although the number of patients by the talazoparib capsule used at the start of treatment was limited, and discussion has limitations, as there were no clear differences in the efficacy and safety of talazoparib between (1) and (2), the use of the talazoparib capsules that have not been demonstrated to be bioequivalent in the EMBRACA study was unlikely to impact the assessment of the efficacy and safety of talazoparib.

PMDA accepted the above explanation by the applicant.

7.1.R.2 Efficacy

On the basis of the following considerations, PMDA concluded that the efficacy of talazoparib in patients with g*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy was demonstrated.

7.1.R.2.1 Study population and control group

The applicant's explanation about the study population and control group for the EMBRACA study:

Given the following points, patients who had received prior treatment with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated were enrolled in the EMBRACA study, and a physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) was chosen as comparator.

- At the time when the EMBRACA study was designed, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN) guidelines (Breast cancer) (v.3.2013) recommended anthracyclines or taxanes as adjuvant or neoadjuvant treatment of HER2-negative breast cancer and listed capecitabine, eribulin, gemcitabine, or vinorelbine, in addition to anthracyclines and taxanes, as first-line treatment options for inoperable or recurrent breast cancer.
- At the time when the EMBRACA study was designed, the Japanese clinical practice guidelines (Breast cancer) (2011) recommended anthracyclines or taxanes as adjuvant or neoadjuvant treatment of HER2-negative breast cancer. Either an anthracycline or a taxane, whichever not used in the adjuvant or neoadjuvant setting, was recommended as first-line treatment for inoperable or recurrent breast cancer.
- In clinical practice, capecitabine, eribulin, gemcitabine, or vinorelbine were treatment options for patients with inoperable or recurrent breast cancer in whom anthracyclines or taxanes were contraindicated.

Patients in whom anthracyclines or taxanes were medically contraindicated as well as patients who had received prior treatment with an anthracycline and/or taxane were eligible for the EMBRACA study.

PMDA's discussion:

The applicant's explanation (capecitabine, eribulin, gemcitabine, and vinorelbine were treatment options for patients who had received prior treatment with an anthracycline and/or a taxane among the patient population of the EMBRACA study) is understandable. On the other hand, given the following points, it is difficult to

conclude that capecitabine, eribulin, gemcitabine, and vinorelbine were treatment options for patients in whom anthracyclines or taxanes were medically contraindicated.

- In the EMBRACA study, as patients in whom anthracyclines or taxanes were medically contraindicated, patients who had the option of either anthracyclines or taxanes were also eligible for enrollment.
- According to the Japanese clinical practice guidelines (Breast cancer) (2011), either an anthracycline or a taxane, whichever not used in the adjuvant or neoadjuvant setting, was recommended as first-line treatment for inoperable or recurrent breast cancer.

Thus, the appropriateness of grouping patients previously treated with an anthracycline and/or a taxane and patients in whom anthracyclines or taxanes were medically contraindicated together for efficacy evaluation of talazoparib is unknown.

On the basis of the above, the efficacy of talazoparib should be evaluated after reviewing the results of subgroup analysis by prior anthracycline or taxane treatment in addition to the results of analysis of the overall population. Taking account of these considerations, the clinical positioning of talazoparib and the target population should be determined [see Section 7.1.R.4.1].

7.1.R.2.2 Efficacy endpoint

The applicant's explanation about the appropriateness of selecting IRF-assessed PFS as the primary endpoint for the EMBRACA study:

In patients with inoperable or recurrent breast cancer, longer PFS is expected to delay worsening of clinical symptoms associated with disease progression by prolonging the time to tumor progression and is considered clinically meaningful. Thus, selecting PFS as the primary endpoint for the study was appropriate.

PMDA's discussion:

Since the patient population of the EMBRACA study is treated with an expectation of survival benefit, OS should have been selected as the primary endpoint for the EMBRACA study. However, as the above explanation by the applicant (longer PFS in these patients is clinically meaningful to a certain extent) is understandable, the efficacy of talazoparib can be evaluated based on the results of the primary endpoint of PFS after reviewing the results of OS in the EMBRACA study.

7.1.R.2.3 Results of efficacy assessment

The EMBRACA study demonstrated the superiority of talazoparib to chemotherapy in the primary endpoint of PFS as assessed by the IRF per RECIST ver.1.1 [see Section 7.1.1.2.3]. Table 35 shows the results of subgroup analysis of PFS according to chemotherapy choice determined prior to randomization (capecitabine, eribulin, gemcitabine, vinorelbine). Chemotherapy choices in the control group had no impact on the efficacy assessment of talazoparib.

Table 35. Results of subgroup analysis of PFS according to chemotherapy choice determined prior to randomization (IRF assessment, ITT, data cutoff date on September 15, 2017)

Chemotherapy agent	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio [95% CI]
Capecitabine	Talazoparib	127	79 (62.2)	9.0 [7.3, 10.3]	0.49 [0.32, 0.74]
	Chemotherapy	63	38 (60.3)	5.5 [2.7, 8.7]	
Eribulin	Talazoparib	115	81 (70.4)	7.2 [5.4, 8.9]	0.62 [0.39, 0.96]
	Chemotherapy	58	30 (51.7)	5.6 [2.9, 8.2]	
Gemcitabine	Talazoparib	21	13 (61.9)	9.4 [4.4, —]	0.56 [0.20, 1.55]
	Chemotherapy	14	9 (64.3)	5.8 [3.5, 6.7]	
Vinorelbine	Talazoparib	24	13 (54.2)	13.4 [6.8, 25.6]	0.51 [0.16, 1.60]
	Chemotherapy	9	6 (66.7)	8.6 [1.0, —]	

—, Not estimable

In the EMBRACA study, if the test for the primary endpoint of PFS as assessed by the IRF per RECIST ver.1.1 was statistically significant, an interim analysis of a secondary endpoint of OS was to be conducted at the time of PFS primary analysis. The final analysis of OS was to be conducted when approximately 321 deaths had been observed. In order to control the type I error rate from the interim analysis of OS, a two-sided alpha of 0.0001 and a two-sided alpha of 0.0499 were allocated to the interim and final analyses, respectively.

The results of the final analysis of a secondary endpoint of OS (data cutoff date on September 30, 2019) and the Kaplan-Meier curves are shown in Table 36 and Figure 3, respectively.

Table 36. Results of final analysis of OS (ITT, data cutoff date on September 30, 2019)

	Talazoparib	Chemotherapy
N	287	144
No. of events (%)	216 (75.3)	108 (75.0)
Median [95% CI] (months)	19.3 [16.6, 22.5]	19.5 [17.4, 22.4]
Hazard ratio [95% CI][*1]	0.85 [0.67, 1.07][*2]	
P-value (two-sided)[*3]	0.1693	

*1 A Cox proportional-hazards model stratified by the number of previous cytotoxic chemotherapy regimens for inoperable or recurrent breast cancer (0, 1/2/3), HR status (positive, negative), and history of CNS metastasis (yes, no); *2 The 95.01% CI corresponding to the significance level was [0.67, 1.07]; *3 A stratified log-rank test (the same stratification factors as were used for the stratified Cox proportional-hazards model), a significance level (two-sided) of 0.0499

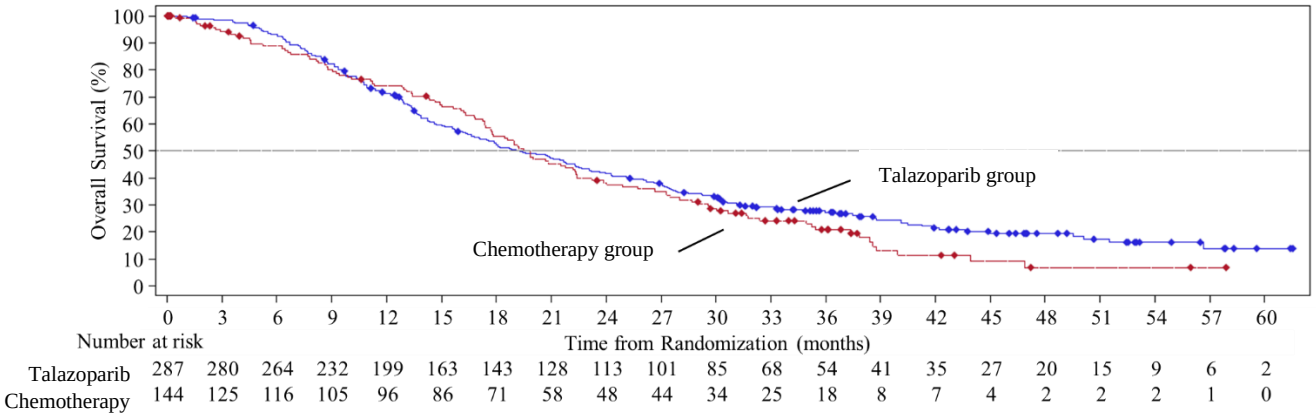

Figure 3. Kaplan-Meier curves of OS at final analysis (ITT, data cutoff date on September 30, 2019)

The applicant's explanation about the efficacy of talazoparib in Japanese patients:

In the expansion part of Study 030, the primary endpoint of the objective response rate as assessed by the investigator per RECIST ver.1.1 [90% CI] (%) was 57.9 [36.8, 77.0]. Since the lower limit of the 90% confidence interval exceeded the pre-defined null proportion of 18.4% [see Section 7.1.1.1.1], and there was no trend towards inferiority as compared with the objective response rate in the talazoparib group of the EMBRACA study[48)] etc., the efficacy of talazoparib is expected in Japanese patients with g*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy.

On the basis of the considerations in Section "7.1.R.2.1 Study population and control group," PMDA asked the applicant to explain the efficacy of talazoparib in the following subgroups of patients with inoperable or recurrent breast cancer after prior chemotherapy from the EMBRACA study: (1) a subgroup of patients previously treated with an anthracycline and a taxane, (2) a subgroup of patients previously treated with an anthracycline only, and (3) a subgroup of patients previously treated with a taxane only.

The applicant's response:

Table 37 shows the results of PFS in the above patient subgroups (1)(2)(3) in the EMBRACA study, and the efficacy of talazoparib was demonstrated in all patient subgroups.

Table 37. Results of PFS by prior anthracycline or taxane treatment (IRF assessment, ITT, data cutoff date on September 15, 2017)

Prior treatment*1	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio*2 [95% CI]
(1)	Talazoparib	225	147 (65.3)	8.6 [7.1, 9.8]	0.46 [0.33, 0.63]
	Chemotherapy	106	62 (58.5)	5.5 [3.1, 6.7]	
(2)	Talazoparib	18	13 (72.2)	6.9 [1.4, 9.2]	0.55 [0.11, 2.78]
	Chemotherapy	9	5 (55.6)	3.3 [1.6, —]	
(3)	Talazoparib	37	25 (67.6)	9.0 [5.8, 12.9]	0.91 [0.42, 1.99]
	Chemotherapy	24	13 (54.2)	9.0 [5.4, —]	

—, Not estimable; *1 (1) Subgroup of patients previously treated with an anthracycline and a taxane, (2) Subgroup of patients previously treated with an anthracycline only, and (3) Subgroup of patients previously treated with a taxane only; *2 A Cox proportional-hazards model stratified by the number of previous cytotoxic chemotherapy regimens for inoperable or recurrent breast cancer (0, 1/2/3), HR status (positive, negative), and history of CNS metastasis (yes, no)

PMDA's discussion:

For the following reasons etc., the efficacy of talazoparib was demonstrated in patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer previously treated with an anthracycline and a taxane.

- The EMBRACA study demonstrated the superiority of talazoparib to chemotherapy in the primary endpoint of IRF-assessed PFS, and the PFS benefit derived from talazoparib was clinically meaningful.
- The EMBRACA study showed no trend towards clear differences in PFS results between the subgroup of patients previously treated with an anthracycline and a taxane and the overall population.
- The EMBRACA study showed no trend towards shorter OS in the talazoparib group than in the chemotherapy group.

48) The objective response rate as assessed by the investigator per RECIST ver.1.1 [95% CI] (%) was 50.2 [43.4, 57.0].

- The limited number of Japanese patients were evaluated for the efficacy of talazoparib, and there are limitations to evaluating the efficacy of talazoparib in Japanese patients. Meanwhile, given the following points etc. in addition to the above explanation by the applicant, the applicant's explanation that the efficacy of talazoparib is expected also in Japanese patients is understandable.
  - In the expansion part of Study 030, a secondary endpoint of the objective response rate as assessed by blinded independent central review (BICR) per RECIST ver.1.1 [90% CI] (%) was 52.6 [32.0, 72.6], which did not tend to clearly differ from the result of the primary endpoint of the objective response rate as assessed by the investigator per RECIST ver.1.1.
  - There were no clear differences in the pharmacokinetics of talazoparib or the diagnosis of or treatment paradigms for inoperable or recurrent breast cancer between Japanese and non-Japanese populations.

There are limitations to evaluating the efficacy of talazoparib in a subgroup of patients previously untreated with an anthracycline or a taxane based on the exploratory results from the limited number of patients, and it is difficult to conclude that the EMBRACA study demonstrated the efficacy of talazoparib in this patient subgroup. The clinical positioning of talazoparib in patients previously untreated with an anthracycline or a taxane is described in Section "7.1.R.4.1 Clinical positioning of talazoparib and indication."

7.1.R.3 Safety [for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies"]

PMDA's conclusion:

On the basis of Section "7.R.1 Safety (Events that require attention following administration of talazoparib, etc.)" and the following considerations, adverse events that require particular attention following administration of talazoparib in patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy are myelosuppression, interstitial lung disease (ILD), thromboembolism, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and second primary malignancies (other than MDS/AML). Attention should be paid to the possible occurrence of these adverse events during treatment with talazoparib.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with talazoparib, talazoparib is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., monitoring for and management of adverse events and dose interruption/dose reduction/discontinuation of talazoparib.

7.1.R.3.1 Safety profile

The applicant's explanation about the safety profile of talazoparib based on the safety information from the EMBRACA study:

Safety data from the EMBRACA study are summarized in Table 38.

Table 38. Summary of safety data (EMBRACA study)

	n (%)	
	Talazoparib N = 286	Chemotherapy N = 126
All adverse events	282 (98.6)	123 (97.6)
Grade ≥3 adverse events	201 (70.3)	81 (64.3)
Adverse events leading to death	6 (2.1)	4 (3.2)
Serious adverse events	103 (36.0)	39 (31.0)
Adverse events leading to treatment discontinuation	15 (5.2)	7 (5.6)
Adverse events leading to dose interruption	192 (67.1)	65 (51.6)
Adverse events leading to dose reduction	58 (20.3)	30 (23.8)

In the EMBRACA study, adverse events of any grade reported at a ≥5% higher incidence in the talazoparib group than in the chemotherapy group were anaemia (155 subjects [54.2%] in the talazoparib group, 24 subjects [19.0%] in the chemotherapy group), fatigue (147 subjects [51.4%], 54 subjects [42.9%]), headache (97 subjects [33.9%], 29 subjects [23.0%]), back pain (69 subjects [24.1%], 20 subjects [15.9%]), cough (65 subjects [22.7%], 20 subjects [15.9%]), arthralgia (55 subjects [19.2%], 15 subjects [11.9%]), dizziness (53 subjects [18.5%], 13 subjects [10.3%]), thrombocytopenia (50 subjects [17.5%], 7 subjects [5.6%]), asthenia (45 subjects [15.7%], 12 subjects [9.5%]), insomnia (38 subjects [13.3%], 10 subjects [7.9%]), viral upper respiratory tract infection (36 subjects [12.6%], 8 subjects [6.3%]), platelet count decreased (36 subjects [12.6%], 4 subjects [3.2%]), white blood cell count decreased (32 subjects [11.2%], 5 subjects [4.0%]), urinary tract infection (31 subjects [10.8%], 3 subjects [2.4%]), depression (24 subjects [8.4%], 4 subjects [3.2%]), and influenza like illness (20 subjects [7.0%], 2 subjects [1.6%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in the talazoparib group than in the chemotherapy group were anaemia (115 subjects [40.2%], 6 subjects [4.8%]), thrombocytopenia (23 subjects [8.0%], 2 subjects [1.6%]), platelet count decreased (19 subjects [6.6%], 0 subjects), pulmonary embolism (9 subjects [3.1%], 1 subject [0.8%]), and lymphocyte count decreased (6 subjects [2.1%], 0 subjects). Serious adverse events reported at a ≥2% higher incidence in the talazoparib group than in the chemotherapy group were anaemia (18 subjects [6.3%], 0 subjects) and pulmonary embolism (6 subjects [2.1%], 0 subjects). Adverse events leading to dose interruption of study drug reported at a ≥2% higher incidence in the talazoparib group than in the chemotherapy group were anaemia (105 subjects [36.7%], 2 subjects [1.6%]), neutropenia (53 subjects [18.5%], 16 subjects [12.7%]), thrombocytopenia (29 subjects [10.1%], 1 subject [0.8%]), platelet count decreased (19 subjects [6.6%], 1 subject [0.8%]), white blood cell count decreased (15 subjects [5.2%], 3 subjects [2.4%]), and lymphocyte count decreased (7 subjects [2.4%], 0 subjects). Adverse events leading to dose reduction of study drug reported at a ≥2% higher incidence in the talazoparib group than in the chemotherapy group were anaemia (33 subjects [11.5%], 1 subject [0.8%]) and thrombocytopenia (8 subjects [2.8%], 0 subjects). There were no adverse events leading to death or study drug discontinuation that were reported at a ≥2% higher incidence in the talazoparib group than in the chemotherapy group.

PMDA's discussion:

Although there were adverse events, Grade ≥3 adverse events, and serious adverse events that were reported at a higher incidence in the talazoparib group in the EMBRACA study, those events were manageable with dose interruption/dose reduction/discontinuation etc. of talazoparib. Given the above point, talazoparib is

tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., management of and monitoring for adverse events and dose interruption/dose reduction/discontinuation of talazoparib.

7.1.R.3.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in the safety of talazoparib between Japanese and non-Japanese populations based on the safety information from the talazoparib group of the EMBRACA study and the expansion part of Study 030:

Safety data from the talazoparib group of the EMBRACA study and Study 030 are summarized in Table 39.

Table 39. Summary of safety data (Talazoparib group of EMBRACA study and Study 030)

	n (%)	
	EMBRACA study Talazoparib group	Study 030 Expansion part
	N = 286	N = 19
All adverse events	282 (98.6)	19 (100)
Grade ≥3 adverse events	201 (70.3)	11 (57.9)
Adverse events leading to death	6 (2.1)	0
Serious adverse events	103 (36.0)	1 (5.3)
Adverse events leading to treatment discontinuation	15 (5.2)	0
Adverse events leading to dose interruption	192 (67.1)	8 (42.1)
Adverse events leading to dose reduction	58 (20.3)	9 (47.4)

Adverse events of any grade reported at a ≥10% higher incidence in Japanese patients than in non-Japanese patients were anaemia (13 Japanese patients [68.4%], 155 non-Japanese patients [54.2%]), neutrophil count decreased (12 Japanese patients [63.2%], 30 non-Japanese patients [10.5%]), white blood cell count decreased (8 Japanese patients [42.1%], 32 non-Japanese patients [11.2%]), stomatitis (7 Japanese patients [36.8%], 24 non-Japanese patients [8.4%]), platelet count decreased (6 Japanese patients [31.6%], 36 non-Japanese patients [12.6%]), malaise (5 Japanese patients [26.3%], 6 non-Japanese patients [2.1%]), and cheilitis (2 Japanese patients [10.5%], 0 non-Japanese patients). Grade ≥3 adverse events reported at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were anaemia (9 Japanese patients [47.4%], 115 non-Japanese patients [40.2%]), neutrophil count decreased (4 Japanese patients [21.1%], 13 non-Japanese patients [4.5%]), white blood cell count decreased (2 Japanese patients [10.5%], 11 non-Japanese patients [3.8%]), and cholelithiasis (1 Japanese patient [5.3%], 0 non-Japanese patients). Serious adverse events reported at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were cholelithiasis (1 Japanese patient [5.3%], 0 non-Japanese patients). Adverse events leading to dose interruption of study drug reported at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were neutrophil count decreased (2 Japanese patients [10.5%], 15 non-Japanese patients [5.2%]). Adverse events leading to dose reduction of study drug reported at a ≥5% higher incidence in Japanese patients than in non-Japanese patients were anaemia (8 Japanese patients [42.1%], 33 non-Japanese patients [11.5%]) and neutrophil count decreased (4 Japanese patients [21.1%], 2 non-Japanese patients [0.7%]). There were no adverse events leading to death or study drug discontinuation that were reported at a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's discussion:

Although the number of Japanese patients treated with talazoparib was limited, and there are limitations to rigorous comparison of safety between Japanese and non-Japanese populations, the incidences of adverse events of anaemia etc. were higher in Japanese patients than in non-Japanese patients, and attention should be paid to the possible occurrence of these events during treatment with talazoparib. However, as to anaemia etc., there was no trend towards clearly higher incidences of adverse events leading to death or serious adverse events in Japanese patients than in non-Japanese patients, and talazoparib will be used by physicians with adequate knowledge of and experience in cancer chemotherapy. Given these points, talazoparib is tolerable also in Japanese patients.

7.1.R.4 Clinical positioning and indication

The proposed indication for talazoparib is "*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer." The following statements are included in the PRECAUTIONS CONCERNING INDICATIONS section of the proposed package insert.

- The efficacy and safety of talazoparib in the neoadjuvant or adjuvant setting have not been established.
- Talazoparib should be used in patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

PMDA's conclusion:

On the basis of Sections "7.1.R.2 Efficacy" and "7.1.R.3 Safety" and the considerations in the following section, the following statements should be included in the PRECAUTIONS CONCERNING INDICATIONS section, and then the appropriate indication for talazoparib should be "*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy."

- The efficacy and safety of talazoparib in the neoadjuvant or adjuvant setting have not been established.
- Talazoparib should be used in the following patients:
  - Patients previously treated with anthracycline- and taxane-containing chemotherapy
  - Patients previously treated with either anthracycline- or taxane-containing chemotherapy if the other agent is contraindicated.
- Talazoparib should be used in patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

7.1.R.4.1 Clinical positioning of talazoparib and indication

Talazoparib for patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer is described as follows in the Japanese and foreign clinical practice guidelines and the major textbook of clinical oncology.

- NCCN guidelines (Breast cancer) (v.4.2023)
  - Talazoparib is strongly recommended as first-line treatment for patients with *BRCA*-mutated HR-positive HER2-negative inoperable or recurrent breast cancer with endocrine-refractory disease or visceral crisis.

- Talazoparib is strongly recommended as first-line treatment for patients with *BRCA*-mutated triple-negative breast cancer[49)] with a combined positive score (CPS) <10 and as second-line treatment for patients with *BRCA*-mutated triple-negative breast cancer.

- Japanese clinical practice guidelines (Breast cancer) (2022)
  - A PARP inhibitor is a treatment option for patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer previously treated with anthracycline- and taxane-containing chemotherapy.

The applicant's explanation about the clinical positioning of talazoparib for patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy and the target population:
On the basis of the results from the EMBRACA study and the expansion part of Study 030, talazoparib is positioned as a treatment option for patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy. When to use talazoparib and when to use approved platinum-containing chemotherapy regimen, S-1, or olaparib in those patients, and when to use talazoparib and when to use the approved drug, trastuzumab deruxtecan (genetical recombination), in those patients with HER2-low disease, are unknown because there are no clinical study data comparing the efficacy and safety of talazoparib versus these agents at present. Treatment will be chosen with an understanding of the efficacy and safety of the individual agents, according to individual patients' conditions.

In the EMBRACA study, g*BRCA* mutations were detected by testing with "the BRACAnalysis diagnostic system." On the basis of a database of previously classified variants, g*BRCA* variants were classified into one of the following 5 categories [(1) deleterious, (2) suspected deleterious, (3) variant of uncertain significance (VUS), (4) favor polymorphism, (5) polymorphism]. Patients with a (1) deleterious or (2) suspected deleterious g*BRCA* mutation (a positive result) were eligible for enrollment. Thus, "the BRACAnalysis diagnostic system" should be used as a companion diagnostic etc. for the detection of deleterious or suspected deleterious g*BRCA* mutations.

On the basis of the above, the following statements were included in the PRECAUTIONS CONCERNING INDICATIONS section, and then the indication of "*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer" was proposed.

- The efficacy and safety of talazoparib in the neoadjuvant or adjuvant setting have not been established.
- Talazoparib should be used in patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

PMDA's discussion:
PMDA largely accepted the above explanation by the applicant. However, as the EMBRACA study population was patients previously treated with chemotherapy, the INDICATIONS section should clarify that talazoparib is indicated for patients previously treated with chemotherapy.

[49)] HR-negative, HER2-negative breast cancer

On the basis of the considerations in Section "7.1.R.2 Efficacy," it is difficult to conclude that the efficacy of talazoparib was demonstrated in a subgroup of patients previously untreated with an anthracycline or a taxane [see Section 7.1.R.2.3]. Thus, either an anthracycline or a taxane, whichever is not contraindicated, should be used before treatment with talazoparib. Meanwhile, there is no need to restrict the use of talazoparib in patients previously treated with either anthracycline- or taxane-containing chemotherapy if the other agent is contraindicated, taking account of the results in patients previously treated with anthracycline- and taxane-containing chemotherapy.

Thus, talazoparib should be indicated for patients previously treated with anthracycline- and taxane-containing chemotherapy and patients previously treated with either anthracycline- or taxane-containing chemotherapy if the other agent is contraindicated. The relevant precautionary statement should be included in the package insert.

On the basis of the above, the appropriate indication for talazoparib should be "*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy," and the following statements should be included in the PRECAUTIONS CONCERNING INDICATIONS section.

- The efficacy and safety of talazoparib in the neoadjuvant or adjuvant setting have not been established.
- Talazoparib should be used in the following patients:
  - Patients previously treated with anthracycline- and taxane-containing chemotherapy
  - Patients previously treated with either anthracycline- or taxane-containing chemotherapy if the other agent is contraindicated
- Talazoparib should be used in patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

7.1.R.5 Dosage and administration

The proposed dosage and administration statement is "The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition." After regulatory submission, the applicant explained that the proposed statements in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section would be amended as follows.

[All indications]

- If a patient vomits or misses a dose of talazoparib, the next prescribed dose should be taken at the usual time. Do not take a double dose per day.
- Recommended dosage modifications for adverse reactions
- The recommended starting dose of talazoparib in patients with renal impairment

[*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer]

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.

PMDA's conclusion:

On the basis of the results of a food effect study of talazoparib [see Section 6.1.1.1], Sections "6.R.3 Use of talazoparib in patients with renal impairment," "7.1.R.2 Efficacy," and "7.1.R.3 Safety," and the considerations in the following section, the statements in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section should be presented by indication, instead of presenting the statements for all indications, and the following statements for *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer should be included. Then, the proposed dosage and administration statement of "The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition." is appropriate.

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.
- For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the recommended starting dose of talazoparib is 0.75 mg once daily.
- Do not use the 0.25-mg capsule to administer a 1 mg dose of talazoparib because the bioequivalence between the 1-mg and 0.25-mg capsules has not been demonstrated.
- Recommended dosage modifications for adverse reactions

Recommended dosage modifications for adverse reactions are discussed in Section "7.R.2 Recommended dosage modifications for talazoparib."

7.1.R.5.1 Dosing regimen of talazoparib

The applicant's explanation about the dosing rationale for talazoparib for *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer:

The dosing regimen selected based on the results of the following clinical studies etc. was used in the EMBRACA study and the expansion part of Study 030, and the efficacy and safety of talazoparib in the patient populations of these studies were demonstrated. Thus, the proposed dosing regimen was selected based on the EMBRACA study and the expansion part of Study 030.

- In Foreign Study 007, DLTs were observed in 1 of 6 subjects in the talazoparib 0.9 mg group (Grade 3 thrombocytopenia) and 2 of 6 subjects in the talazoparib 1.1 mg group (Grade 3 thrombocytopenia; and Grade 4 thrombocytopenia [1 subject each]). Thus, talazoparib 1 mg QD orally was selected as the RP2D.
- In the dose-escalation part of Japanese Study 030, talazoparib 0.75 or 1 mg QD was administered. No DLTs were observed, and talazoparib was well tolerated. Thus, talazoparib 1 mg QD orally was selected as the RP2D for Japanese patients.

As to the starting dose of talazoparib in patients with renal impairment in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert, based on the results of Study 001 etc., a starting dose of talazoparib 0.75 mg QD was recommended for patients with moderate renal impairment (CLcr ≥30 mL/min and <60 mL/min), and a starting dose of talazoparib 0.5 mg QD was recommended for patients with severe renal impairment (CLcr ≥15 mL/min and <30 mL/min) [see Section 6.R.3].

Since no clinical study has evaluated the efficacy and safety of talazoparib in combination with other anti-neoplastic drugs, talazoparib in combination with other anti-neoplastic drugs is not recommended.

On the basis of the above, the following statements were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the dosage administration statement of "The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition." was proposed.

[All indications]

- If a patient vomits or misses a dose of talazoparib, the next prescribed dose should be taken at the usual time. Do not take a double dose per day.
- Recommended dosage modifications for adverse reactions
- For patients with renal impairment, adjust the starting dose of talazoparib based on CLcr as per the table below (for breast cancer).

Starting dose of talazoparib

CLcr (mL/min)	*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer
≥60	1 mg once daily
≥30 and <60	0.75 mg once daily
≥15 and <30	0.5 mg once daily

[*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer]

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.

PMDA's discussion:
PMDA accepted the applicant's explanation about talazoparib in combination with other anti-neoplastic drugs.

As to the starting dose of talazoparib in patients with renal impairment in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert, based on the considerations in Section "6.R.3 Use of talazoparib in patients with renal impairment," information on the starting dose of talazoparib in patients with severe renal impairment should be deleted, and the severity of renal impairment should be defined by eGFR. Then, a precautionary statement regarding the starting dose of talazoparib in patients with moderate renal impairment should be included.

Since the bioequivalence between the 1-mg and 0.25-mg capsules has not been demonstrated at present [see Section 6.R.2], the use of the 1-mg capsule interchangeably with the 0.25-mg capsule in patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer is not recommended.

Since advice in case of vomiting or missing dose is general information, there is no need to include this information in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert.

On the basis of the above, the statements in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section should be presented by indication. The following statements for *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer should be included, and then the proposed dosage and administration statement of "The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition." is appropriate.

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.
- For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the recommended starting dose of talazoparib is 0.75 mg once daily.
- Do not use the 0.25-mg capsule to administer a 1 mg dose of talazoparib because the bioequivalence between the 1-mg and 0.25-mg capsules has not been demonstrated.
- Recommended dosage modifications for adverse reactions

7.2 Data for prostate cancer and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from a total of 2 studies presented in Table 40: 1 global phase III study and 1 foreign phase II study. The applicant also submitted the results from a total of 9 studies as reference data: 7 foreign phase I studies (Studies 001, 002, 003, 004, 005, 022, and 023) and 2 foreign phase II studies (Studies 010 and 020). The reference data are presented in the section for data for breast cancer [see Section 7.1].

Table 40. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Global	TALAPRO-2	III	Patients with mCRPC who had received no prior systemic therapy for mCRPC	[Part 1] 19 [Part 2 (Cohort 1)] (1) 402 (2) 403	[Part 1] Talazoparib 0.5 or 1 mg QD orally in combination with enzalutamide 160 mg QD orally [Part 2 (Cohort 1)] (1) Talazoparib 0.5 mg*1 or (2) placebo QD orally in combination with enzalutamide 160 mg QD orally	Efficacy Safety
	Foreign	TALAPRO-1	II	Patients with mCRPC who had received prior systemic therapy for mCRPC	128	Talazoparib 1 mg*2 QD orally	Efficacy Safety

*1 Patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) were to receive talazoparib 0.35 mg QD orally.
*2 Patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) were to receive talazoparib 0.75 mg QD orally.

The clinical studies are summarized below.

The main adverse events other than deaths observed in the clinical studies are described in Section "7.3 Adverse events etc. observed in clinical studies."

7.2.1 Evaluation data

7.2.1.1 Global study

7.2.1.1.1 Global phase III study (CTD 5.3.5.1.1.CRPC: TALAPRO-2 study Part 1 and Part 2 [Cohort 1] [[redacted] 2017 to August 2022])

A 2-part study in patients with mCRPC who had received no prior systemic therapy for mCRPC (target sample size, 12 subjects in Part 1 and 750 subjects[50)] in Part 2 [Cohort 1]) was conducted at 221 sites in 26 countries including Japan. Part 1[51)] (the safety assessment portion) aimed to evaluate the tolerability, safety, etc. of talazoparib/enzalutamide, and Part 2 (Cohort 1)[52)] (the randomized, double-blind, placebo-controlled portion) aimed to compare the efficacy and safety of talazoparib plus enzalutamide vs. placebo plus enzalutamide.

The eligibility criteria as to prior treatment are shown below.

- No prior systemic therapy for CRPC, with the exception of androgen deprivation therapy (ADT) and first-generation anti-androgens such as bicalutamide and flutamide received prior to randomization.
- Prior treatment with platinum-based chemotherapy was allowed if discontinued ≥6 months prior to randomization.
- Prior docetaxel, biologic therapy, and radionuclide therapy prior to the diagnosis of mCRPC were allowed if discontinued ≥4 weeks prior to randomization.
- Prior abiraterone prior to the diagnosis of mCRPC was allowed if discontinued prior to randomization.

The dosing regimens are shown below, and treatment was to continue until disease progression or any withdrawal criterion was met.

[Part 1]

- Talazoparib 0.5 or 1 mg QD orally in combination with enzalutamide 160 mg QD orally

[Part 2 (Cohort 1)]

- Talazoparib group: Talazoparib 0.5 mg QD orally in combination with enzalutamide 160 mg QD orally Patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) were to receive talazoparib 0.35 mg QD orally
- Placebo group: Placebo QD orally in combination with enzalutamide 160 mg QD orally

In Part 1, all of 19 enrolled subjects received talazoparib and were included in the safety population. In Part 2 (Cohort 1), 805 enrolled subjects (402 in the talazoparib group, 403 in the placebo group) were included in the

[50)] For the primary endpoint of rPFS as assessed by BICR, based on 1:1 randomization ratio between the talazoparib and placebo groups, 333 rPFS events were considered necessary to provide 85% power at a 1-sided significance level of 0.0125 to detect a hazard ratio of 0.696. Considering the duration of follow-up etc., a target sample size of 750 subjects was chosen.

[51)] Japan did not participate in Part 1.

[52)] Cohort 1 (target sample size, 750 subjects) and Cohort 2 (target sample size, 268 subjects) were studied separately in Part 2. Patients unselected for HRR status were enrolled in Cohort 1, and patients with known HRR gene mutations prior to randomization were enrolled in Cohort 2. Cohort 2 was for the randomized, double-blind, placebo-controlled portion to compare the efficacy and safety of talazoparib plus enzalutamide vs. placebo plus enzalutamide in patients with mCRPC with HRR gene mutations who had received no prior systemic therapy for mCRPC, and enrollment in Cohort 2 started upon completed enrollment in Cohort 1. Part 2 Cohort 2 was ongoing at the time of regulatory submission and was not submitted as the evaluation or reference data in the present application.

ITT population, which was used for efficacy analyses (including 60 Japanese patients in the talazoparib group and 56 Japanese patients in the placebo group). Among the ITT population, 799 subjects (398 in the talazoparib group, 401 in the placebo group) after excluding 6 subjects who did not receive study drug were included in the safety population (including 60 Japanese patients in the talazoparib group and 56 Japanese patients in the placebo group).

As to tolerability evaluation in Part 1, adverse events leading to dose interruption of talazoparib occurred in 10 of 13 subjects in the talazoparib 1 mg group (anaemia [9 subjects]; platelet count decreased; and neutrophil count decreased [3 subjects each]; and white blood cell count decreased [1 subject] [some subjects had more than 1 event]), and adverse events leading to dose reduction of talazoparib occurred in 8 of 13 subjects in the talazoparib 1 mg group (anaemia [4 subjects]; fatigue; neutrophil count decreased; and platelet count decreased [2 subjects each]; and dyspnoea; headache; lethargy; and nausea [1 subject each] [some subjects had more than 1 event]). Then, additional patients were enrolled in the talazoparib 0.5 mg group, and its safety etc. was evaluated. Since adverse events leading to dose interruption of talazoparib occurred in 4 of 6 subjects (anaemia [4 subjects]), and adverse events leading to dose reduction of talazoparib occurred in 2 of 6 subjects (anaemia [2 subjects]), talazoparib 0.5 mg QD orally was selected as the RP2D in combination with enzalutamide, and talazoparib 0.35 mg QD orally was recommended for patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2).

The primary endpoint for Part 2 (Cohort 1) was rPFS[53)] as assessed by BICR per RECIST ver.1.1, and when 167 and 333 rPFS events had been observed, an interim analysis for futility and the final analysis were to be conducted, respectively.

The results of the final analysis of the primary efficacy endpoint of rPFS as assessed by BICR per RECIST ver.1.1 (data cutoff date on August 16, 2022) and the Kaplan-Meier curves are shown in Table 41 and Figure 4, respectively. The superiority of talazoparib plus enzalutamide to placebo plus enzalutamide was demonstrated.

[53)] rPFS was defined as the time from randomization to the first occurrence of any of the following events (1)(2)(3).
(1) Progression of bone lesions observed by bone scintigraphy (either (i) or (ii) shown below)
(i) ≥2 new lesions compared to baseline on the Week 8 (from randomization) bone scan, with ≥2 additional new lesions on the next scan ≥6 weeks later (The date of event was the date of the scan that showed ≥2 new lesions compared to baseline).
(ii) If the Week 8 scan did not show ≥2 new lesions compared to baseline, the Week 8 scan was to be considered as the new baseline scan. The first scan with ≥2 new lesions compared to new baseline was observed after the Week 8 scan, and the continued presence of these new lesions was confirmed by a subsequent scan ≥6 weeks later (The date of event was the date of the scan that showed ≥2 new lesions compared to new baseline).
(2) Progression of soft tissue lesions measured by CT or MRI per RECIST ver.1.1
(3) Death from any cause

Table 41. Results of final analysis of rPFS (BICR assessment, ITT, data cutoff date on August 16, 2022)

	ITT population	
	Talazoparib	Placebo
N	402	403
No. of events (%)	151 (37.6)	191 (47.4)
Median [95% CI] (%)	— [27.5, —]	21.9 [16.6, 25.1]
Hazard ratio [95% CI][*1]	0.63 [0.51, 0.78][*2]	
P-value (one-sided)[*3]	<0.0001[*4]	

—, Not estimable; *1 A Cox proportional-hazards model stratified by previous treatment with anti-androgen or chemotherapy such as docetaxel (yes, no) and HRR mutation status (positive, negative/unknown); *2 The 97.5% CI corresponding to the significance level was [0.49, 0.80]; *3 A stratified log-rank test (the same stratification factors as were used for the stratified Cox proportional-hazards model); *4 A significance level (one-sided) of 0.0125

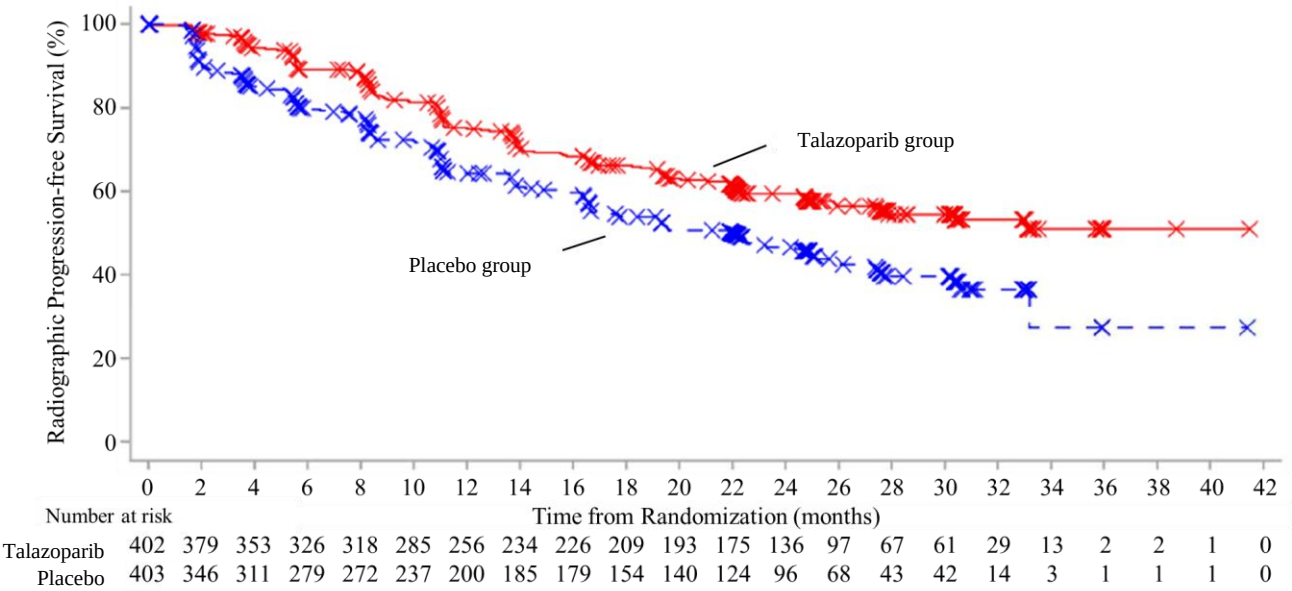

Figure 4. Kaplan-Meier curves of rPFS at final analysis (BICR assessment, ITT, data cutoff date on August 16, 2022)

Regarding safety, 1 of 13 subjects (7.7%) (0 in the talazoparib 0.5 mg group, 1 in the talazoparib 1 mg group) in Part 1 and 14 of 398 subjects (3.5%) in the talazoparib group and 20 of 401 subjects (5.0%) in the placebo group in Part 2 (Cohort 1) died during the talazoparib treatment period or within 28 days after the last dose (including 2 Japanese patients in the talazoparib group and 0 Japanese patients in the placebo group in Part 2 [Cohort 1]). The causes of deaths other than disease progression (0 subjects in Part 1, 4 subjects in the talazoparib group and 7 subjects in the placebo group in Part 2 [Cohort 1]) were necrotising pneumonia (1 subject) in Part 1 and unknown (3 subjects); pneumonia (2 subjects); and SARS-CoV-2 test positive; cardiac arrest; cardiac failure; disseminated intravascular coagulation; and sepsis (1 subject each) in the talazoparib group and unknown (4 subjects); SARS-CoV-2 test positive; and cardiac failure (2 subjects each); and brain contusion, cerebral haemorrhage, and craniocerebral injury; acute pulmonary oedema; lung neoplasm malignant; sepsis; and study drug's toxicity (1 subject each) in the placebo group in Part 2 (Cohort 1). A causal relationship to study drug could not be ruled out for necrotising pneumonia (1 subject) in Part 1 and unknown; and study drug's toxicity (1 subject each) in the placebo group in Part 2 (Cohort 1) (Among the Japanese patients, the cause of death other than disease progression (1 subject in the talazoparib group in Part 2 [Cohort 1]) was cardiac failure (1 subject) in the talazoparib group, and its causal relationship to study drug was denied.).

7.2.1.2 Foreign study

7.2.1.2.1 Foreign phase II study (CTD 5.3.5.2.1.CRPC: TALAPRO-1 study [July 2017 to September 2020])

An open-label, uncontrolled study was conducted at 43 sites overseas to evaluate the efficacy, safety, etc. of talazoparib in patients with mCRPC with HRR gene mutations who had received prior systemic therapy for mCRPC[54)] (target sample size, 100 subjects).

Talazoparib 1 mg QD was to be administered orally,[55)] and treatment was to continue until disease progression or any withdrawal criterion was met.

Among 128 subjects enrolled in the study, 127 received talazoparib and were included in the safety population. Of whom, 104 subjects with measurable disease at enrollment were included in the efficacy population.

Regarding efficacy, the objective response rate (%) as assessed by BICR per RECIST ver.1.1 was 29.8 (31 of 104 subjects).

Regarding safety, 11 of 127 subjects (8.7%) died during the talazoparib treatment period or within 28 days after the last dose of talazoparib. The causes of deaths other than disease progression (9 subjects) were subdural haematoma; and pulmonary embolism (1 subject each), and a causal relationship to study drug was denied for both cases.

7.2.R Outline of the review conducted by PMDA

7.2.R.1 Review strategy

Regarding the efficacy and safety of talazoparib/enzalutamide, PMDA decided to focus its review on Part 2 of the TALAPRO-2 study. Its efficacy in Japanese patients is evaluated systematically based on the TALAPRO-2 study etc., in accordance with "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), partial revision of "Basic Principles on Global Clinical Trials (Reference Cases)"(Administrative Notice dated December 10, 2021), "Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018), etc.

7.2.R.2 Efficacy

On the basis of the following considerations, PMDA concluded that the efficacy of talazoparib/enzalutamide is expected in patients with *BRCA*-mutated mCRPC who have received no prior systemic therapy for mCRPC.

[54)] Patients with mCRPC with HRR gene mutations who had received prior taxane-based chemotherapy and progressed on abiraterone or enzalutamide were enrolled.

[55)] Patients who were determined to have moderate renal impairment at screening (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2 per central laboratory) were to receive talazoparib 0.75 mg QD orally.

7.2.R.2.1 Study population

Patients with mCRPC who had received no prior systemic therapy for mCRPC were enrolled in the TALAPRO-2 study. The applicant explained that the primary mechanism of talazoparib/enzalutamide in inhibiting prostate cancer growth differs between patients with HRR gene mutation-positive mCRPC and patients with HRR gene mutation-negative mCRPC [see Section 3.R.1].

PMDA asked the applicant to explain the reason for selecting non-*BRCA* HRR genes as classifiers for HRR gene mutations in the TALAPRO-2 study.

The applicant's response:
Various HRR genes such as *BRCA*, *ATM*, and *CHEK2* have been reported to be involved in homologous recombination repair (*Nat Rev Mol Cell Biol*. 2021; 22: 796-814, *Int J Mol Sci*. 2021; 23: 348, etc.). Thus, in the TALAPRO-2 study, focusing on the 12 HRR genes reported to be involved in homologous recombination repair (*MRE11A*, *NBN*, *ATR*, *ATM*, *CHEK2*, *BRCA1*, *BRCA2*, *PALB2*, *CDK12*, *FANCA*, *RAD51C*, *MLH1*), patients with a mutation in these genes were considered HRR gene mutation-positive patients.

PMDA's discussion:
The proposed primary mechanism of talazoparib/enzalutamide in inhibiting prostate cancer growth differs between patients with HRR gene mutation-positive mCRPC and patients with HRR gene mutation-negative mCRPC, and it is difficult to conclude that the mechanisms of action independent of HRR gene mutation status are supported by non-clinical studies etc. [see Section 3.R.1]. Given these points, the appropriateness of grouping patients with mCRPC with and without HRR gene mutations together for efficacy evaluation of talazoparib/enzalutamide is unknown.

As to HRR gene mutation-positive patients, given that the degrees of contribution of non-BRCA HRR factors to homologous recombination repair are unknown, it cannot be concluded that the efficacy of talazoparib is expected in patients with non-*BRCA* HRR gene mutations as in patients with *BRCA* mutations [see Section 3.R.1]. Thus, the appropriateness of grouping patients with *BRCA* mutations and patients with non-*BRCA* HRR gene mutations together for efficacy evaluation of talazoparib/enzalutamide is unknown.

On the basis of the above, the efficacy of talazoparib/enzalutamide in patients with mCRPC who have received no prior systemic therapy for mCRPC needs to be determined carefully, taking account of the results in the overall population in Part 2 (Cohort 1) of the TALAPRO-2 study and the analysis results in the subgroups of patients with *BRCA* mutations, patients with non-*BRCA* HRR gene mutations, and patients without HRR gene mutations.

7.2.R.2.2 Control group

The applicant's explanation about the reason for choosing placebo/enzalutamide as a comparator in Part 2 of the TALAPRO-2 study:

At the time when the TALAPRO-2 study was designed, the NCCN guidelines (Prostate cancer) (v.3.2016) and the Japanese clinical practice guidelines (Prostate cancer) (2016) recommended enzalutamide for patients with mCRPC who have received no prior systemic therapy for mCRPC, i.e., the patient population of the TALAPRO-2 study. Thus, placebo/enzalutamide was chosen as a comparator in Part 2 of the TALAPRO-2 study.

PMDA accepted the applicant's explanation.

7.2.R.2.3 Efficacy endpoint

The applicant's explanation about the appropriateness of selecting BICR-assessed rPFS as the primary endpoint for Part 2 of the TALAPRO-2 study:

Longer rPFS in the patient population of Part 2 of the TALAPRO-2 study preserves the physical function and quality of life (QOL) of patients by reducing the symptoms associated with disease progression and prolonging the time to the initiation of treatment with cytotoxic anti-neoplastic drugs, which is burdensome to the body, etc. and is clinically meaningful. Thus, selecting rPFS as the primary endpoint for Part 2 of the TALAPRO-2 study was appropriate.

PMDA's discussion:

Since the patient population of Part 2 of the TALAPRO-2 study is treated with an expectation of survival benefit, OS should have been selected as the primary endpoint for Part 2 of the TALAPRO-2 study. However, as the above explanation by the applicant (longer rPFS in these patients is clinically meaningful to a certain extent) is understandable, the efficacy of talazoparib/enzalutamide can be evaluated based on the results of the primary endpoint of rPFS, after reviewing the results of OS in Part 2 of the TALAPRO-2 study.

7.2.R.2.4 Results of efficacy assessment

Part 2 (Cohort 1) of the TALAPRO-2 study demonstrated the superiority of talazoparib plus enzalutamide to placebo plus enzalutamide in the primary endpoint of BICR-assessed rPFS [see Section 7.2.1.1.1].

In Part 2 (Cohort 1) of the TALAPRO-2 study, if rPFS was statistically significant at the final analysis, an interim analysis of a secondary endpoint of OS was planned to be conducted. The final analysis of OS was to be conducted when 438 events had been observed. An additional interim analysis was performed when 330 events had been observed. The Lan-DeMets O'Brien-Fleming α-spending function was used to control the type I error rate for the interim analyses, and a one-sided alpha of 0.0006 and a one-sided alpha of 0.003 were allocated to the first and second interim analyses, respectively.

The results of the first interim analysis of OS (data cutoff date on August 16, 2022) and the Kaplan-Meier curves are shown in Table 42 and Figure 5, respectively.

Table 42. Results of first interim analysis of OS (ITT population, data cutoff date on August 16, 2022)

	Talazoparib	Placebo
N	402	403
No. of events (%)	123 (30.6)	129 (32.0)
Median [95% CI] (months)	36.4 [33.5, －]	－ [33.7, －]
Hazard ratio [95% CI][*1]	0.89 [0.69, 1.14][*2]	
P-value (one-sided)[*3]	0.1736[*4]	

－, Not estimable; *1 A Cox proportional-hazards model stratified by previous treatment with anti-androgen or chemotherapy such as docetaxel (yes, no) and HRR mutation status (positive, negative/unknown); *2 The 99.88% CI corresponding to the significance level was [0.59, 1.34]; *3 A stratified log-rank test (the same stratification factors as were used for the stratified Cox proportional-hazards model); *4 A significance level (one-sided) of 0.0006

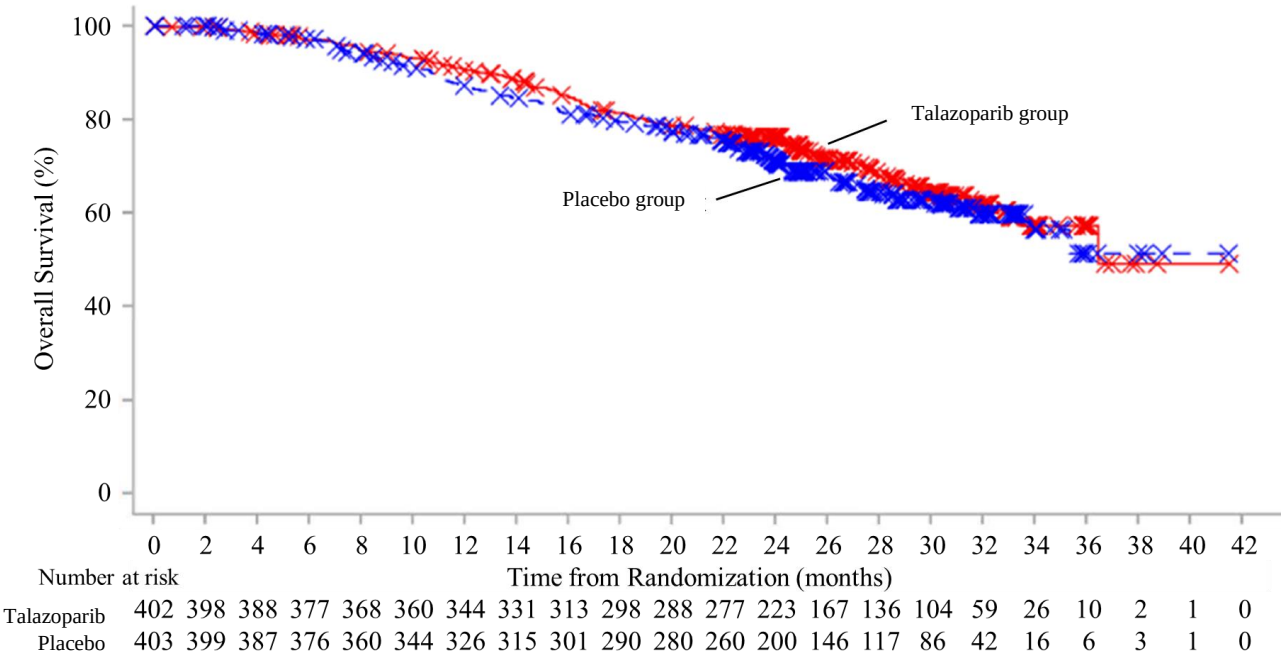

Figure 5. Kaplan-Meier curves of OS at first interim analysis (ITT population, data cutoff date on August 16, 2022)

The results of the second interim analysis (data cutoff date on March 28, 2023) and the Kaplan-Meier curves are shown in Table 43 and Figure 6, respectively.

Table 43. Results of second interim analysis of OS (ITT population, data cutoff date on March 28, 2023)

	Talazoparib	Placebo
N	402	403
No. of events (%)	156 (38.8)	174 (43.2)
Median [95% CI] (months)	— [37.3, —]	38.2 [34.1, 43.1]
Hazard ratio [95% CI][*1]	0.84 [0.67, 1.04][*2]	
P-value (one-sided)[*3]	0.0537[*4]	

—, Not estimable; *1 A Cox proportional-hazards model stratified by previous treatment with anti-androgen or chemotherapy such as docetaxel (yes, no) and HRR mutation status (positive, negative/unknown); *2 The 99.4% CI corresponding to the significance level was [0.62, 1.14]; *3 A stratified log-rank test (the same stratification factors as were used for the stratified Cox proportional-hazards model); *4 A significance level (one-sided) of 0.003

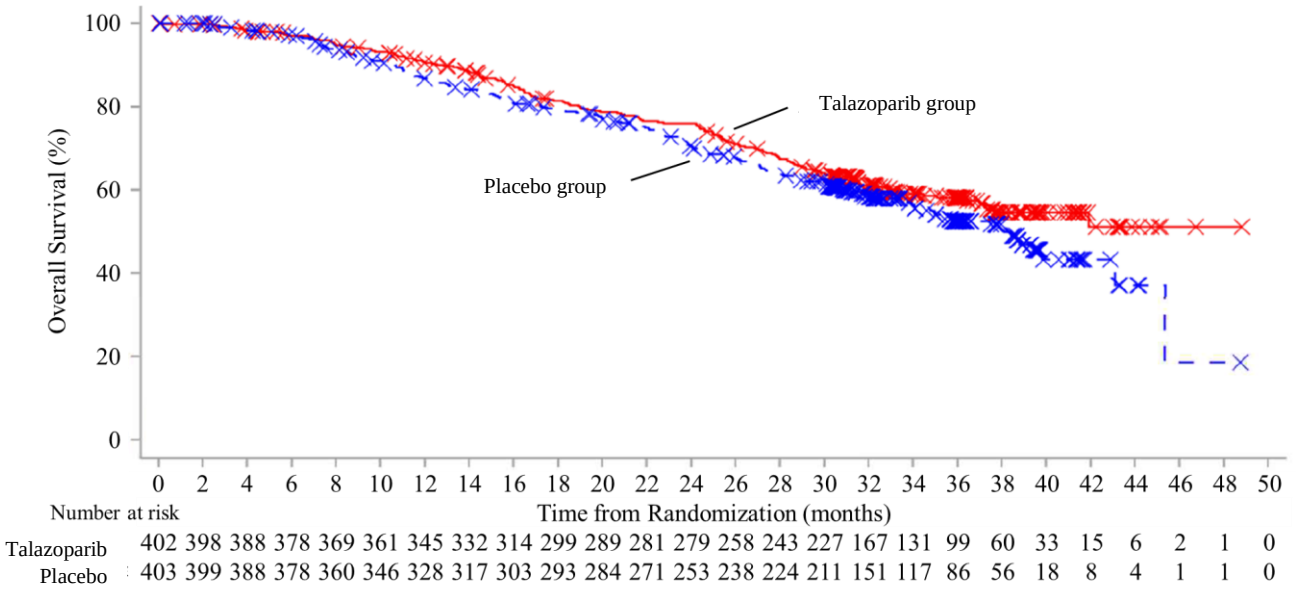

Figure 6. Kaplan-Meier curves of OS at second interim analysis
(ITT population, data cutoff date on March 28, 2023)

In addition, the results of the final analysis of rPFS and the Kaplan-Meier curves in the Japanese subgroup in Part 2 (Cohort 1) of the TALAPRO-2 study are shown in Table 44 and Figure 7, respectively.

Table 44. Results of final analysis of rPFS in Japanese subgroup
(BICR assessment, ITT population, data cutoff date on August 16, 2022)

	Talazoparib	Placebo
N	60	56
No. of events (%)	19 (31.7)	16 (28.6)
Median [95% CI] (months)	— [27.9, —]	— [24.9, —]
Hazard ratio [95% CI]*	0.89 [0.45, 1.75]	

—, Not estimable; * A Cox proportional-hazards model stratified by previous treatment with anti-androgen or chemotherapy such as docetaxel (yes, no) and HRR mutation status (positive, negative/unknown)

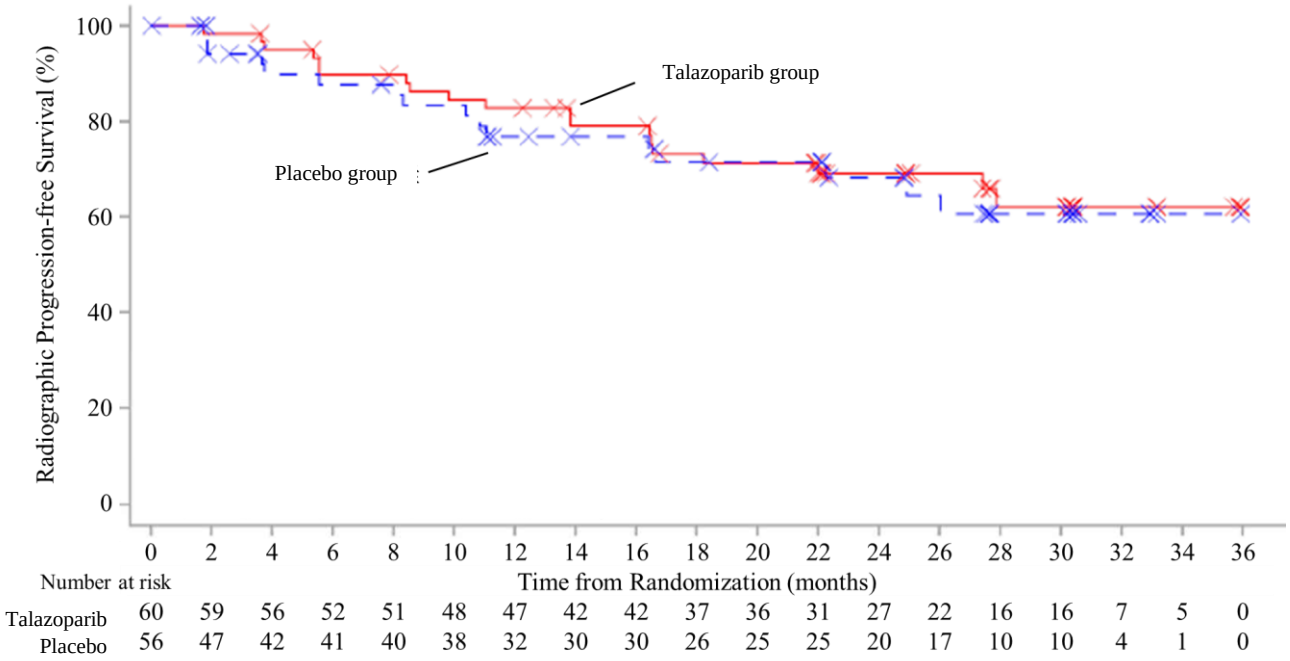

Figure 7. Kaplan-Meier curves of rPFS in Japanese subgroup
(BICR assessment, ITT population, data cutoff date on August 16, 2022)

On the basis of the considerations in Section "7.2.R.2.1 Study population," PMDA asked the applicant to explain the efficacy of talazoparib/enzalutamide in the subgroups of patients with *BRCA* mutations, patients with non-*BRCA* HRR gene mutations, and patients without HRR gene mutations in the ITT population.

The applicant's response:

In Part 2 (Cohort 1) of the TALAPRO-2 study, though patients unselected for HRR mutation status were enrolled, assessment of HRR gene mutations[56)] from a tumor tissue sample or a plasma sample completed using the FoundationOne CDx or FoundationOne Liquid CDx, respectively, prior to randomization, was required for stratification (prospective testing). For patients with unknown HRR mutation status by prospective testing, a plasma sample collected prior to randomization was analyzed for HRR gene mutations using the FoundationOne Liquid CDx after randomization (retrospective testing). The non-*BRCA*-mutated HRR-deficient subgroup was defined as patients with non-*BRCA* (*BRCA1* or *BRCA2*) HRR gene mutations by analysis of a tumor tissue sample or a plasma sample, and the *BRCA*-mutated subgroup was defined as patients with *BRCA* (*BRCA1* or *BRCA2*) mutations by analysis of a tumor tissue sample or a plasma sample, among patients with a positive result for HRR gene mutations by prospective testing and patients with unknown status by prospective testing and a positive result for HRR gene mutations by retrospective testing. The non-*BRCA*-mutated HRR-deficient subgroup included patients with more than 1 mutation in the non-*BRCA* genes, and the *BRCA*-mutated subgroup included patients with *BRCA* and non-*BRCA* mutations. The HRR gene mutation-negative subgroup was defined as patients with a negative result by prospective testing and patients with unknown status by prospective testing and a negative result by retrospective testing if

[56)] Test result for each gene analyzed was reported as positive, negative, or unknown.

a negative result was obtained from both tumor tissue and plasma samples, or a result from only a tumor tissue or plasma sample was available, and a negative result from that sample was obtained. Patients with unknown HRR mutation status by both prospective and retrospective analyses were excluded from the analysis.

Regarding efficacy in the *BRCA*-mutated subgroup, the non-*BRCA*-mutated HRR-deficient subgroup, and the HRR gene mutation-negative subgroup in the ITT population, the results of the final analysis of rPFS, the first interim analysis of OS, and the second interim analysis of OS are shown in Table 45 and Figure 8, Table 46 and Figure 9, and Table 47 and Figure 10, respectively (data cutoff date: August 16, 2022 for the final analysis of rPFS and the first interim analysis of OS, March 28, 2023 for the second interim analysis of OS).

Table 45. Results of final analysis of rPFS by genetic mutation status (BICR assessment, ITT population, data cutoff date on August 16, 2022)

Genetic mutation	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio[*1] [95% CI]
BRCA-mutated	Talazoparib	30	10 (33.3)	— [16.8, —]	0.27 [0.13, 0.56]
	Placebo	39	27 (69.2)	11.0 [5.9, 21.9]	
Non-*BRCA*-mutated HRR-deficient	Talazoparib	77	38 (49.4)	24.6 [16.5, —]	0.72 [0.46, 1.14]
	Placebo	68	35 (51.5)	19.3 [11.0, 27.7]	
HRR gene mutation-negative	Talazoparib	270	95 (35.2)	— [33.1, —]	0.72 [0.55, 0.94]
	Placebo	277	121 (43.7)	23.3 [19.2, 30.5]	

—, Not estimable; *1 An unstratified Cox proportional-hazards model

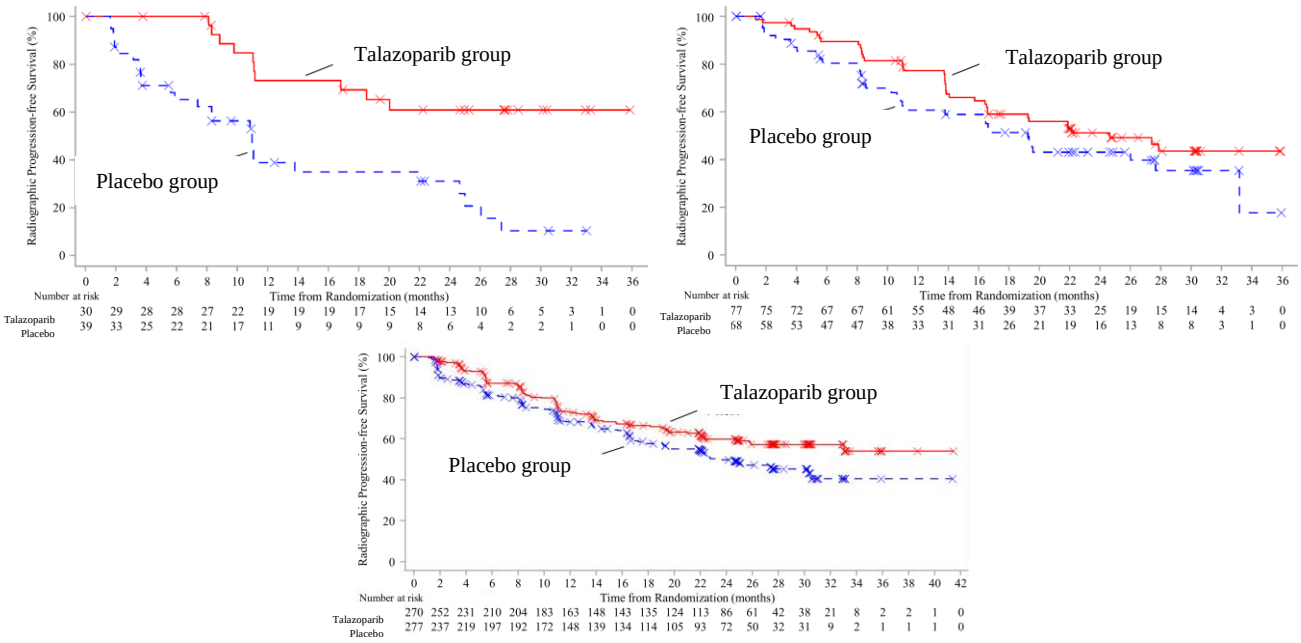

Figure 8. Kaplan-Meier curves of rPFS by genetic mutation status at final analysis (BICR assessment, ITT population, data cutoff date on August 16, 2022) (Left upper figure, *BRCA*-mutated; Right upper figure, Non-*BRCA*-mutated HRR-deficient; Lower figure, HRR gene mutation-negative)

Table 46. Results of first interim analysis of OS by genetic mutation status (ITT population, data cutoff date on August 16, 2022)

Genetic mutation	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio[*1] [95% CI]
BRCA-mutated	Talazoparib	30	11 (36.7)	— [24.4, —]	0.60 [0.28, 1.26]
	Placebo	39	18 (46.2)	26.1 [15.2, —]	
Non-*BRCA*-mutated HRR-deficient	Talazoparib	77	19 (24.7)	36.4 [36.4, —]	0.76 [0.40, 1.45]
	Placebo	68	19 (27.9)	— [30.8, —]	
HRR gene mutation-negative	Talazoparib	270	87 (32.2)	— [32.3, —]	1.02 [0.76, 1.38]
	Placebo	277	87 (31.4)	35.3 [33.7, —]	

—, Not estimable; *1 An unstratified Cox proportional-hazards model

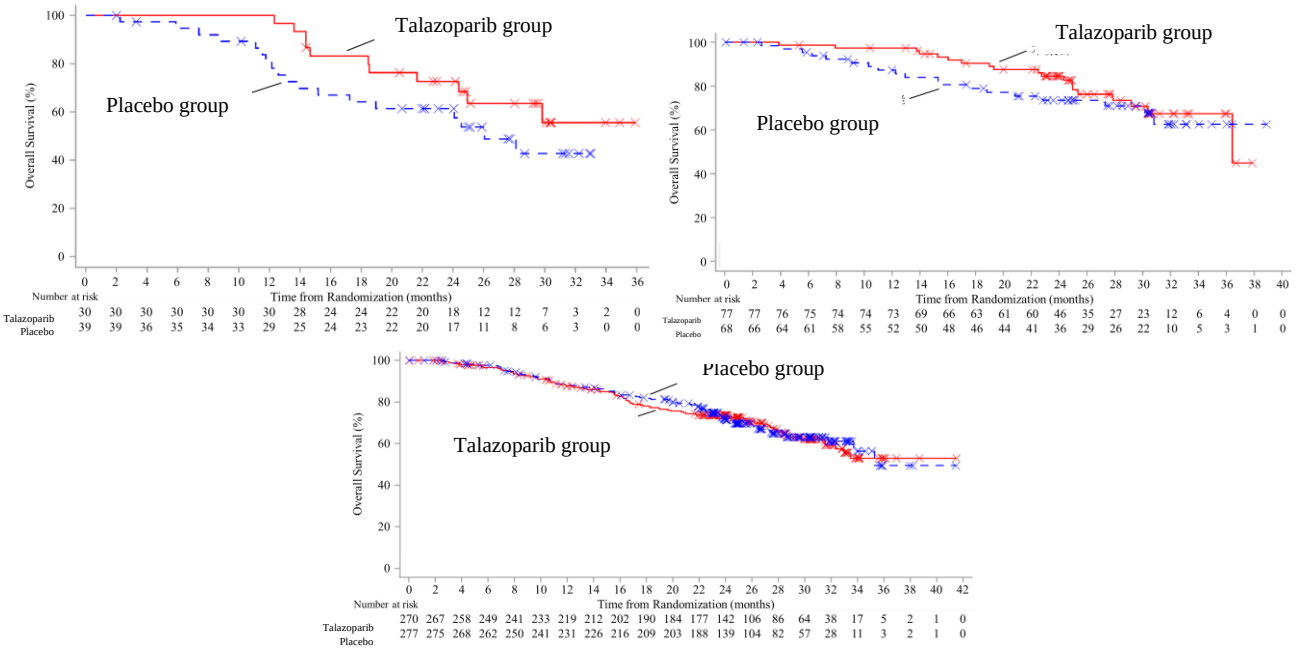

Figure 9. Kaplan-Meier curves of OS by genetic mutation status at first interim analysis (ITT population, data cutoff date on August 16, 2022) (Left upper figure, *BRCA*-mutated; Right upper figure, Non-*BRCA*-mutated HRR-deficient; Lower figure, HRR gene mutation-negative)

Table 47. Results of second interim analysis of OS by genetic mutation status (ITT population, data cutoff date on March 28, 2023)

Genetic mutation	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio[*1] [95% CI]
BRCA-mutated	Talazoparib	30	14 (46.7)	41.9 [24.4, —]	0.61 [0.31, 1.22]
	Placebo	39	21 (53.8)	26.1 [15.2, —]	
Non-*BRCA*-mutated HRR-deficient	Talazoparib	77	28 (36.4)	— [34.5, —]	0.73 [0.44, 1.22]
	Placebo	68	31 (45.6)	38.2 [30.2, —]	
HRR gene mutation-negative	Talazoparib	270	108 (35.2)	— [33.0, —]	0.98 [0.75, 1.28]
	Placebo	277	114 (43.7)	38.7 [35.0, —]	

—, Not estimable; *1 An unstratified Cox proportional-hazards model

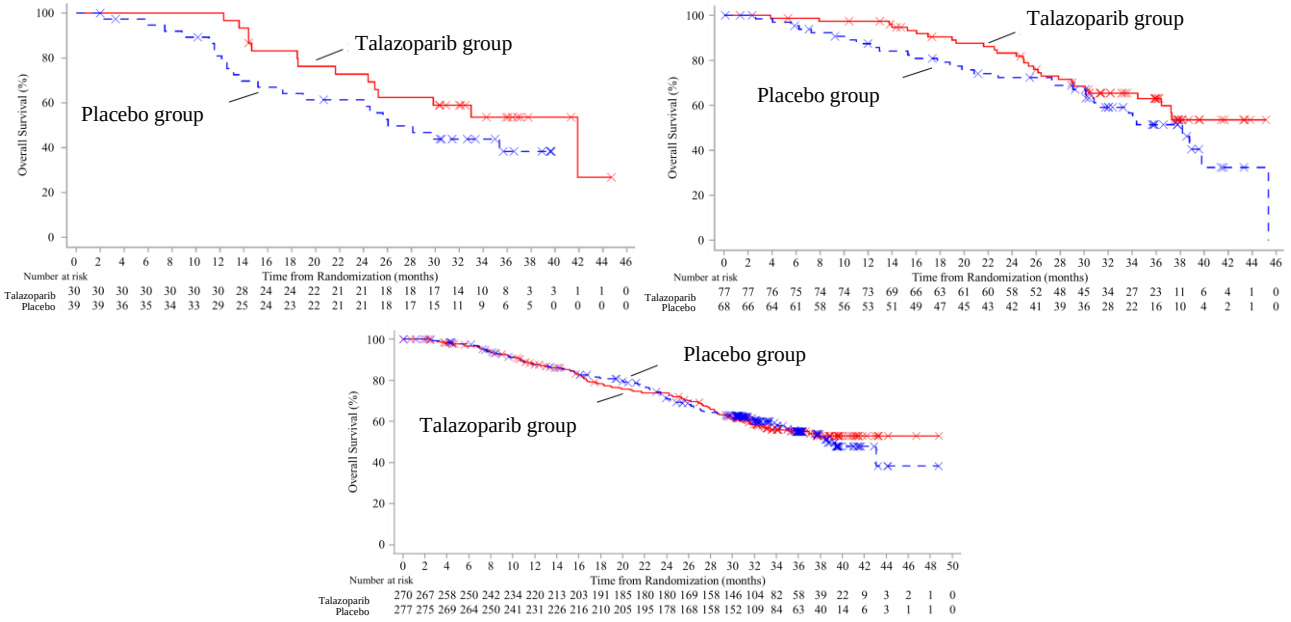

Figure 10. Kaplan-Meier curves of OS by genetic mutation status at second interim analysis (ITT population, data cutoff date on March 28, 2023)
(Left upper figure, *BRCA*-mutated; Right upper figure, Non-*BRCA*-mutated HRR-deficient; Lower figure, HRR gene mutation-negative)

As shown in the above, the results of rPFS and OS in the ITT population tended to differ among (1) the *BRCA*-mutated subgroup, (2) the non-*BRCA*-mutated HRR-deficient subgroup, and (3) the HRR gene mutation-negative subgroup. Given this finding, the following analyses etc. were performed. The results did not suggest any effect of imbalances in patient characteristics between the treatment groups in (1)(2)(3).

- Analyses adjusted for imbalances[57] in patient characteristics potentially affecting rPFS and OS in prostate cancer patients[58] were performed for the subgroups (1)(2)(3). The adjusted rPFS and OS hazard ratios for the talazoparib group vs. the placebo group[59] were not clearly different from the unadjusted hazard ratios.

Regarding efficacy in the *BRCA*-mutated subgroup, the non-*BRCA*-mutated HRR-deficient subgroup, and the HRR gene mutation-negative subgroup among patients assessed for HRR gene mutations including *BRCA* mutations by testing of tumor tissue only, the results of the final analysis of rPFS and the second interim analysis of OS in these subgroups are shown in Table 48 and Figure 11 and Table 49 and Figure 12, respectively (data cutoff date: August 16, 2022 for the final analysis of rPFS, March 28, 2023 for the second interim analysis of OS).

[57] Patient characteristics imbalanced (≥10% differences) between the treatment groups were selected.
[58] As patient characteristics potentially affecting rPFS and OS in prostate cancer patients, age (<65 years, ≥65 and <75 years, ≥75 years), ECOG PS (0, 1), metastases at initial diagnosis (M per AJCC) (0, 1), Gleason score (<8, ≥8), baseline PSA (ng/mL) (≤16.8, >16.8), the number of bone metastases (0, 1, 2-4, 5-9, 10-20, >20), pain score per BP-SF (0/1/2, 2/3, ≥3), CTC count (cells/7.5 ml blood) (<5, ≥5), type of progression (radiographic progression, PSA progression), site of metastasis at screening (bone only, soft tissue only, both bone and soft tissue), visceral disease (yes, no), prior taxane or endocrine therapy (yes, no), prior taxane (yes, no), and prior endocrine therapy (yes, no) were identified.
[59] A stratified Cox proportional-hazards model with treatment as an explanatory variable and stratification factors as covariates

Table 48. Results of final analysis of rPFS by genetic mutation status by testing of tumor tissue (BICR assessment, ITT population, data cutoff date on August 16, 2022)

Genetic mutation	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio [*1] [95% CI]
BRCA-mutated[*2]	Talazoparib	26	8 (30.8)	— [11.2, —]	0.24 [0.10, 0.55]
	Placebo	30	20 (66.7)	11.0 [8.3, 24.6]	
Non-*BRCA*-mutated HRR-deficient[*2]	Talazoparib	57	28 (49.1)	27.4 [16.4, —]	0.61 [0.36, 1.04]
	Placebo	50	27 (54.0)	16.7 [10.9, 27.7]	
HRR gene mutation-negative[*3]	Talazoparib	198	70 (35.4)	— [25.8, —]	0.67 [0.49, 0.91]
	Placebo	214	96 (44.9)	22.1 [16.6, —]	

—, Not estimable; *1 An unstratified Cox proportional-hazards model; *2 The non-*BRCA*-mutated HRR-deficient subgroup was defined as patients with non-*BRCA* (*BRCA1* or *BRCA2*) HRR gene mutations by testing of tumor tissue, and the *BRCA*-mutated subgroup was defined as patients with *BRCA* (*BRCA1* or *BRCA2*) mutations by testing of tumor tissue. The non-*BRCA*-mutated HRR-deficient subgroup included patients with more than 1 mutation in non-*BRCA* genes, and the *BRCA*-mutated subgroup included patients with *BRCA* and non-*BRCA* mutations; *3 The HRR gene mutation-negative subgroup was defined as patients assessed as negative for HRR gene mutations by testing of tumor tissue.

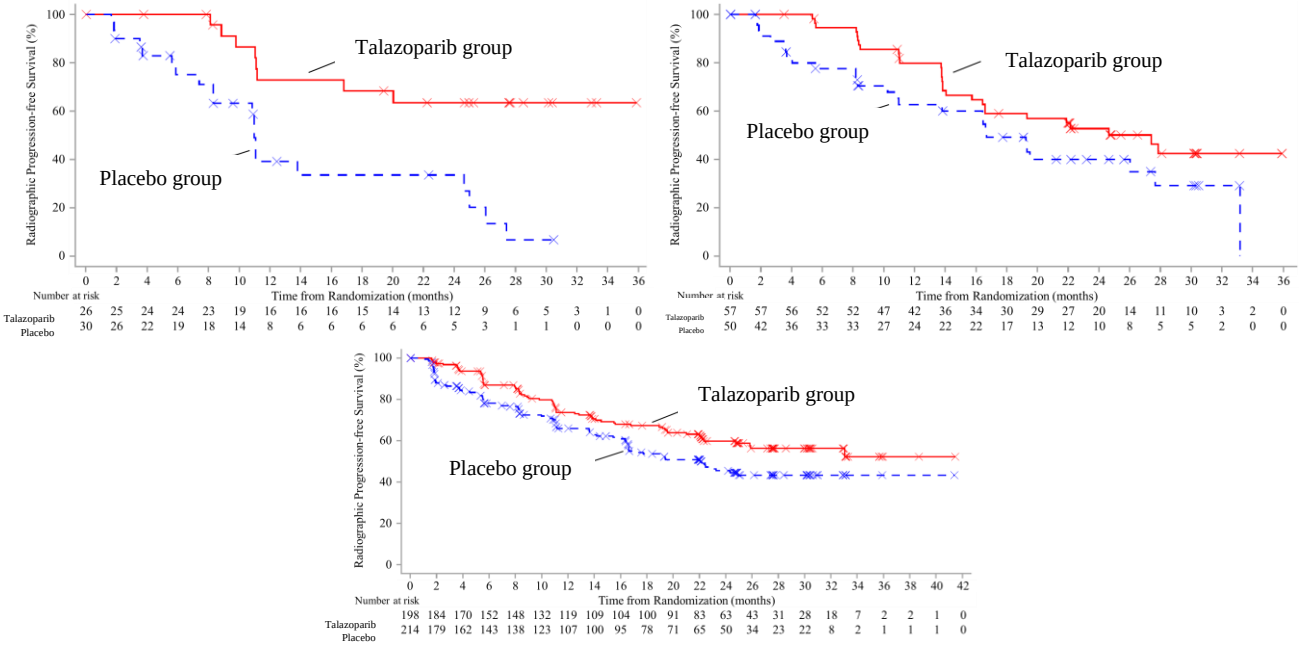

Figure 11. Kaplan-Meier curves of rPFS by genetic mutation status by testing of tumor tissue at final analysis (BICR assessment, ITT population, data cutoff date on August 16, 2022) (Left upper figure, *BRCA*-mutated; Right upper figure, Non-*BRCA*-mutated HRR-deficient; Lower figure, HRR gene mutation-negative)

Table 49. Results of second interim analysis of OS by genetic mutation status by testing of tumor tissue (ITT population, data cutoff date on March 28, 2023)

Genetic mutation	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio[*1] [95% CI]
BRCA-mutated[*2]	Talazoparib	26	12 (46.2)	41.9 [24.9, —]	0.61 [0.28, 1.32]
	Placebo	30	16 (53.3)	28.1 [17.2, —]	
Non-*BRCA*-mutated HRR-deficient[*2]	Talazoparib	57	17 (29.8)	— [36.4, —]	0.49 [0.26, 0.91]
	Placebo	50	24 (48.0)	33.7 [27.3, —]	
HRR gene mutation-negative[*3]	Talazoparib	198	78 (39.4)	— [33.0, —]	0.85 [0.63, 1.14]
	Placebo	214	96 (44.9)	37.5 [33.7, —]	

—: Not estimable; *1 An unstratified Cox proportional-hazards model; *2 The non-*BRCA*-mutated HRR-deficient subgroup was defined as patients with non-*BRCA* (*BRCA1* or *BRCA2*) HRR gene mutations by testing of tumor tissue, and the *BRCA*-mutated subgroup was defined as patients with *BRCA* (*BRCA1* or *BRCA2*) mutations by testing of tumor tissue. The non-*BRCA*-mutated HRR-deficient subgroup included patients with more than 1 mutation in non-*BRCA* genes, and the *BRCA*-mutated subgroup included patients with *BRCA* and non-*BRCA* mutations; *3 The HRR gene mutation-negative subgroup was defined as patients assessed as negative for HRR gene mutations by testing of tumor tissue.

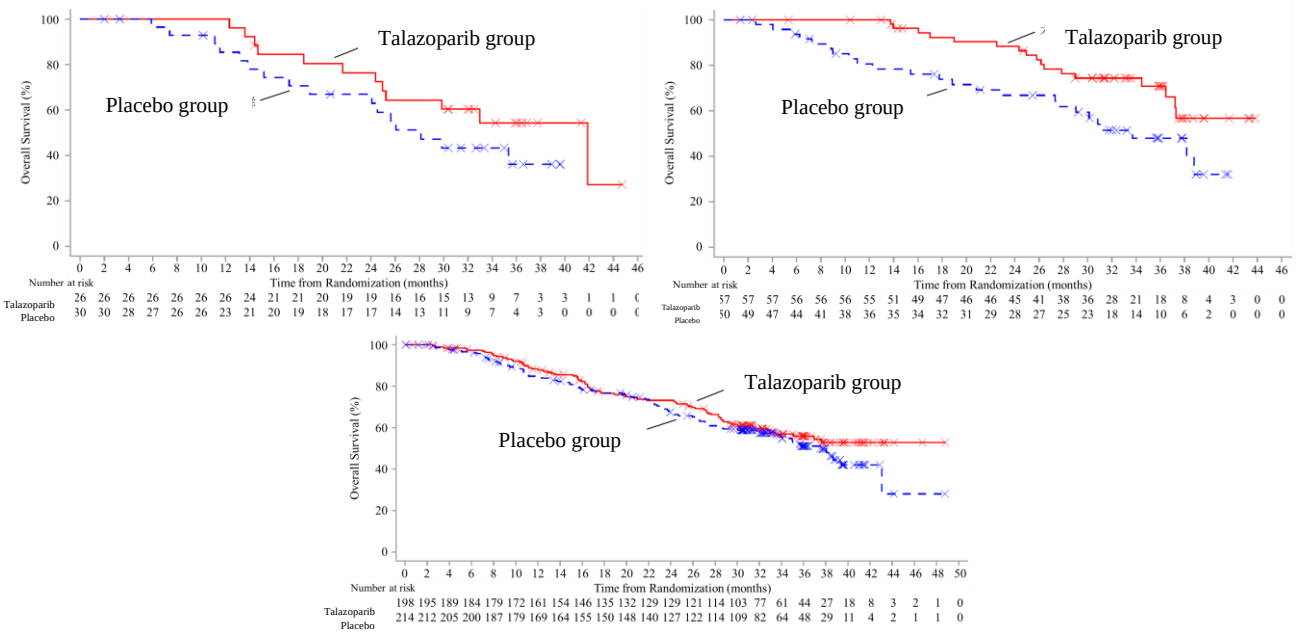

Figure 12. Kaplan-Meier curves of OS by genetic mutation status by testing of tumor tissue at second interim analysis (ITT population, data cutoff date on March 28, 2023)
(Left upper figure, *BRCA*-mutated; Right upper figure, Non-*BRCA*-mutated HRR-deficient; Lower figure, HRR gene mutation-negative)

Given the above analysis results and the following points, the efficacy of talazoparib/enzalutamide is expected, regardless of HRR gene mutation status.

- There was no trend towards clear differences in the results of rPFS between the HRR gene mutation-negative subgroup and the overall population, and a clinically meaningful improvement of rPFS was shown.
- Regarding the results of OS, given the limited number of OS events, there was no trend towards shorter OS with talazoparib/enzalutamide in the HRR gene mutation-negative subgroup.

In order to assess the efficacy of talazoparib/enzalutamide in the HRR-deficient population, PMDA asked the applicant to explain its efficacy in Part 2 (Cohort 2) of the TALAPRO-2 study in HRR-deficient patients with mCRPC who had received no prior systemic therapy for mCRPC.

The applicant's response:

In Part 2 of the TALAPRO-2 study, additional 230 patients were enrolled in Cohort 2 after completed enrollment in Cohort 1. The HRR-deficient population for the efficacy and safety analyses of talazoparib/enzalutamide was planned to include patients with HRR gene mutations enrolled in Cohorts 1 and 2. Patients with HRR gene mutations by prospective testing and patients with unknown status by prospective testing and HRR gene mutations by retrospective testing from Cohort 1 and patients enrolled in Cohort 2 were combined (the combined HRR-deficient population) to assess the efficacy of talazoparib/enzalutamide by *BRCA* mutation status as of the data cutoff date for these analyses. The non-*BRCA*-mutated HRR-deficient subgroup included patients with more than 1 mutation in non-*BRCA* genes, and the *BRCA*-mutated subgroup included patients with *BRCA* and non-*BRCA* mutations. The results of rPFS (data cutoff date: August 16, 2022

for Cohort 1, October 3, 2022 for Cohort 2) and OS (data cutoff date: March 28, 2023 for Cohort 1, October 3, 2022 for Cohort 2) by *BRCA* mutation status in the combined HRR-deficient population are shown in Table 50 and Figure 13 and Table 51 and Figure 14, respectively.

Table 50. Results of analysis of rPFS by *BRCA* mutation status
(BICR assessment; Combined HRR-deficient population; data cutoff date, August 16, 2022 for Cohort 1, October 3, 2022 for Cohort 2)

Genetic mutation	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio*1 [95% CI]
BRCA-mutated	Talazoparib	74	17 (23.0)	— [—, —]	0.22 [0.13, 0.38]
	Placebo	91	59 (64.8)	11.0 [8.3, 11.2]	
Non-*BRCA*-mutated HRR-deficient	Talazoparib	148	60 (40.5)	24.6 [16.6, —]	0.74 [0.51, 1.06]
	Placebo	131	58 (44.3)	16.7 [13.8, 27.7]	

—, Not estimable; *1 An unstratified Cox proportional-hazards model

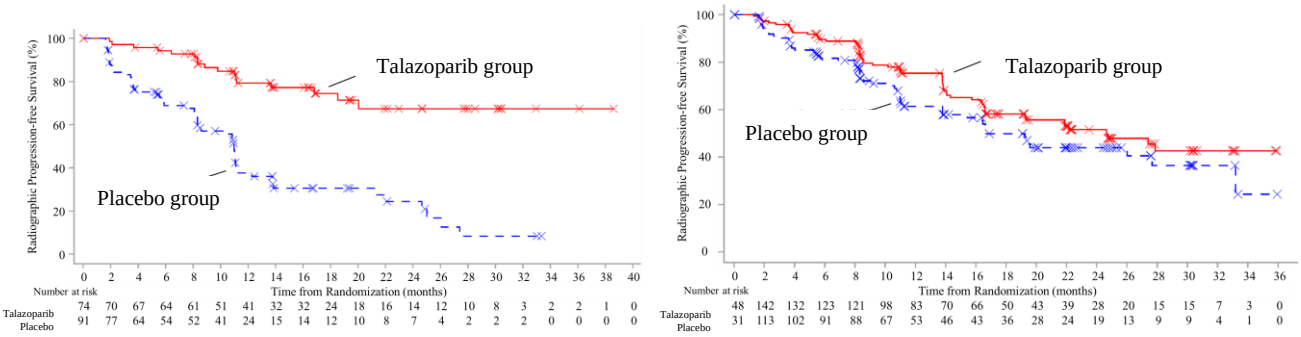

Figure 13. Kaplan-Meier curves of rPFS by *BRCA* mutation status
(BICR assessment; Combined HRR-deficient population; data cutoff date, August 16, 2022 for Cohort 1, October 3, 2022 for Cohort 2)
(Left figure, *BRCA*-mutated; Right figure, Non-*BRCA*-mutated HRR-deficient)

Table 51. Results of analysis of OS by *BRCA* mutation status
(Combined HRR-deficient population; data cutoff date, March 28, 2023 for Cohort 1, October 3, 2022 for Cohort 2)

Genetic mutation	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio*1 [95% CI]
BRCA-mutated	Talazoparib	74	18 (24.3)	41.9 [25.2, —]	0.66 [0.36, 1.22]
	Placebo	91	27 (29.7)	35.4 [24.5, —]	
Non-*BRCA*-mutated HRR-deficient	Talazoparib	148	45 (30.4)	37.3 [30.1, —]	0.85 [0.56, 1.28]
	Placebo	131	44 (33.6)	34.4 [30.2, —]	

—, Not estimable; *1 An unstratified Cox proportional-hazards model

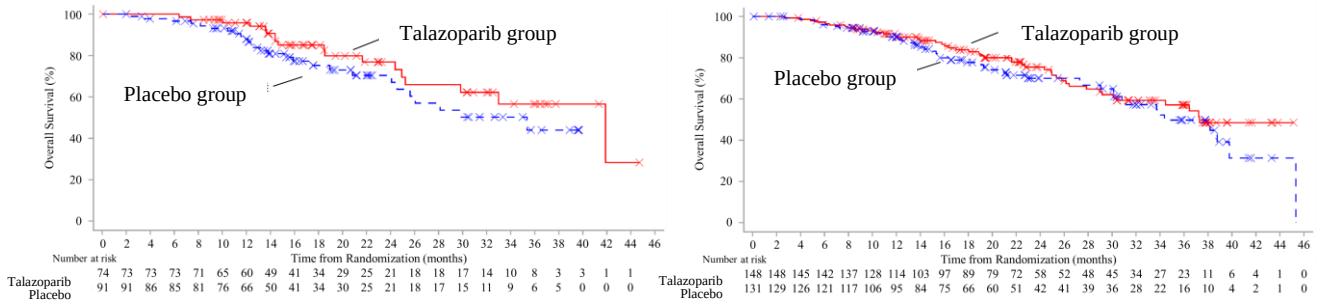

Figure 14. Kaplan-Meier curves of OS by *BRCA* mutation status
(Combined HRR-deficient population, March 28, 2023 for Cohort 1, October 3, 2022 for Cohort 2)
(Left figure, *BRCA*-mutated; Right figure, Non-*BRCA*-mutated HRR-deficient)

As shown in the above, talazoparib plus enzalutamide tended to be superior to placebo plus enzalutamide in prolonging rPFS and OS in both subgroups of the combined HRR-deficient population. Thus, the efficacy of talazoparib/enzalutamide is expected also in patients with non-*BRCA* HRR gene mutations.

PMDA's discussion:
On the basis of the considerations in Section "7.2.R.2.1 Study population," the efficacy of talazoparib/enzalutamide in the overall population in Part 2 (Cohort 1) of the TALAPRO-2 study and by genetic mutation status was assessed.

For the following reasons etc., the efficacy of talazoparib/enzalutamide was demonstrated in the overall population in Part 2 (Cohort 1) of the TALAPRO-2 study including Japanese patients.

- The superiority of talazoparib plus enzalutamide to placebo plus enzalutamide in the primary endpoint of rPFS was demonstrated, and a clinically meaningful improvement of rPFS was shown.
- There was no trend towards clearly shorter OS (a secondary endpoint) in the talazoparib group than in the placebo group.
- Although there are limitations to evaluation due to the limited number of Japanese patients, the above results in the Japanese subgroup did not tend to be clearly different from the results in the overall population.

However, taking account of the results of subgroup analyses, PMDA's view on the efficacy of talazoparib/enzalutamide in the *BRCA*-mutated subgroup, the non-*BRCA*-mutated HRR-deficient subgroup, and the HRR gene mutation-negative subgroup is as follows:

- In the *BRCA*-mutated subgroup, given a clinically meaningful improvement of rPFS and a trend towards longer OS, the efficacy of talazoparib/enzalutamide is expected through a mechanism of action based on HRR deficiency due to a *BRCA* mutation.
- In the non-*BRCA*-mutated HRR-deficient subgroup, the applicant's explanation (non-BRCA HRR factors also play a certain role in homologous recombination repair, and talazoparib can exhibit anti-tumor activity against tumors harboring mutations in the non-*BRCA* HRR genes through a mechanism of action similar to that for *BRCA*-mutated tumors) [see Section 3.R.1] is understandable to a certain extent. Meanwhile, the degrees of contribution of individual genetic mutations to DNA repair function are unknown, and the rPFS benefit in these patients was limited and tended to be clearly different from rPFS in the *BRCA*-mutated subgroup in Part 2 (Cohort 1 and Cohort 2) of the TALAPRO-2 study. In addition, it is difficult to conclude that there was a trend towards longer OS in the combined HRR-deficient population. Thus, it cannot be concluded that a similar efficacy is expected in this subgroup as in the *BRCA*-mutated subgroup.
- In the HRR gene mutation-negative subgroup, it is difficult to conclude that the mechanisms of action of talazoparib/enzalutamide are supported by the results of non-clinical studies [see Section 3.R.1]. The rPFS benefit in the talazoparib group relative to the placebo group was small, and there was no trend towards longer OS. Thus, it cannot be concluded that the efficacy of talazoparib/enzalutamide is expected.

The clinical positioning of talazoparib/enzalutamide in the *BRCA*-mutated subgroup, the non-*BRCA*-mutated HRR-deficient subgroup, and the HRR gene mutation-negative subgroup is described in Section "7.2.R.4.1 Clinical positioning of talazoparib/enzalutamide and indication."

7.2.R.3 Safety [for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies"]

PMDA's conclusion:

On the basis of Section "7.R.1 Safety (Events that require attention following administration of talazoparib, etc.)" and the following considerations, adverse events that require particular attention following administration of talazoparib/enzalutamide in patients with mCRPC who have received no prior systemic therapy for mCRPC are myelosuppression, ILD, thromboembolism, MDS/AML, and second primary malignancies (other than MDS/AML). Attention should be paid to the possible occurrence of these adverse events during treatment with talazoparib.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with talazoparib, talazoparib/enzalutamide is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., monitoring for and management of adverse events and dose interruption/dose reduction/discontinuation of talazoparib or enzalutamide.

7.2.R.3.1 Safety profile

The applicant's explanation about the safety profile of talazoparib/enzalutamide based on the safety information from Part 2 (Cohort 1) of the TALAPRO-2 study:

Safety data from Part 2 (Cohort 1) of the TALAPRO-2 study are summarized in Table 52.

Table 52. Summary of safety data [Part 2 (Cohort 1) of TALAPRO-2 study]

	n (%)	
	Talazoparib N = 398	Placebo N = 401
All adverse events	392 (98.5)	379 (94.5)
Grade ≥3 adverse events	299 (75.1)	181 (45.1)
Adverse events leading to death	13 (3.3)	18 (4.5)
Serious adverse events	157 (39.4)	107 (26.7)
Adverse events leading to treatment discontinuation[*1]	75 (18.8)	49 (12.2)
Talazoparib or placebo[*2]	39 (9.8)	8 (2.0)
Enzalutamide[*2]	6 (1.5)	3 (0.7)
Adverse events leading to dose interruption[*1]	256 (64.3)	93 (23.2)
Talazoparib or placebo[*2]	169 (42.5)	25 (6.2)
Enzalutamide[*2]	65 (16.3)	16 (4.0)
Adverse events leading to dose reduction[*1]	232 (58.3)	50 (12.5)
Talazoparib or placebo[*2]	201 (50.5)	21 (5.2)
Enzalutamide[*2]	44 (11.1)	24 (6.0)

*1 Adverse events leading to discontinuation, dose interruption, or dose reduction of talazoparib, placebo, or enzalutamide
*2 Adverse events leading to discontinuation, dose interruption, or dose reduction of the relevant drug only

In Part 2 (Cohort 1) of the TALAPRO-2 study, adverse events of any grade reported at a ≥5% higher incidence in the talazoparib group than in the placebo group were anaemia (262 subjects [65.8%] in the talazoparib group, 70 subjects [17.5%] in the placebo group), neutrophil count decreased (142 subjects [35.7%], 28 subjects [7.0%]), platelet count decreased (98 subjects [24.6%], 14 subjects [3.5%]), white blood cell count decreased

(88 subjects [22.1%], 18 subjects [4.5%]), decreased appetite (86 subjects [21.6%], 63 subjects [15.7%]), nausea (82 subjects [20.6%], 50 subjects [12.5%]), dizziness (48 subjects [12.1%], 24 subjects [6.0%]), lymphocyte count decreased (45 subjects [11.3%], 20 subjects [5.0%]), and alopecia (33 subjects [8.3%], 10 subjects [2.5%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in the talazoparib group than in the placebo group were anaemia (185 subjects [46.5%], 17 subjects [4.2%]), neutrophil count decreased (73 subjects [18.3%], 6 subjects [1.5%]), platelet count decreased (29 subjects [7.3%], 4 subjects [1.0%]), white blood cell count decreased (25 subjects [6.3%], 0 subjects), lymphocyte count decreased (20 subjects [5.0%], 4 subjects [1.0%]), fatigue (16 subjects [4.0%], 8 subjects [2.0%]), and asthenia (11 subjects [2.8%], 3 subjects [0.7%]). Serious adverse events reported at a ≥2% higher incidence in the talazoparib group than in the placebo group were anaemia (55 subjects [13.8%], 1 subject [0.2%]). Adverse events leading to discontinuation of any study drug[60)] reported at a ≥2% higher incidence in the talazoparib group than in the placebo group were anaemia (33 subjects [8.3%], 6 subjects [1.5%]) and neutrophil count decreased (13 subjects [3.3%], 0 subjects). Adverse events leading to dose interruption of any study drug [60)] reported at a ≥2% higher incidence in the talazoparib group than in the placebo group were anaemia (181 subjects [45.5%], 10 subjects [2.5%]), neutrophil count decreased (56 subjects [14.1%], 5 subjects [1.2%]), platelet count decreased (31 subjects [7.8%], 1 subject [0.2%]), white blood cell count decreased (22 subjects [5.5%], 1 subject [0.2%]), fatigue (17 subjects [4.3%], 7 subjects [1.7%]), nausea (15 subjects [3.8%], 5 subjects [1.2%]), and decreased appetite (15 subjects [3.8%], 7 subjects [1.7%]). Adverse events leading to dose reduction of any study drug [60)] reported at a ≥2% higher incidence in the talazoparib group than in the placebo group were anaemia (177 subjects [44.5%], 5 subjects [1.2%]), neutrophil count decreased (64 subjects [16.1%], 4 subjects [1.0%]), platelet count decreased (24 subjects [6.0%], 1 subject [0.2%]), and white blood cell count decreased (9 subjects [2.3%], 1 subject [0.2%]). There were no adverse events leading to death that were reported at a ≥2% higher incidence in the talazoparib group than in the placebo group.

PMDA's discussion:
Although there were adverse events, Grade ≥3 adverse events, and serious adverse events that were reported at a higher incidence in the talazoparib group than in the placebo group in Part 2 (Cohort 1) of the TALAPRO-2 study, many of these events were manageable with dose interruption/dose reduction/discontinuation etc. of talazoparib or enzalutamide. Given the above point, talazoparib/enzalutamide is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., management of and monitoring for adverse events and dose interruption/dose reduction/discontinuation of talazoparib or enzalutamide.

7.2.R.3.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in the safety of talazoparib/enzalutamide between Japanese and non-Japanese populations based on the safety information from Part 2 (Cohort 1) of the TALAPRO-2 study:

[60)] Talazoparib, placebo, or enzalutamide

Safety data from Japanese and non-Japanese patients in the talazoparib group in Part 2 (Cohort 1) of the TALAPRO-2 study are summarized in Table 53.

Table 53. Summary of safety data from Japanese and non-Japanese patients [Talazoparib group in Part 2 (Cohort 1) of TALAPRO-2 study, data cutoff date on August 16, 2022]

	n (%)	
	Japanese patients N = 60	Non-Japanese patients N = 338
All adverse events	60 (100)	332 (98.2)
Grade ≥3 adverse events	52 (86.7)	247 (73.1)
Adverse events leading to death	2 (3.3)	11 (3.3)
Serious adverse events	20 (33.3)	137 (40.5)
Adverse events leading to treatment discontinuation*	16 (26.7)	59 (17.5)
Adverse events leading to dose interruption*	50 (83.3)	206 (60.9)
Adverse events leading to dose reduction*	47 (78.3)	185 (54.7)

* Adverse events leading to discontinuation, dose interruption, or dose reduction of talazoparib or enzalutamide

Averse events of any grade reported at a ≥10% higher incidence in Japanese patients than in non-Japanese patients were anaemia (45 subjects [75.0%] in the Japanese subgroup, 217 subjects [64.2%] in the non-Japanese subgroup), neutrophil count decreased (35 subjects [58.3%], 107 subjects [31.7%]), platelet count decreased (22 subjects [36.7%], 76 subjects [22.5%]), malaise (21 subjects [35.0%], 4 subjects [1.2%]), white blood cell count decreased (19 subjects [31.7%], 69 subjects [20.4%]), fall (17 subjects [28.3%], 54 subjects [16.0%]), lymphocyte count decreased (16 subjects [26.7%], 29 subjects [8.6%]), and pyrexia (11 subjects [18.3%], 18 subjects [5.3%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were anaemia (33 subjects [55.0%], 152 subjects [45.0%]), neutrophil count decreased (23 subjects [38.3%], 50 subjects [14.8%]), white blood cell count decreased (8 subjects [13.3%], 17 subjects [5.0%]), and lymphocyte count decreased (6 subjects [10.0%], 14 subjects [4.1%]). Adverse events leading to dose interruption of either study drug[61)] reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were anaemia (33 subjects [55.0%], 148 subjects [43.8%]), neutrophil count decreased (17 subjects [28.3%], 39 subjects [11.5%]), decreased appetite (9 subjects [15.0%], 6 subjects [1.8%]), white blood cell count decreased (6 subjects [10.0%], 16 subjects [4.7%]), and malaise (3 subjects [5.0%], 0 subjects). Adverse events leading to dose reduction of either study drug[61)] reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were anaemia (31 subjects [51.7%], 146 subjects [43.2%]), neutrophil count decreased (21 subjects [35.0%], 43 subjects [12.7%]), decreased appetite (8 subjects [13.3%], 4 subjects [1.2%]), and malaise (3 subjects [5.0%], 0 subjects).

There were no adverse events leading to death, serious adverse events, or adverse events leading to discontinuation of either study drug [61)] that were reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

[61)] Talazoparib or enzalutamide

PMDA's discussion:
Although the number of Japanese patients evaluated in Part 2 (Cohort 1) of the TALAPRO-2 study was limited, and there are limitations to rigorous comparison of safety between Japanese and non-Japanese populations, the incidences of adverse events of anaemia etc. were higher in the Japanese subgroup than in the non-Japanese subgroup, and attention should be paid to the possible occurrence of these events during treatment with talazoparib. However, as to anaemia, there was no trend towards clearly higher incidences of adverse events leading to death and serious adverse events in the Japanese subgroup than in the non-Japanese subgroup, and talazoparib will be used by physicians with adequate knowledge of and experience in cancer chemotherapy. Given these points, talazoparib/enzalutamide is tolerable also in Japanese patients.

7.2.R.4 Clinical positioning and indication

The proposed indication for talazoparib is "castration-resistant prostate cancer." The following statement is included in the PRECAUTIONS CONCERNING INDICATIONS section of the proposed package insert.

- The efficacy and safety of talazoparib in the adjuvant setting have not been established.

PMDA's conclusion:
On the basis of Sections "7.2.R.2 Efficacy" and "7.2.R.3 Safety" and the considerations in the following section, the following statements should be included in the PRECAUTIONS CONCERNING INDICATIONS section, and then the appropriate indication for talazoparib should be "*BRCA*-mutated metastatic castration-resistant prostate cancer."

- The efficacy and safety of talazoparib in the adjuvant setting have not been established.
- Talazoparib should be used in patients with a *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

7.2.R.4.1 Clinical positioning of talazoparib/enzalutamide and indication

There is no mention of talazoparib/enzalutamide for patients with mCRPC who have received no prior systemic therapy for mCRPC in the Japanese and foreign clinical practice guidelines or the major textbooks of clinical oncology.

The applicant's explanation about the clinical positioning of talazoparib/enzalutamide and the indication:
Since the TALAPRO-2 study in patients with mCRPC who had received no prior systemic therapy for mCRPC demonstrated the clinical usefulness of talazoparib/enzalutamide, regardless of HRR gene mutation status [see Sections 7.2.R.2 and 7.2.R.3], talazoparib/enzalutamide is positioned as a treatment option for these patients. As to when to use talazoparib or the currently approved drugs, abiraterone or docetaxel, in these patients, although there are no clinical study data comparing the efficacy and safety of talazoparib/enzalutamide versus these agents at present, given that the median OS in the talazoparib group in the all comers population (patients unselected for HRR mutation status) of the TALAPRO-2 study was longer than the median OS with

abiraterone or docetaxel in foreign phase III studies (Study COU-AA-302[62)] and Study TAX-327[63)]), etc., talazoparib/enzalutamide should be preferred over abiraterone or docetaxel.

On the basis of the above, the following statement was included in the PRECAUTIONS CONCERNING INDICATIONS section, and then the indication of "castration-resistant prostate cancer" was proposed.

- The efficacy and safety of talazoparib in the adjuvant setting have not been established.

PMDA's discussion:

Given that the TALAPRO-2 study in patients with mCRPC who had received no prior systemic therapy for mCRPC demonstrated the clinical usefulness of talazoparib/enzalutamide [see Sections 7.2.R.2 and 7.2.R.3] and based on the considerations in Sections "7.2.R.2.4 Results of efficacy assessment" and "7.2.R.3 Safety," the efficacy of talazoparib/enzalutamide is expected in patients with *BRCA*-mutated mCRPC who have received no prior systemic therapy for mCRPC, and talazoparib/enzalutamide is clinically meaningful for these patients. On the other hand, it cannot be concluded that the expected therapeutic benefits outweigh the possible risks in non-*BRCA*-mutated HRR-deficient patients and HRR gene mutation-negative (non-HRR-deficient) patients. Thus, the INDICATIONS section should clarify that talazoparib/enzalutamide is indicated for patients with *BRCA*-mutated metastatic CRPC.

On the basis of the above, the proposed statement regarding talazoparib use as adjuvant therapy should be included in the PRECAUTIONS CONCERNING INDICATIONS section, and then the appropriate indication should be "*BRCA*-mutated metastatic castration-resistant prostate cancer."

Since there are no clinical study data comparing the efficacy and safety of talazoparib/enzalutamide versus the currently approved drugs, abiraterone or docetaxel, which drug should be preferred is unknown at present, and appropriate treatment should be chosen according to individual patients' conditions.

7.2.R.4.2 *BRCA* mutation test and target population for talazoparib

On the basis of the results of the TALAPRO-2 study, talazoparib/enzalutamide was considered clinically meaningful for patients with *BRCA*-mutated mCRPC (Section 7.2.R.4.1). PMDA asked the applicant to explain *BRCA* mutation test to be used for selection of eligible patients.

The applicant's response:

In the TALAPRO-2 study, Foundation Medicine's "FoundationOne CDx" for analysis of tumor tissue was used as a test at the central laboratory for patient enrollment, and the efficacy of talazoparib is expected in patients tested positive for *BRCA* mutations in the TALAPRO-2 study. Thus, Chugai Pharmaceutical Co., Ltd.'s

[62)] In a foreign phase III study to compare the efficacy and safety of abiraterone plus prednisolone versus prednisolone in patients with mCRPC who had received no prior systemic therapy for mCRPC, the median OS [95% CI] (months) in the abiraterone plus prednisolone group was 34.7 [32.7, 36.8].

[63)] In a foreign phase III study to compare the efficacy and safety of docetaxel plus prednisolone versus mitoxantrone plus prednisolone in patients with mCRPC who had received no prior systemic therapy for mCRPC, the median OS [95% CI] (months) in the docetaxel plus prednisolone group was 18.9 [17.0, 21.2].

"FoundationOne CDx Cancer Genomic Profile" should be used for selection of patients after the market launch of talazoparib.

The future development of "[redacted]" for analysis of plasma samples is under consideration.

PMDA's discussion:
PMDA accepted the above explanation by the applicant and concluded that the following statement should be included in the PRECAUTIONS CONCERNING INDICATIONS section.

- Talazoparib should be used in patients with a *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

7.2.R.5 Dosage and administration

The proposed dosage and administration statement is "The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition." After regulatory submission, the applicant explained that the proposed statements in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section would be amended as follows.

[All indications]

- If a patient vomits or misses a dose of talazoparib, the next prescribed dose should be taken at the usual time. Do not take a double dose per day.
- Recommended dosage modifications for adverse reactions
- The recommended starting dose of talazoparib in patients with renal impairment

[Castration-resistant prostate cancer]

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.
- The efficacy and safety of talazoparib in patients not surgically or medically castrated have not been established.
- Do not use the 0.1-mg capsule to administer a 0.5 mg dose of talazoparib because the bioequivalence between the 0.1-mg and 0.25-mg capsules has not been demonstrated.

PMDA's conclusion:
On the basis of the results of a food effect study of talazoparib [see Section 6.1.1.1], Sections "6.R.3 Use of talazoparib in patients with renal impairment," "7.2.R.2 Efficacy," and "7.2.R.3 Safety," and the considerations in the following section, the statements in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section should be presented by indication, instead of presenting the statements for all indications, and the following statements for mCRPC should be included. Then, the proposed dosage and administration statement of "The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in

combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition." is appropriate.

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.
- The efficacy and safety of talazoparib in patients not surgically or medically castrated have not been established.
- For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the recommended starting dose of talazoparib is 0.35 mg once daily.
- Do not use the 0.1-mg capsule to administer a 0.5 mg dose of talazoparib because the bioequivalence between the 0.1-mg and 0.25-mg capsules has not been demonstrated.
- Recommended dosage modifications for adverse reactions

Recommended dosage modifications for adverse reactions are discussed in Section "7.R.2 Recommended dosage modifications for talazoparib."

7.2.R.5.1 Dosing regimen of talazoparib

The applicant's explanation about the dosing rationale for talazoparib for CRPC:

In Part 1 of the TALAPRO-2 study, based on evaluation of the safety etc. of talazoparib/enzalutamide, talazoparib 0.5 mg QD was selected as the RP2D. Thus, this dosing regimen was selected for the talazoparib group in Part 2 of the TALAPRO-2 study. Since Part 2 of the TALAPRO-2 study demonstrated the clinical usefulness of talazoparib/enzalutamide in patients with mCRPC who had received no prior systemic therapy for mCRPC, the dosing regimen of talazoparib for prostate cancer was selected based on Part 2 of the TALAPRO-2 study.

Since no clinical study has evaluated the clinical usefulness of talazoparib in combination with anti-neoplastic drugs other than enzalutamide in patients with mCRPC, the DOSAGE AND ADMINISTRATION section should specify that talazoparib is taken in combination with enzalutamide, and the following precautionary statement should be included in the package insert: The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.

As to the starting dose of talazoparib in patients with renal impairment in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert, based on the results of the TALAPRO-2 study etc. [see Section 6.R.3], a starting dose of talazoparib 0.35 mg QD was recommended for patients with moderate renal impairment (CLcr ≥30 mL/min and <60 mL/min), and a starting dose of talazoparib 0.25 mg QD was recommended for patients with severe renal impairment (CLcr ≥15 mL/min and <30 mL/min).

On the basis of the above, the following statements were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the dosage administration statement of "The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition." was proposed.

[All indications]

- If a patient vomits or misses a dose of talazoparib, the next prescribed dose should be taken at the usual time. Do not take a double dose per day.
- Recommended dosage modifications for adverse reactions
- For patients with renal impairment, adjust the starting dose of talazoparib based on CLcr as per the table below (for prostate cancer).

Starting dose of talazoparib

CLcr (mL/min)	Castration-resistant prostate cancer
≥60	0.5 mg once daily
≥30 and <60	0.35 mg once daily
≥15 and <30	0.25 mg once daily

[Castration-resistant prostate cancer]

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.
- The efficacy and safety of talazoparib in patients not surgically or medically castrated have not been established.
- Do not use the 0.1-mg capsule to administer a 0.5 mg dose of talazoparib because the bioequivalence between the 0.1-mg and 0.25-mg capsules has not been demonstrated.

PMDA's discussion:
PMDA accepted the applicant's explanation about talazoparib in combination with other anti-neoplastic drugs.

As to the starting dose of talazoparib in patients with renal impairment in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert, based on the considerations in Section "6.R.3 Use of talazoparib in patients with renal impairment," information on the starting dose of talazoparib in patients with severe renal impairment should be deleted, and the severity of renal impairment should be defined by eGFR. Then, a precautionary statement regarding the starting dose of talazoparib in patients with moderate renal impairment should be included.

Since the bioequivalence between the 0.1-mg and 0.25-mg capsules has not been demonstrated at present [see Section 6.R.2], the use of the 0.1-mg capsule interchangeably with the 0.25-mg capsule is not recommended.

Since advice in case of vomiting or missing dose is general information, there is no need to include this information in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the package insert.

On the basis of the above, the statements in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section should be presented by indication. The following statements for patients

with mCRPC should be included, and then the proposed dosage and administration statement of "The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition." is appropriate.

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.
- The efficacy and safety of talazoparib in patients not surgically or medically castrated have not been established.
- For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the recommended starting dose of talazoparib is 0.35 mg once daily.
- Do not use the 0.1-mg capsule to administer a 0.5 mg dose of talazoparib because the bioequivalence between the 0.1-mg and 0.25-mg capsules has not been demonstrated.
- Recommended dosage modifications for adverse reactions

7.R.1 Safety (Events that require attention following administration of talazoparib, etc.)

In the following sections, based on the safety results etc. from the EMBRACA study, the expansion part of Study 030, and Part 2 (Cohort 1) of the TALAPRO-2 study, PMDA examined events that require attention following administration of talazoparib, etc.

7.R.1.1 Myelosuppression

The applicant's explanation about myelosuppression associated with talazoparib:

In the EMBRACA study and the expansion part of Study 030, events in the MedDRA SMQ "haematopoietic cytopenias (narrow)" and MedDRA PTs "anaemia," "haematocrit decreased," "haemoglobin decreased," and "normochromic normocytic anaemia" were counted as myelosuppression. In Part 2 (Cohort 1) of the TALAPRO-2 study, MedDRA PTs "anaemia," "haematocrit decreased," "haemoglobin decreased," "red blood cell count decreased," "thrombocytopenia," "platelet count decreased," "neutrophil count decreased," "neutropenia," "agranulocytosis," "granulocyte count decreased," "granulocytopenia," "febrile neutropenia," "neutrophil percentage decreased," "band neutrophil count decreased," "band neutrophil percentage decreased," "neutropenic sepsis," "neutropenic infection," "neutrophil count abnormal," "white blood cell count decreased," "leukopenia," "lymphopenia," and "lymphocyte count decreased" were counted as myelosuppression.

The incidences of myelosuppression in the EMBRACA study and the expansion part of Study 030 and the incidence of myelosuppression in Part 2 (Cohort 1) of the TALAPRO-2 study are shown in Table 54 and Table 55, respectively.

Table 54. Incidence of myelosuppression (EMBRACA study and expansion part of Study 030)

PT (MedDRA ver.25.0)	n (%)					
	EMBRACA study				Expansion part of Study 030 N = 19	
	Talazoparib N = 286		Chemotherapy N = 126			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression	201 (70.3)	163 (57.0)	64 (50.8)	49 (38.9)	17 (89.5)	10 (52.6)
Anaemia	155 (54.2)	115 (40.2)	24 (19.0)	6 (4.8)	13 (68.4)	9 (47.4)
Neutropenia	78 (27.3)	54 (18.9)	38 (30.2)	31 (24.6)	0	0
Thrombocytopenia	50 (17.5)	23 (8.0)	7 (5.6)	2 (1.6)	0	0
Platelet count decreased	36 (12.6)	19 (6.6)	4 (3.2)	0	6 (31.6)	0
White blood cell count decreased	32 (11.2)	11 (3.8)	5 (4.0)	4 (3.2)	8 (42.1)	2 (10.5)
Neutrophil count decreased	30 (10.5)	13 (4.5)	18 (14.3)	13 (10.3)	12 (63.2)	4 (21.1)
Leukopenia	24 (8.4)	10 (3.5)	12 (9.5)	7 (5.6)	0	0
Lymphocyte count decreased	13 (4.5)	6 (2.1)	2 (1.6)	0	1 (5.3)	0
Lymphopenia	13 (4.5)	5 (1.7)	2 (1.6)	1 (0.8)	0	0
Haematocrit decreased	5 (1.7)	0	1 (0.8)	0	0	0
Haemoglobin decreased	5 (1.7)	2 (0.7)	0	0	0	0
Red blood cell count decreased	5 (1.7)	1 (0.3)	1 (0.8)	0	0	0
Pancytopenia	3 (1.0)	2 (0.7)	0	0	0	0
Febrile neutropenia	1 (0.3)	1 (0.3)	1 (0.8)	1 (0.8)	0	0
Monocyte count decreased	0	0	1 (0.8)	0	0	0

Table 55. Incidence of myelosuppression [Part 2 (Cohort 1) of TALAPRO-2 study]

PT (MedDRA ver.25.0)	n (%)			
	Talazoparib N = 398		Placebo N = 401	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression	291 (73.1)	228 (57.3)	114 (28.4)	29 (7.2)
Anaemia	262 (65.8)	185 (46.5)	70 (17.5)	17 (4.2)
Neutrophil count decreased	142 (35.7)	73 (18.3)	28 (7.0)	6 (1.5)
Platelet count decreased	98 (24.6)	29 (7.3)	14 (3.5)	4 (1.0)
White blood cell count decreased	88 (22.1)	25 (6.3)	18 (4.5)	0
Lymphocyte count decreased	45 (11.3)	20 (5.0)	20 (5.0)	4 (1.0)
Haematocrit decreased	4 (1.0)	0	2 (0.5)	0
Red blood cell count decreased	3 (0.8)	0	4 (1.0)	0
Haemoglobin decreased	2 (0.5)	1 (0.3)	0	0
Leukopenia	2 (0.5)	0	2 (0.5)	0
Thrombocytopenia	1 (0.3)	0	0	0
Neutrophil percentage decreased	1 (0.3)	0	0	0
Lymphopenia	0	0	3 (0.7)	0
Neutropenia	0	0	1 (0.2)	0

In the EMBRACA study, serious myelosuppression occurred in 26 of 286 subjects (9.1%) in the talazoparib group (anaemia [18 subjects]; platelet count decreased [4 subjects]; neutropenia [3 subjects]; thrombocytopenia; and pancytopenia [2 subjects each]; and leukopenia; febrile neutropenia; and neutrophil count decreased [1 subject each] [some patients had more than 1 event]) and 6 of 126 subjects (4.8%) in the chemotherapy group (neutropenia [4 subjects]; neutrophil count decreased [2 subjects]; and febrile neutropenia [1 subject] [some patients had more than 1 event]). A causal relationship to study drug could not be ruled out for anaemia (16 subjects); platelet count decreased; and neutropenia (3 subjects each); thrombocytopenia (2 subjects); and pancytopenia; leukopenia; febrile neutropenia; and neutrophil count decreased (1 subject each) in the talazoparib group and neutropenia (4 subjects); neutrophil count decreased (2 subjects); and febrile neutropenia (1 subject) in the chemotherapy group. Myelosuppression leading to treatment

discontinuation occurred in 5 of 286 subjects (1.7%) in the talazoparib group (anaemia [3 subjects]; and thrombocytopenia; and neutropenia [1 subject each]) and 1 of 126 subjects (0.8%) in the chemotherapy group (neutropenia [1 subject]). Myelosuppression leading to dose interruption occurred in 159 of 286 subjects (55.6%) in the talazoparib group (anaemia [105 subjects]; neutropenia [53 subjects]; thrombocytopenia [29 subjects]; platelet count decreased [19 subjects]; neutrophil count decreased; and white blood cell count decreased [15 subjects each]; leukopenia [10 subjects]; lymphopenia; and lymphocyte count decreased [7 subjects each]; haemoglobin decreased [4 subjects]; and febrile neutropenia [1 subject] [some patients had more than 1 event]) and 28 of 126 subjects (22.2%) in the chemotherapy group (neutropenia [16 subjects]; neutrophil count decreased [11 subjects]; leukopenia; and white blood cell count decreased [3 subjects each]; anaemia [2 subjects]; and thrombocytopenia; lymphopenia; and platelet count decreased [1 subject each] [some patients had more than 1 event]). Myelosuppression leading to dose reduction occurred in 50 of 286 subjects (17.5%) in the talazoparib group (anaemia [33 subjects]; thrombocytopenia; and neutropenia [8 subjects each]; leukopenia; neutrophil count decreased; and white blood cell count decreased [2 subjects each]; and lymphopenia; haematocrit decreased; lymphocyte count decreased; and platelet count decreased [1 subject each] [some patients had more than 1 event]) and 8 of 126 subjects (6.3%) in the chemotherapy group (neutropenia [3 subjects]; neutrophil count decreased [2 subjects]; and anaemia; leukopenia; and febrile neutropenia [1 subject each]). No myelosuppression leading to death was reported. In the talazoparib group, 112 patients (39.2%) received RBC transfusion, 10 patients (3.5%) received a platelet transfusion, and 25 patients (8.7%) received immunostimulants including growth factor support.

In the expansion part of Study 030, myelosuppression leading to dose interruption occurred in 7 of 19 subjects (36.8%) (anaemia [6 subjects]; and neutrophil count decreased [2 subjects] [some patients had more than 1 event]). Myelosuppression leading to dose reduction occurred in 9 of 19 subjects (47.4%) (anaemia [8 subjects]; neutrophil count decreased [4 subjects]; and platelet count decreased [1 subject] [some patients had more than 1 event]). There was no myelosuppression leading to death, serious myelosuppression, or myelosuppression leading to treatment discontinuation. Five patients (26.3%) received RBC transfusion, and no patients received platelet transfusions or immunostimulants including growth factor support.

In Part 2 (Cohort 1) of the TALAPRO-2 study, serious myelosuppression occurred in 58 of 398 subjects (14.6%) in the talazoparib group (anaemia [55 subjects]; platelet count decreased [4 subjects]; neutrophil count decreased [3 subjects]; and haemoglobin decreased [1 subject] [some patients had more than 1 event]) and 2 of 401 subjects (0.5%) in the placebo group (anaemia; and platelet count decreased [1 subject each]). A causal relationship to study drug could not be ruled out for anaemia (50 subjects); platelet count decreased (4 subjects); neutrophil count decreased (3 subjects); and haemoglobin decreased (1 subject) in the talazoparib group and platelet count decreased (1 subject) in the placebo group. Myelosuppression leading to discontinuation of any study drug [60)] occurred in 43 of 398 subjects (10.8%) in the talazoparib group (anaemia [33 subjects]; neutrophil count decreased [13 subjects]; platelet count decreased [2 subjects]; and white blood cell count decreased [1 subject] [some patients had more than 1 event]) and 8 of 401 subjects (2.0%) in the placebo group (anaemia [6 subjects]; and platelet count decreased [2 subjects]). Myelosuppression leading to

dose interruption of any study drug[60)] occurred in 205 of 398 subjects (51.5%) in the talazoparib group (anaemia [181 subjects]; neutrophil count decreased [56 subjects]; platelet count decreased [31 subjects]; white blood cell count decreased [22 subjects]; lymphocyte count decreased [2 subjects]; and haemoglobin decreased [1 subject] [some patients had more than 1 event]) and 18 of 401 subjects (4.5%) in the placebo group (anaemia [10 subjects]; neutrophil count decreased [5 subjects]; and lymphopenia; platelet count decreased; white blood cell count decreased; lymphocyte count decreased; and red blood cell count decreased [1 subject each] [some patients had more than 1 event]). Myelosuppression leading to dose reduction of any study drug[60)] occurred in 207 of 398 subjects (52.0%) in the talazoparib group (anaemia [177 subjects]; neutrophil count decreased [64 subjects]; platelet count decreased [24 subjects]; white blood cell count decreased [9 subjects]; and lymphocyte count decreased [1 subject] [some patients had more than 1 event]) and 10 of 401 subjects (2.5%) in the placebo group (anaemia [5 subjects]; neutrophil count decreased [4 subjects]; and platelet count decreased; and white blood cell count decreased [1 subject each] [some patients had more than 1 event]). No myelosuppression leading to death was reported. In the talazoparib group, 156 patients (39.2%) received RBC transfusion, 13 patients (3.3%) received a platelet transfusion, and 36 patients (9.0%) received immunostimulants including growth factor support.

The median times to the first onset of myelosuppression (min., max.) (days) in the talazoparib and chemotherapy groups of the EMBRACA study, the expansion part of Study 030, and the talazoparib and placebo groups in Part 2 (Cohort 1) of the TALAPRO-2 study were 47 (1, 1,541), 15 (1, 384), 29 (1, 253), 71 (1, 869), and 84 (1, 978), respectively.

In the EMBRACA study and Part 2 (Cohort 1) of the TALAPRO-2 study, the details of patients with serious Grade ≥4 myelosuppression related to talazoparib are shown in Table 56. In the expansion part of Study 030, no patients experienced serious Grade ≥4 myelosuppression related to talazoparib.

Table 56. Listing of patients with serious Grade ≥4 myelosuppression related to talazoparib

Study ID	Age	Sex	Dosing regimen	PT*	Time to onset (days)	Duration (days)	Action taken with talazoparib	Outcome
EMBRACA	3[redacted]	F	1 mg QD	Leukopenia	24	5	None	Resolved
				Neutropenia	34	8	Interrupted	Resolved
				Leukopenia	34	8	Interrupted	Resolved
			0.75 mg QD	Neutropenia	91	6	Unknown	Resolved
				Anaemia	91	2	Unknown	Resolved
	3[redacted]	F	1 mg QD	Neutropenia	26	3	Interrupted	Resolved
	5[redacted]	F	1 mg QD	Pancytopenia	1,708	10	Unknown	Resolved
	3[redacted]	F	1 mg QD	Febrile neutropenia	36	15	Interrupted	Resolved
	3[redacted]	F	0.75 mg QD	Thrombocytopenia	177	12	Discontinued	Resolved
	4[redacted]	F	1 mg QD	Thrombocytopenia	17	2	Interrupted	Resolved
	7[redacted]	F	1 mg QD	Platelet count decreased	27	1	Interrupted	Resolved
				Neutrophil count decreased	28	1	Interrupted	Resolved
TALAPRO-2 Part 2 (Cohort 1)	6[redacted]	M	0.5 mg QD	Anaemia	119	2	Interrupted	Resolved
	8[redacted]	M	0.5 mg QD	Anaemia	56	5	Interrupted	Resolved
	7[redacted]	M	0.5 mg QD	Anaemia	36	2	Interrupted	Resolved
	6[redacted]	M	0.5 mg QD	Anaemia	170	2	Interrupted	Resolved
	7[redacted]	M	0.5 mg QD	Anaemia	141	9	Discontinued	Resolved
	7[redacted]	M	0.35 mg QD	Anaemia	101	8	Interrupted	Resolved
	6[redacted]	M	0.35 mg QD	Anaemia	863	11	Interrupted	Resolved
	5[redacted]	M	0.5 mg QD	Platelet count decreased	69	1	Interrupted	Resolved
	8[redacted]	M	0.5 mg QD	Anaemia	112	4	Interrupted	Resolved
	7[redacted]	M	0.1 mg QD	Anaemia	196	3	Interrupted	Resolved
	7[redacted]	M	0.5 mg QD	Anaemia	97	5	Interrupted	Resolved
	7[redacted]	M	0.5 mg QD	Platelet count decreased	31	9	Dose reduced	Resolved
			0.35 mg QD	Platelet count decreased	87	15	Dose reduced	Resolved
	7[redacted]	M	0.35 mg QD	Anaemia	170	2	Interrupted	Resolved

* MedDRA ver.25.0

PMDA's discussion:

In the EMBRACA study and Part 2 (Cohort 1) of the TALAPRO-2 study, the incidence of myelosuppression was higher in the talazoparib group than in the control group (the chemotherapy or placebo group). The incidence of anaemia was particularly high, and serious events of anaemia that required transfusions etc. were also reported. In the clinical studies submitted, serious myelosuppression for which a causal relationship to talazoparib could not be ruled out was reported. Myelosuppression is a known risk associated with other PARP inhibitors. Given these points, attention should be paid to the possible occurrence of myelosuppression during treatment with talazoparib. Thus, the package insert etc. should appropriately advise healthcare professionals in clinical practice about the incidence and management of myelosuppression, etc., in the clinical studies.

7.R.1.2 ILD

The applicant's explanation about ILD associated with talazoparib:

Events in the MedDRA SMQ "interstitial lung disease (narrow)" were counted as ILD.

Table 57 shows the incidence of ILD in Part 2 (Cohort 1) of the TALAPRO-2 study. No ILD was reported in the EMBRACA study or the expansion part of Study 030.

Table 57. Incidence of ILD (Part 2 of TALAPRO-2 study)

PT (MedDRA ver.25.0)	n (%)			
	Talazoparib N = 398		Placebo N = 401	
	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD	6 (1.5)	1 (0.3)	1 (0.2)	0
Interstitial lung disease	2 (0.5)	1 (0.3)	0	0
Idiopathic interstitial pneumonia	1 (0.3)	0	0	0
Lung infiltration	1 (0.3)	0	0	0
Pneumonitis	1 (0.3)	0	0	0
Pulmonary toxicity	1 (0.3)	0	0	0
Bronchiolitis	0	0	1 (0.2)	0

In Part 2 (Cohort 1) of the TALAPRO-2 study, serious ILD occurred in 1 of 398 subjects (0.3%) in the talazoparib group (interstitial lung disease), and its causal relationship to study drug could not be ruled out (none in the placebo group). ILD leading to discontinuation of any study drug [60)] occurred in 1 of 398 subjects (0.3%) in the talazoparib group (interstitial lung disease) (none in the placebo group). ILD leading to dose interruption of any study drug[60)] occurred in 3 of 398 subjects (0.8%) in the talazoparib group (interstitial lung disease; pneumonitis; and pulmonary toxicity [1 subject each]) (none in the placebo group). ILD leading to dose reduction of any study drug[60)] occurred in 1 of 398 subjects (0.3%) in the talazoparib group (idiopathic interstitial pneumonia) (none in the placebo group). No ILD leading to death was reported.

The median times to the first onset of ILD (min., max.) (days) in the talazoparib and placebo groups in Part 2 (Cohort 1) of the TALAPRO-2 study were 554.5 (111, 917) and 665 (665, 665), respectively.

In all clinical studies with talazoparib including the above clinical study, the details of patients with serious ILD related to talazoparib are shown in Table 58. In the overseas marketing experience, no patients experienced serious ILD for which a causal relationship to talazoparib could not be ruled out.

Table 58. Listing of patients with serious ILD related to talazoparib

Study ID	Age	Sex	Dosing regimen	PT[*1]	Grade	Time to onset (days)	Duration (days)	Action taken with talazoparib	Outcome
TALAPRO-2 Part 2 (Cohort 1)	7[redacted]	M	0.5 mg QD	Interstitial lung disease	3	694	10	Interrupted	Resolved
TALASUR[*2]	6[redacted]	M	0.75 mg QD	Interstitial lung disease	Unknown	50	Unknown	Discontinued	Not resolved

*1 MedDRA ver.25.0; *2 A foreign phase II study in patients with urothelial carcinoma

PMDA's discussion:

Given that serious ILD for which a causal relationship to talazoparib could not be ruled out was reported in the clinical studies submitted, and that ILD is a known risk associated with other PARP inhibitors, attention should be paid to the possible occurrence of ILD during treatment with talazoparib. Thus, the package insert etc. should appropriately advise healthcare professionals in clinical practice about the incidence of ILD in the clinical studies.

7.R.1.3 Thromboembolism

The applicant's explanation about thromboembolism associated with talazoparib:

Events in the MedDRA HLGT "embolism and thrombosis," events in the MedDRA SMQs "embolic and thrombotic events, arterial (narrow)," "embolic and thrombotic events, venous (narrow)," and "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous," and MedDRA PTs "ischaemia," "peripheral ischaemia," and "phlebitis" were counted as thromboembolism.

The incidences of thromboembolism in the EMBRACA study and Part 2 (Cohort 1) of the TALAPRO-2 study are shown in Table 59 and Table 60, respectively. In the expansion part of Study 030, no thromboembolism was reported.

Table 59. Incidence of thromboembolism (EMBRACA study)

PT (MedDRA ver.25.0)	n (%)			
	Talazoparib N = 286		Chemotherapy N = 126	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Thromboembolism	19 (6.6)	12 (4.2)	9 (7.1)	1 (0.8)
Pulmonary embolism	9 (3.1)	9 (3.1)	1 (0.8)	1 (0.8)
Thrombosis	3 (1.0)	0	1 (0.8)	0
Deep vein thrombosis	3 (1.0)	1 (0.3)	4 (3.2)	0
Venoocclusive liver disease	1 (0.3)	1 (0.3)	0	0
Jugular vein thrombosis	1 (0.3)	0	0	0
Embolism	1 (0.3)	0	0	0
Phlebitis	1 (0.3)	0	1 (0.8)	0
Arterial thrombosis	1 (0.3)	1 (0.3)	0	0
Transient ischaemic attack	1 (0.3)	1 (0.3)	0	0
Monoparesis	1 (0.3)	0	0	0
Thrombosis in device	1 (0.3)	0	1 (0.8)	0
Portal vein thrombosis	0	0	1 (0.8)	0
Pelvic venous thrombosis	0	0	1 (0.8)	0
Venous thrombosis	0	0	1 (0.8)	0
Vena cava thrombosis	0	0	1 (0.8)	0
Cerebrovascular accident	0	0	1 (0.8)	1 (0.8)

Table 60. Incidence of thromboembolism [Part 2 (Cohort 1) of TALAPRO-2 study]

PT (MedDRA ver.25.0)	n (%)			
	Talazoparib N = 398		Placebo N = 401	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Thromboembolism	16 (4.0)	10 (2.5)	3 (0.7)	3 (0.7)
Pulmonary embolism	10 (2.5)	9 (2.3)	3 (0.7)	3 (0.7)
Deep vein thrombosis	2 (0.5)	0	0	0
Jugular vein thrombosis	1 (0.3)	1 (0.3)	0	0
Venous thrombosis	1 (0.3)	0	0	0
Venous embolism	1 (0.3)	0	0	0
Superficial vein thrombosis	1 (0.3)	0	0	0
Renal vein thrombosis	1 (0.3)	0	0	0

In the EMBRACA study, thromboembolism leading to death occurred in 1 of 286 subjects (0.3%) in the talazoparib group (venoocclusive liver disease), and its causal relationship to study drug could not be ruled out (none in the chemotherapy group). Serious thromboembolism occurred in 9 of 286 subjects (3.1%) in the talazoparib group (pulmonary embolism [6 subjects]; and venoocclusive liver disease; deep vein thrombosis;

and transient ischaemic attack [1 subject each]) and 3 of 126 subjects (2.4%) in the chemotherapy group (deep vein thrombosis [2 subjects]; and cerebrovascular accident [1 subject]). A causal relationship to study drug could not be ruled out for pulmonary embolism; and venoocclusive liver disease (1 subject each) in the talazoparib group. Thromboembolism leading to treatment discontinuation occurred in 1 of 286 subjects (0.3%) in the talazoparib group (transient ischaemic attack) (none in the chemotherapy group). Thromboembolism leading to dose interruption occurred in 5 of 286 subjects (1.7%) in the talazoparib group (pulmonary embolism [4 subjects]; and deep vein thrombosis [1 subject]) and 1 of 286 subjects (0.8%) in the chemotherapy group (cerebrovascular accident). No thromboembolism leading to dose reduction was reported.

In Part 2 (Cohort 1) of the TALAPRO-2 study, serious thromboembolism occurred in 8 of 398 subjects (2.0%) in the talazoparib group (pulmonary embolism [6 subjects]; and jugular vein thrombosis; deep vein thrombosis; and renal vein thrombosis [1 subject each] [some patients had more than 1 event]) and 2 of 401 subjects (0.5%) in the placebo group (pulmonary embolism [2 subjects]). A causal relationship to study drug could not be ruled out for pulmonary embolism (2 subjects); and renal vein thrombosis (1 subject) in the talazoparib group and pulmonary embolism (1 subject) in the placebo group. Thromboembolism leading to discontinuation of any study drug[60)] occurred in 2 of 398 subjects (0.5%) in the talazoparib group (jugular vein thrombosis; and pulmonary embolism [1 subject each]) (none in the placebo group). Thromboembolism leading to dose interruption of any study drug[60)] occurred in 3 of 398 subjects (0.8%) in the talazoparib group (pulmonary embolism [3 subjects]; and deep vein thrombosis [1 subject]) (none in the placebo group). There was no thromboembolism leading to death or dose reduction of any study drug.

The median times to the first onset of thromboembolism (min., max.) (days) in the talazoparib and chemotherapy groups of the EMBRACA study and the talazoparib and placebo groups in Part 2 (Cohort 1) of the TALAPRO-2 study were 145 (15, 966), 41 (9, 135), 141.5 (14, 532), and 242 (51, 511), respectively.

In all clinical studies with talazoparib including the above clinical studies and the overseas marketing experience, the details of patients with serious thromboembolism related to talazoparib are shown in Table 61.

Table 61. Listing of patients with serious thromboembolism related to talazoparib

Study ID	Age	Sex	Dosing regimen	PT[*1]	Grade	Time to onset (days)	Duration (days)	Action taken with talazoparib	Outcome
EMBRACA	3[redacted]	F	0.75 mg QD	Venoocclusive liver disease	3	186	6	Unknown	Resolved
				Venoocclusive liver disease	5	192	1	Unknown	Fatal
	6[redacted]	F	1 mg QD	Pulmonary embolism	3	240	35	Interrupted	Resolved
TALAPRO-2 Part 2 (Cohort 1)	7[redacted]	M	0.25 mg QD	Pulmonary embolism	3	344	80	Discontinued	Resolved
	6[redacted]	M	0.5 mg QD	Pulmonary embolism	3	106	4	None	Resolved
Talazoparib-IST[*2]	6[redacted]	M	Unknown	Pulmonary embolism	3	309	63	None	Resolved
006	6[redacted]	M	1 mg QD	Pulmonary embolism	Unknown	51	57	None	Resolved
B9991033[*3]	5[redacted]	F	0.75 mg QD	Pulmonary embolism	Unknown	15	Unknown	Discontinued	Not resolved
				Deep vein thrombosis	Unknown	15	Unknown	Discontinued	Not resolved
WI204033[*4]	5[redacted]	M	1 mg QD	Myocardial infarction	3	Unknown	Unknown	Discontinued	Resolved
MedOPP234[*5]	7[redacted]	M	0.5 mg QD	Pulmonary embolism	3	253	106	Interrupted	Resolved
				Pulmonary infarction	3	253	106	Interrupted	Resolved
	8[redacted]	M	0.5 mg QD	Acute myocardial infarction	3	66	21	Discontinued	Resolved
C3441047[*6]	4[redacted]	F	Unknown	Device related thrombosis	Unknown	Unknown	Unknown	Unknown	Fatal
UW-20396[*7]	5[redacted]	M	0.5 mg QD	Pulmonary embolism	4	48	1	Discontinued	Resolved
20476[*8]	6[redacted]	M	1 mg QD	Pulmonary embolism	Unknown	161	Unknown	Interrupted	Not resolved

*1 MedDRA ver.25.0; *2 A general term that refers to any study not conducted by the applicant; *3 A foreign phase I/II study in patients with advanced solid tumors; *4 A foreign phase II study in patients with advanced solid tumors; *5 A foreign phase II study in prostate cancer; *6 A foreign post-marketing observational study; *7 A foreign phase II study in glioma; *8 A foreign phase II study in prostate cancer

PMDA's discussion:

Given that serious thromboembolism for which a causal relationship to talazoparib could not be ruled out was reported in the clinical studies submitted, and that thromboembolism is a known risk associated with other PARP inhibitors, attention should be paid to the possible occurrence of thromboembolism during treatment with talazoparib. Thus, the package insert etc. should appropriately advise healthcare professionals in clinical practice about the incidence of thromboembolism in the clinical studies.

7.R.1.4 MDS/AML

The applicant's explanation about MDS/AML associated with talazoparib:

In the EMBRACA study and the expansion part of Study 030, events in the MedDRA SMQ "myelodysplastic syndrome (broad)" were counted as MDS. In Part 2 (Cohort 1) of the TALAPRO-2 study, events in the MedDRA SMQ "myelodysplastic syndrome (narrow)" were counted as MDS. Events listed in Table 62 were counted as AML.

Table 62. Event terms counted as AML

	Event terms counted
EMBRACA study and expansion part of Study 030	MedDRA PTs: "acute bilineal leukaemia," "acute erythroid leukaemia," "acute leukaemia," "acute leukaemia in remission," "acute megakaryocytic leukaemia," "acute megakaryocytic leukaemia (in remission)," "acute monocytic leukaemia," "acute monocytic leukaemia (in remission)," "acute myeloid leukaemia," "acute myeloid leukaemia (in remission)," "acute myeloid leukaemia recurrent," "acute myeloid leukaemia refractory," "acute myelomonocytic leukaemia," "acute promyelocytic leukaemia," "acute undifferentiated leukaemia," "blast crisis in myelogenous leukaemia," "bone marrow leukaemic cell infiltration," "chronic myelomonocytic leukaemia with *N-ras* gene mutation," "leukaemia," "leukaemia basophilic," "leukaemia cutis," "leukaemia granulocytic," "leukaemia in remission," "leukaemia monocytic," "leukaemia recurrent," "leukaemic cardiac infiltration," "leukaemic infiltration," "leukaemic infiltration extramedullary," "leukaemic infiltration gingiva," "leukaemic infiltration hepatic," "leukaemic infiltration ovary," "leukaemic infiltration pulmonary," "leukaemic infiltration renal," "leukaemic lymphoma," "lineage switch leukaemia," "monocytic leukaemia in remission," "myeloid leukaemia," "myeloid leukaemia in remission," "philadelphia positive acute lymphocytic leukaemia," "philadelphia positive chronic myeloid leukaemia," "precursor T-lymphoblastic leukaemia acute"
Part 2 (Cohort 1) of TALAPRO-2 study	MedDRA PTs: "acute erythroid leukaemia," "acute leukaemia," "acute leukaemia in remission," "acute megakaryocytic leukaemia," "acute megakaryocytic leukaemia (in remission)," "acute monocytic leukaemia," "acute monocytic leukaemia (in remission)," "acute myeloid leukaemia," "acute myeloid leukaemia (in remission)," "acute myeloid leukaemia recurrent," "acute myelomonocytic leukaemia," "acute promyelocytic leukaemia," "acute undifferentiated leukaemia," "blast crisis in myelogenous leukaemia," "bone marrow leukaemic cell infiltration," "leukaemia," "leukaemia basophilic," "leukaemia cutis," "leukaemia granulocytic," "leukaemia in remission," "leukaemia monocytic," "leukaemia recurrent," "leukaemic cardiac infiltration," "leukaemic infiltration," "leukaemic infiltration extramedullary," "leukaemic infiltration gingiva," "leukaemic infiltration hepatic," "leukaemic infiltration ovary," "leukaemic infiltration pulmonary," "leukaemic infiltration renal," "leukaemic lymphoma," "monocytic leukaemia in remission," "myeloid leukaemia," "myeloid leukaemia in remission"

Table 63 shows the incidence of MDS/AML in the EMBRACA study and Part 2 (Cohort 1) of the TALAPRO-2 study. In the expansion part of Study 030, no MDS/AML was reported.

Table 63. Incidence of MDS/AML
[EMBRACA study and Part 2 (Cohort 1) of TALAPRO-2 study]

PT (MedDRA ver.25.0)	n (%)							
	EMBRACA study				Part 2 of TALAPRO-2 study			
	Talazoparib N = 286		Chemotherapy N = 126		Talazoparib N = 398		Placebo N = 401	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
MDS/AML	3 (1.0)	2 (0.7)	1 (0.8)	1 (0.8)	1 (0.3)	1 (0.3)	0	0
Pancytopenia	3 (1.0)	2 (0.7)	0	0	0	0	0	0
Myelodysplastic syndrome	1 (0.3)	1 (0.3)	0	0	1 (0.3)	1 (0.3)	0	0
Acute promyelocytic leukaemia	0	0	1 (0.8)	1 (0.8)	0	0	0	0

The median times to the first onset of MDS/AML (min., max.) (days) in the talazoparib and chemotherapy groups of the EMBRACA study and the talazoparib group in Part 2 (Cohort 1) of the TALAPRO-2 study were 133 (51, 1,708), 198 (198, 198), and 353 (353, 353), respectively.

In all clinical studies with talazoparib including the above clinical studies, patients with MDS/AML related to talazoparib are shown in Table 64.

Table 64. Listing of patients with serious MDS/AML related to talazoparib

Study ID	Age	Dose (mg)	PT[*1]	Grade	Time to onset (days)	Action taken with talazoparib	Outcome
EMBRACA	5[redacted]	0.75	AML	5	719	Discontinued	Fatal
	5[redacted]	1	MDS	4	1,708	Unknown	Resolved
			AML	4	1,759	Unknown	Resolved
			AML	5	1,803	Unknown	Fatal
TALAPRO-1	6[redacted]	0.75	MDS	Unknown	1,161	Unknown	Fatal
TALAPRO-2 Part 2 (Cohort 1)	8[redacted]	0.1	MDS	3	353	Discontinued	Not resolved
	7[redacted]	0.25	AML	4	457	Discontinued	Not resolved
010	6[redacted]	0.75	Leukaemia	Unknown	112	Discontinued	Not resolved
C3441047[*2]	7[redacted]	Unknown	MDS	Unknown	Unknown	Interrupted	Not resolved

*1 MedDRA ver.25.0; *2 A foreign post-marketing observational study

PMDA's discussion:

Since there were no clear differences in the incidence of MDS/AML between the talazoparib and placebo groups in the clinical study submitted, etc., it is difficult at present to draw a definitive conclusion on the risk of MDS/AML associated with talazoparib. However, as MDS/AML may take long time to develop, it is necessary to collect post-marketing information, and any useful information should be provided appropriately to healthcare professionals in clinical practice.

7.R.1.5 Second primary malignancies (other than MDS/AML)

The applicant's explanation about second primary malignancies (other than MDS/AML) associated with talazoparib:

In the EMBRACA study and the expansion part of Study 030, events in the MedDRA SMQ "malignant or unspecified tumours (narrow)" excluding events counted as MDS/AML [see Section 7.R.1.4] and MedDRA PTs containing "metastatic," "aggravated," "worsened," "progression," and "recurrent" were counted as second primary malignancies. In Part 2 (Cohort 1) of the TALAPRO-2 study, events in the MedDRA SMQ "malignant or unspecified tumours (narrow)" excluding events in the MedDRA HLT "myeloproliferative disorders (excl leukaemias)," events in the MedDRA SMQ "myelodysplastic syndrome (narrow)," MedDRA PTs containing "metastatic" and "prostate cancer," and MedDRA PTs "congenital fibrosarcoma," "congenital malignant neoplasm," "congenital retinoblastoma," "metastatic neoplasm," "carcinoid tumour of the prostate," "neoplasm prostate," "basal cell carcinoma," "basosquamous carcinoma," "basosquamous carcinoma of skin," "keratoacanthoma," "skin cancer," "skin cancer metastatic," "squamous cell carcinoma," "squamous cell carcinoma of skin," and "lip squamous cell carcinoma" were counted as second primary malignancies.

Table 65 shows the incidence of second primary malignancies in the EMBRACA study and Part 2 (Cohort 1) of the TALAPRO-2 study. In the expansion part of Study 030, no second primary malignancies were reported.

Table 65. Incidence of second primary malignancies [EMBRACA study and Part 2 (Cohort 1) of TALAPRO-2 study]

PT (MedDRA ver.25.0)	n (%)							
	EMBRACA study				Part 2 (Cohort 1) of TALAPRO-2 study			
	Talazoparib N = 286		Chemotherapy N = 126		Talazoparib N = 398		Placebo N = 401	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Second primary malignancies	4 (1.4)	1 (0.3)	1 (0.8)	1 (0.8)	12 (3.0)	9 (2.3)	20 (5.0)	15 (3.7)
Basal cell carcinoma	2 (0.7)	0	0	0	0	0	0	0
Glioblastoma multiforme	1 (0.3)	1 (0.3)	0	0	0	0	0	0
Squamous cell carcinoma of skin	1 (0.3)	0	0	0	0	0	0	0
Malignant melanoma	0	0	1 (0.8)	1 (0.8)	0	0	2 (0.5)	1 (0.2)
Second primary malignancy	0	0	1 (0.8)	1 (0.8)	0	0	0	0
Lung neoplasm malignant	0	0	0	0	2 (0.5)	2 (0.5)	3 (0.7)	3 (0.7)
Colon cancer	0	0	0	0	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Lung carcinoma cell type unspecified recurrent	0	0	0	0	2 (0.5)	2 (0.5)	0	0
Bladder transitional cell carcinoma	0	0	0	0	2 (0.5)	2 (0.5)	1 (0.2)	0
Gastric cancer	0	0	0	0	1 (0.3)	1 (0.3)	0	0
Small cell lung cancer	0	0	0	0	1 (0.3)	1 (0.3)	0	0
Lung adenocarcinoma	0	0	0	0	1 (0.3)	1 (0.3)	0	0
Lentigo maligna	0	0	0	0	1 (0.3)	0	0	0
Rectal neoplasm	0	0	0	0	1 (0.3)	0	0	0
Bladder cancer	0	0	0	0	1 (0.3)	0	0	0
Neoplasm malignant	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Transitional cell carcinoma	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Hepatocellular carcinoma	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Nodular melanoma	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Laryngeal neoplasm	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Thyroid cancer	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Gastrointestinal stromal tumour	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Invasive ductal breast carcinoma	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Tonsil cancer	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Bowen's disease	0	0	0	0	0	0	1 (0.2)	0
Non-small cell lung cancer	0	0	0	0	0	0	1 (0.2)	0
Malignant melanoma in situ	0	0	0	0	0	0	1 (0.2)	0

The median times to the first onset of second primary malignancies (min., max.) (days) in the talazoparib and chemotherapy groups of the EMBRACA study and the talazoparib and placebo groups in Part 2 (Cohort 1) of the TALAPRO-2 study were 399 (45, 1,376), 205 (205, 205), 311.5 (1, 932), and 261.5 (11, 862), respectively.

In all clinical studies with talazoparib including the above clinical studies, there were no second primary malignancies for which a causal relationship to talazoparib could not be ruled out.

PMDA's discussion:

There were no clear differences in the incidence of second primary malignancies between the talazoparib and placebo groups in the clinical study submitted, and no serious second primary malignancies for which a causal relationship to talazoparib could not be ruled out were reported, etc. Thus, it is difficult at present to draw a definitive conclusion on the risk of second primary malignancies associated with talazoparib. However, as second primary malignancies may take long time to develop, it is necessary to collect post-marketing information, and any useful information should be provided appropriately to healthcare professionals in clinical practice.

7.R.1.6 Others

(1) Neurologic disorders

The applicant's explanation about neurologic disorders associated with talazoparib:

Events in the MedDRA SOC "nervous system disorders" were counted as neurologic disorders.

Neurologic disorders reported by ≥1% of subjects and ≥2 subjects in the EMBRACA study, the expansion part of Study 030, or Part 2 (Cohort 1) of the TALAPRO-2 study are shown in Table 66 and Table 67.

Table 66. Neurologic disorders reported by ≥1% of subjects and ≥2 subjects in either group (EMBRACA study and expansion part of Study 030)

PT (MedDRA ver.25.0)	n (%)					
	EMBRACA study				Expansion part of Study 030 N = 19	
	Talazoparib N = 286		Chemotherapy N = 126			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Neurologic disorders	159 (55.6)	15 (5.2)	70 (55.6)	7 (5.6)	8 (42.1)	0
Headache	97 (33.9)	5 (1.7)	29 (23.0)	2 (1.6)	4 (21.1)	0
Dizziness	53 (18.5)	1 (0.3)	13 (10.3)	2 (1.6)	3 (15.8)	0
Dysgeusia	22 (7.7)	0	8 (6.3)	0	2 (10.5)	0
Neuropathy peripheral	19 (6.6)	0	9 (7.1)	1 (0.8)	0	0
Paraesthesia	12 (4.2)	1 (0.3)	15 (11.9)	0	0	0
Taste disorder	9 (3.1)	0	3 (2.4)	0	0	0
Dysaesthesia	6 (2.1)	0	2 (1.6)	0	0	0
Hypoaesthesia	6 (2.1)	0	3 (2.4)	0	0	0
Somnolence	6 (2.1)	0	3 (2.4)	0	0	0
Disturbance in attention	6 (2.1)	0	2 (1.6)	0	0	0
Lethargy	6 (2.1)	0	1 (0.8)	0	0	0
Tremor	4 (1.4)	0	1 (0.8)	0	0	0
Migraine	4 (1.4)	0	1 (0.8)	0	0	0
Amnesia	3 (1.0)	0	0	0	0	0
Sciatica	3 (1.0)	0	2 (1.6)	0	0	0
Aphasia	3 (1.0)	0	0	0	0	0
Syncope	3 (1.0)	3 (1.0)	0	0	0	0
Seizure	3 (1.0)	1 (0.3)	0	0	0	0
Peripheral sensory neuropathy	2 (0.7)	0	7 (5.6)	0	0	0
Neuralgia	1 (0.3)	0	2 (1.6)	0	0	0
Nervous system disorder	0	0	2 (1.6)	1 (0.8)	0	0

Table 67. Neurologic disorders reported by ≥1% of subjects in either group (Part 2 of TALAPRO-2 study)

PT (MedDRA ver.25.0)	n (%)			
	Talazoparib N = 398		Placebo N = 401	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Neurologic disorders	160 (40.2)	30 (7.5)	146 (36.4)	26 (6.5)
Dizziness	48 (12.1)	4 (1.0)	24 (6.0)	2 (0.5)
Headache	36 (9.0)	1 (0.3)	37 (9.2)	1 (0.2)
Dysgeusia	27 (6.8)	0	15 (3.7)	0
Memory impairment	13 (3.3)	0	14 (3.5)	1 (0.2)
Paraesthesia	12 (3.0)	0	10 (2.5)	0
Syncope	11 (2.8)	9 (2.3)	7 (1.7)	6 (1.5)
Spinal cord compression	11 (2.8)	8 (2.0)	12 (3.0)	6 (1.5)
Hypoaesthesia	8 (2.0)	0	7 (1.7)	0
Amnesia	7 (1.8)	0	9 (2.2)	0
Cognitive disorder	7 (1.8)	0	7 (1.7)	2 (0.5)
Neuropathy peripheral	7 (1.8)	0	8 (2.0)	0
Taste disorder	7 (1.8)	0	3 (0.7)	0
Restless legs syndrome	6 (1.5)	0	9 (2.2)	0
Presyncope	6 (1.5)	3 (0.8)	3 (0.7)	1 (0.2)
Disturbance in attention	6 (1.5)	0	4 (1.0)	0
Peripheral sensory neuropathy	5 (1.3)	0	6 (1.5)	0
Somnolence	4 (1.0)	0	0	0
Tremor	3 (0.8)	0	5 (1.2)	0
Lethargy	3 (0.8)	0	7 (1.7)	0
Sciatica	2 (0.5)	0	7 (1.7)	1 (0.2)

In the EMBRACA study, neurologic disorders leading to death occurred in 2 of 286 subjects (0.7%) in the talazoparib group (neurological symptom; and cerebral haemorrhage [1 subject each]) and 1 of 126 subjects (0.8%) in the chemotherapy group (nervous system disorder [1 subject]), and a causal relationship to study drug was denied for all those cases. Serious neurologic disorders occurred in 13 of 286 subjects (4.5%) in the talazoparib group (headache [5 subjects]; dizziness; and seizure [2 subjects each]; and transient ischaemic attack; aphasia; syncope; neurological symptom; hydrocephalus; and cerebral haemorrhage [1 subject each] [some patients had more than 1 event]) and 4 of 126 subjects (3.2%) in the chemotherapy group (nervous system disorder [2 subjects]; and dizziness; cerebrovascular accident; and encephalopathy [1 subject each] [some patients had more than 1 event]), and a causal relationship to study drug could not be ruled out for headache (1 subject) in the talazoparib group and dizziness; and encephalopathy (1 subject each) in the chemotherapy group. Neurologic disorders leading to treatment discontinuation occurred in 3 of 286 subjects (1.0%) in the talazoparib group (transient ischaemic attack; headache; and cerebral haemorrhage [1 subject each]) (none in the chemotherapy group). Neurologic disorders leading to dose interruption occurred in 15 of 286 subjects (5.2%) in the talazoparib group (headache [4 subjects]; seizure [3 subjects]; paraesthesia; and lethargy [2 subjects each]; and amnesia; aphasia; syncope; hydrocephalus; disturbance in attention; electric shock sensation; dizziness; and migraine [1 subject each] [some patients had more than 1 event]) and 7 of 126 subjects (5.6%) in the chemotherapy group (dizziness [3 subjects]; and headache; paraesthesia; somnolence; nervous system disorder; neurotoxicity; cerebrovascular accident; and encephalopathy [1 subject each] [some patients had more than 1 event]). Neurologic disorders leading to dose reduction occurred in 1 of 286 subjects (0.3%) in the talazoparib group (dementia) and 1 of 126 subjects (0.8%) in the chemotherapy group (neuropathy peripheral; and peripheral sensory neuropathy [1 subject each] [some patients had more than 1 event]).

In the expansion part of Study 030, neurologic disorders leading to dose interruption occurred in 1 of 19 subjects (5.3%) (headache). There were no neurologic disorders leading to death, serious neurologic disorders, neurologic disorders leading to treatment discontinuation, or neurologic disorders leading to dose reduction.

In Part 2 (Cohort 1) of the TALAPRO-2 study, a neurologic disorder leading to death occurred in 1 of 401 subjects (0.2%) in the placebo group (cerebral haematoma), and its causal relationship to study drug was denied (none in the talazoparib group). Serious neurologic disorders occurred in 18 of 398 subjects (4.5%) in the talazoparib group (syncope [4 subjects]; transient ischaemic attack; and dizziness [3 subjects each]; spinal cord compression [2 subjects]; and subarachnoid haemorrhage; loss of consciousness; cerebellar infarction; normal pressure hydrocephalus; cognitive disorder; cerebral infarction; hemiparesis; and dysgeusia [1 subject each] [some patients had more than 1 event]) and 10 of 401 subjects (2.5%) in the placebo group (syncope [3 subjects]; spinal cord compression [2 subjects]; and loss of consciousness; malignant spinal cord compression; paraplegia; cerebrovascular accident; cerebral haematoma; and seizure [1 subject each] [some patients had more than 1 event]), and a causal relationship to study drug could not be ruled out for syncope; transient ischaemic attack; dizziness; and cognitive disorder [1 subject each] in the talazoparib group. Neurologic disorders leading to discontinuation of any study drug[60)] occurred in 7 of 398 subjects (1.8%) in the talazoparib group (spinal cord compression; and dizziness [2 subjects each]; and transient ischaemic attack; headache; cerebral infarction; and dysgeusia [1 subject each] [some patients had more than 1 event]) and 7 of 401 subjects (1.7%) in the placebo group (cognitive disorder [2 subjects]; and spinal cord compression; headache; malignant spinal cord compression; cerebrovascular accident, and cerebral haematoma [1 subject each]). Neurologic disorders leading to dose interruption of any study drug[60)] occurred in 17 of 398 subjects (4.3%) in the talazoparib group (dizziness [4 subjects]; transient ischaemic attack; presyncope; spinal cord compression; cognitive disorder; and dysgeusia [2 subjects each]; and subarachnoid haemorrhage; malignant spinal cord compression; hypoaesthesia; memory impairment; cerebellar infarction; and headache [1 subject each] [some patients had more than 1 event]) and 12 of 401 subjects (3.0%) in the placebo group (dizziness; and spinal cord compression [2 subjects each]; and presyncope; cognitive disorder; malignant spinal cord compression; memory impairment; headache; movement disorder; amnesia; cerebral haematoma; and paraparesis [1 subject each] [some patients had more than 1 event]). Neurologic disorders leading to dose reduction of any study drug[60)] occurred in 8 of 398 subjects (2.0%) in the talazoparib group (dizziness [2 subjects]; and memory impairment; amnesia; disturbance in attention; headache; cognitive disorder; balance disorder; and taste disorder [1 subject each] [some patients had more than 1 event]) and 3 of 401 subjects (0.7%) in the placebo group (memory impairment).

The median times to the first onset of neurologic disorder (min., max.) (days) in the talazoparib and chemotherapy groups of the EMBRACA study, the expansion part of Study 030, and the talazoparib and placebo groups in Part 2 (Cohort 1) of the TALAPRO-2 study were 30 (1, 657), 20.5 (1, 244), 48 (22, 129), 77.5 (1, 903), and 88 (1, 855), respectively.

In all clinical studies with talazoparib including the above clinical studies and the overseas marketing experience, the details of patients with serious neurologic disorders related to talazoparib are shown in Table 68.

Table 68. Listing of patients with serious neurologic disorders related to talazoparib

Study ID	Age	Sex	Dosing regimen	PT[*1]	Grade	Time to onset (days)	Duration (days)	Action taken with talazoparib	Outcome
EMBRACA	5[redacted]	F	1 mg QD	Headache	2	1	92	Interrupted	Resolved
TALAPRO-2 Part 2 (Cohort 1)	7[redacted]	M	0.25 mg QD	Syncope	3	134	2	None	Resolved
	7[redacted]	M	0.35 mg QD	Transient ischaemic attack	2	234	2	Interrupted	Resolved
	7[redacted]	M	0.5 mg QD	Cognitive disorder	2	54	3	Interrupted	Resolved
			0.5 mg QD	Cognitive disorder	1	113	8	None	Resolved
			0.5 mg QD	Cognitive disorder	2	121	21	Interrupted	Resolved
	8[redacted]	M	0.5 mg QD	Dizziness	4	128	7	Discontinued	Resolved
Talazoparib-IST[*2]	4[redacted]	F	1 mg QD	Encephalopathy	3	135	10	None	Resolved
HP-00066370[*3]	6[redacted]	M	0.25 mg QD	Cognitive disorder	3	178	Unknown	None	Not resolved
S1929[*4]	6[redacted]	F	Unknown	Dizziness	3	67	26	Discontinued	Resolved
C3441047[*5]	4[redacted]	F	Unknown	Hyperaesthesia	Unknown	Unknown	Unknown	Unknown	Fatal
9782[*6]	6[redacted]	M	Unknown	Haemorrhage intracranial	5	110	Unknown	Unknown	Fatal
	7[redacted]	M	Unknown	Syncope	3	6	Unknown	Unknown	Resolving

*1 MedDRA ver.25.0; *2 A general term that refers to any study not conducted by the applicant; *3 A foreign phase I/II study in AML;
*4 A foreign phase II study in small cell lung cancer; *5 A foreign post-marketing observational study; *6 A foreign phase I study in patients with advanced solid tumors

(2) Hypertension

The applicant's explanation about hypertension associated with talazoparib:

Events in the MedDRA SMQ "hypertension (narrow)" were counted as hypertension.

The incidences of hypertension in the EMBRACA study and Part 2 (Cohort 1) of the TALAPRO-2 study are shown in Table 69 and Table 70, respectively. Hypertension was not reported in the expansion part of Study 030.

Table 69. Incidence of hypertension (EMBRACA study)

PT (MedDRA ver.25.0)	n (%)			
	Talazoparib N = 286		Chemotherapy N = 126	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension[*]	5 (1.7)	4 (1.4)	2 (1.6)	1 (0.8)
Hypertension	5 (1.7)	4 (1.4)	2 (1.6)	1 (0.8)

* Any event of hypertension

Table 70. Incidence of hypertension [Part 2 (Cohort 1) of TALAPRO-2 study]

PT (MedDRA ver.25.0)	n (%)			
	Talazoparib N = 398		Placebo N = 401	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension*	57 (14.3)	22 (5.5)	66 (16.5)	32 (8.0)
Hypertension	55 (13.8)	21 (5.3)	62 (15.5)	30 (7.5)
Hypertensive crisis	1 (0.3)	1 (0.3)	0	0
Blood pressure systolic increased	1 (0.3)	0	0	0
Blood pressure inadequately controlled	0	0	1 (0.2)	1 (0.2)
Systolic hypertension	0	0	1 (0.2)	0
Blood pressure increased	0	0	2 (0.5)	1 (0.2)

* Any event of hypertension

In the EMBRACA study, hypertension leading to dose interruption occurred in 1 of 286 subjects (0.8%) in the chemotherapy group (hypertension) (none in the talazoparib group). There was no hypertension leading to death, serious hypertension, hypertension leading to treatment discontinuation, or hypertension leading to dose reduction.

In Part 2 (Cohort 1) of the TALAPRO-2 study, serious hypertension occurred in 2 of 398 subjects (0.5%) in the talazoparib group (hypertension; and hypertensive crisis [1 subject each]) and 1 of 401 subjects (0.2%) in the placebo group (hypertension), and a causal relationship to study drug could not be ruled out for hypertensive crisis in the talazoparib group and hypertension in the placebo group. Hypertension leading to dose interruption of any study drug[60)] occurred in 4 of 398 subjects (0.5%) in the talazoparib group (hypertension) and 2 of 401 subjects (0.5%) in the placebo group (hypertension). Hypertension leading to dose reduction of any study drug[60)] occurred in 2 of 398 subjects (0.5%) in the talazoparib group (hypertension) and 4 of 401 subjects (1.0%) in the placebo group (hypertension [3 subjects]; and blood pressure inadequately controlled [1 subject]). There was no hypertension leading to death or discontinuation of any study drug.

The median times to the first onset of hypertension (min., max.) (days) in the talazoparib and chemotherapy groups of the EMBRACA study and the talazoparib and placebo groups in Part 2 of the TALAPRO-2 study were 148 (8, 700), 117 (108, 126), 140 (1, 979), and 91.5 (1, 610), respectively.

In all clinical studies with talazoparib including the above clinical studies, the details of patients with serious hypertension related to talazoparib are shown in Table 71. No patients experienced serious hypertension for which a causal relationship to talazoparib could not be ruled out in the overseas marketing experience.

Table 71. Listing of patients with serious hypertension related to talazoparib

Study ID	Age	Sex	Dosing regimen	PT*	Grade	Time to onset (days)	Duration (days)	Action taken with talazoparib	Outcome
TALAPRO-2 Part 2 (Cohort 1)	7[redacted]	M	0.5 mg QD	Hypertensive crisis	3	21	4	None	Resolved

* MedDRA ver.25.0

PMDA's discussion:
Although neurologic disorders occurred with a certain incidence, and serious neurologic disorders for which a causal relationship to talazoparib could not be ruled out were reported in the clinical studies submitted, as many of the serious neurologic disorders for which a causal relationship to talazoparib could not be ruled out resolved within a short period of time following dose interruption etc., no special precautionary statement concerning neurologic disorders is needed at present, on the premise that information on the incidence of neurologic disorders in the clinical studies will be provided using the package insert etc., that post-marketing information on the incidence of neurologic disorders will be collected, and that any new information will be provided to healthcare professionals in clinical practice.

Although serious hypertension for which a causal relationship to talazoparib could not be ruled out occurred in the clinical studies submitted, as the number of subjects with serious hypertension for which a causal relationship to talazoparib could not be ruled out was limited etc., no special precautionary statement concerning hypertension is needed at present, on the premise that information on the incidence of hypertension in the clinical studies will be provided using the package insert etc., that post-marketing information on the incidence of hypertension will be collected, and that any new information will be provided to healthcare professionals in clinical practice.

7.R.2 Recommended dosage modifications for talazoparib

The applicant's explanation about dose adjustment of talazoparib:
The EMBRACA study and Part 2 (Cohort 1) of the TALAPRO-2 study were conducted according to the specific talazoparib dosage modification guidelines and demonstrated the clinical usefulness of talazoparib. Thus, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert includes a revised version of these dosage modification guidelines as shown below.

- In the EMBRACA study, daily dosing was to be interrupted for the first occurrence or recurrence of platelet count <50,000/μL until resolution to ≥75,000/μL. In Part 2 of the TALAPRO-2 study, daily dosing was to be interrupted for the first occurrence of platelet count <50,000/μL until resolution to ≥50,000/μL, and daily dosing was to be interrupted for the recurrence of platelet count <50,000/μL until resolution to ≥75,000/μL. However, for the following reason etc., in patients with breast cancer or prostate cancer, talazoparib should be withheld for the first occurrence or recurrence of platelet count <50,000/μL and resumed when the levels resolve to ≥50,000/μL.
  - In Part 2 of the TALAPRO-2 study, among patients with dose interruption due to the first occurrence of platelet count <50,000/μL, 3 patients resumed dosing upon resolution to ≥50,000/μL and <75,000/μL. After talazoparib was resumed at a reduced dose, thrombocytopenia did not recur in any of the patients.

PMDA's discussion:
PMDA largely accepted the above explanation by the applicant. However, the clinical usefulness of talazoparib in patients with breast cancer was demonstrated according to the dosage modification guidelines used in the EMBRACA study, and the recommended dose of talazoparib for breast cancer is different from that

for mCRPC. Thus, in patients with breast cancer, in accordance with the dosage modification guidelines in the EMBRACA study, talazoparib should be withheld for the first occurrence or recurrence of platelet count <50,000/μL until resolution to ≥75,000/μL. In patients with mCRPC treated with talazoparib/enzalutamide, given that daily dosing was to be interrupted for the recurrence of thrombocytopenia until resolution to ≥75,000/μL in Part 2 (Cohort 1) of the TALAPRO-2 study, if thrombocytopenia recurs, talazoparib should be resumed upon resolution to ≥75,000/μL. Thus, the recommended dosage modifications in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section should be presented as follows.

[*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy]

- In the event of adverse reactions to talazoparib, withhold talazoparib, reduce the dose of talazoparib, or discontinue talazoparib, as per the tables below.

Dose reduction levels

Usual dose	1 mg once daily
First dose reduction	0.75 mg once daily
Second dose reduction	0.5 mg once daily
Third dose reduction	0.25 mg once daily
Fourth dose reduction	Discontinue

Recommended dosage modifications for adverse reactions

Adverse reactions	Severity*	Dosage modifications
Anemia	Hemoglobin <8 g/dL	Withhold talazoparib until levels resolve to ≥9 g/dL. After resolution, talazoparib may be resumed at the next lower dose level.
Thrombocytopenia	Platelet count <50,000/μL	Withhold talazoparib until levels resolve to ≥75,000/μL. After resolution, talazoparib may be resumed at the next lower dose level.
Neutropenia	Neutrophil count <1,000/μL	Withhold talazoparib until levels resolve to ≥1,500/μL. After resolution, talazoparib may be resumed at the next lower dose level.
Other adverse reactions	Grade 3 or 4	Withhold talazoparib until levels resolve to Grade ≤1. After resolution, talazoparib may be resumed at the next lower dose level.

* Severity grade based on NCI-CTCAE ver.4.03

[*BRCA*-mutated metastatic castration-resistant prostate cancer]

- In the event of adverse reactions to talazoparib, withhold talazoparib, reduce the dose of talazoparib, or discontinue talazoparib, as per the tables below.

Dose reduction levels

Usual dose	0.5 mg once daily
First dose reduction	0.35 mg once daily
Second dose reduction	0.25 mg once daily
Third dose reduction	0.1 mg once daily
Fourth dose reduction	Discontinue

Recommended dosage modifications for adverse reactions

Adverse reactions	Severity*	Dosage modifications
Anemia	Hemoglobin <8 g/dL	Withhold talazoparib until levels resolve to ≥9 g/dL. After resolution, talazoparib may be resumed at the next lower dose level.
Thrombocytopenia	Platelet count <50,000/μL	● For 1st occurrence, withhold talazoparib until levels resolve to ≥50,000/μL. After resolution, talazoparib may be resumed at the next lower dose level. ● For recurrence, withhold talazoparib until levels resolve to ≥75,000/μL. After resolution, talazoparib may be resumed at the next lower dose level.
Neutropenia	Neutrophil count <1,000/μL	Withhold talazoparib until levels resolve to ≥1,500/μL. After resolution, talazoparib may be resumed at the next lower dose level.
Other adverse reactions	Grade 3 or 4	Withhold talazoparib until levels resolve to Grade ≤1. After resolution, talazoparib may be resumed at the next lower dose level.

* Severity grade based on NCI-CTCAE ver.4.03

7.R.3 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:

The applicant plans to conduct post-marketing surveillance in (1) patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer and (2) patients with CRPC to evaluate the safety etc. of talazoparib in clinical practice after marketing. The surveillance plans are summarized below.

(1) Post-marketing surveillance in patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer

- Safety specification: Myelosuppression
- Planned sample size: Taking account of the incidence etc. of adverse events of myelosuppression in Japanese patients in Study 030, assuming an incidence of 50% (which generates the widest 95% confidence interval for the incidence calculated using the Clopper-Pearson method) in this survey, a sample size of 104 patients is required to obtain a 95% confidence interval that with a ≥90% probability would have a width no larger than 20%. However, from the standpoint of the feasibility of the survey based on the expected number of enrolled patients per year (10-16 patients), a sample size of 84 patients was chosen, taking account of the incidence etc. of Grade ≥3 neutropenia, which are events that require particular attention among adverse events of myelosuppression, in Study 030.
- Observation period: Taking account of the time to the onset of the events included in the above safety specification in Study 030, etc., an observation period of 24 weeks was chosen.

(2) Post-marketing surveillance in patients with CRPC

- Safety specification: Myelosuppression
- Planned sample size: Taking account of the incidence etc. of adverse events of myelosuppression in Japanese patients in Part 2 (Cohort 1) of the TALAPRO-2 study, assuming an incidence of 50% (which generates the widest 95% confidence interval for the incidence of adverse events calculated using the Clopper-Pearson method) in this survey, a sample size of 104 patients is required to obtain a 95% confidence interval that with a ≥90% probability would have a width no larger than 20%.
- Observation period: Taking account of the time to the onset of the events included in the above safety specification in Part 2 (Cohort 1) of the TALAPRO-2 study, etc., an observation period of 24 weeks was chosen.

PMDA's discussion:
Since talazoparib safety information from Japanese (1) patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy and (2) patients with *BRCA*-mutated mCRPC is limited etc., it is necessary to conduct post-marketing surveillance to collect talazoparib safety information in clinical practice.

PMDA also made the following conclusions concerning the post-marketing surveillance plans for the above (1) and (2).

- On the basis of the considerations in Sections "7.1.R.5.1 and 7.2.R.5.1 Dosing regimen of talazoparib" and "7.R.1 Safety (Events that require attention following administration of talazoparib, etc.)," myelosuppression, ILD, thromboembolism, and second primary malignancies should be included in the safety specification, and then the information on the safety of talazoparib in patients with renal impairment should also be collected.
- The planned sample size and observation period need to be reviewed, taking account of the incidences of the above events that should be included in the safety specification for the surveillance, in clinical studies.

7.3 Adverse events etc. observed in clinical studies

Among clinical study data submitted for safety evaluation, deaths are described in Sections "7.1.1 Evaluation data," "7.1.2 Reference data," and "7.2.1 Evaluation data." The main adverse events other than deaths are described below. The data are not mentioned if not applicable.

7.3.1 Adverse events etc. observed in clinical studies for breast cancer

7.3.1.1 Japanese phase I study (Study 030)

7.3.1.1.1 Dose-escalation part

Adverse events occurred in all subjects, and those for which a causal relationship to study drug could not be ruled out occurred in (1) 2 of 3 subjects (66.7%) in the 0.75 mg group and (2) 3 of 6 subjects (50.0%) in the 1 mg group. Adverse events reported by ≥2 subjects in each group were (2) stomatitis; anaemia; rash maculo-papular; and platelet count decreased (2 subjects each [33.3%]).

A serious adverse event occurred in (1) 1 of 3 subjects (33.3%). The reported serious adverse event was (1) brain cancer metastatic (1 subject [33.3%]), and its causal relationship to study drug was denied.

There were no adverse events leading to study drug discontinuation.

7.3.1.1.2 Expansion part

Adverse events and those for which a causal relationship to study drug could not be ruled out occurred in all subjects. Adverse events reported by ≥20% of subjects were anaemia (13 subjects [68.4%]); neutrophil count decreased (12 subjects [63.2%]); white blood cell count decreased (8 subjects [42.1%]); stomatitis (7 subjects [36.8%]); alopecia; and platelet count decreased (6 subjects each [31.6%]); nausea; and malaise (5 subjects each [26.3%]); and constipation; and headache (4 subjects each [21.1%]).

A serious adverse event occurred in 1 of 19 subjects (5.3%). The reported serious adverse event was cholelithiasis (1 subject [5.3%]), and its causal relationship to study drug was denied.

There were no adverse events leading to study drug discontinuation.

7.3.1.2 Foreign phase I study (Study 007)

7.3.1.2.1 Dose-escalation part

Adverse events occurred in (1) 2 of 3 subjects (66.7%) in the 0.025 mg group, (2) 3 of 3 subjects (100%) in the 0.05 mg group, (3) 2 of 3 subjects (66.7%) in the 0.1 mg group, (4) 3 of 3 subjects (100%) in the 0.2 mg group, (5) 3 of 3 subjects (100%) in the 0.4 mg group, (6) 6 of 6 subjects (100%) in the 0.6 mg group, (7) 6 of 6 subjects (100%) in the 0.9 mg group, (8) 6 of 6 subjects (100%) in the 1 mg group, and (9) 6 of 6 subjects (100%) in the 1.1 mg group, and those for which a causal relationship to study drug could not be ruled out occurred in (2) 2 of 3 subjects (66.7%), (3) 2 of 3 subjects (66.7%), (4) 2 of 3 subjects (66.7%), (5) 2 of 3 subjects (66.7%), (6) 5 of 6 subjects (83.3%), (7) 6 of 6 subjects (100%), (8) 6 of 6 subjects (100%), and (9) 5 of 6 subjects (83.3%). Adverse events reported by ≥50% of subjects in each group were (1) diarrhoea (2 subjects [66.7%]), (2) flatus (2 subjects [66.7%]), (3) fatigue (2 subjects [66.7%]), (4) nausea (3 subjects [100%]); and abdominal pain; constipation; vomiting; ascites; fatigue; and decreased appetite (2 subjects each [66.7%]), (5) fatigue (3 subjects [100%]); and nausea; and constipation (2 subjects each [66.7%]), (6) nausea; and wheezing (4 subjects each [66.7%]); and fatigue; and cough (3 subjects each [50.0%]), (7) nausea (5 subjects [83.3%]); and constipation; fatigue; pyrexia; and alopecia (3 subjects each [50.0%]), (8) fatigue (5 subjects [83.3%]); anaemia; and alopecia (4 subjects each [66.7%]); and pyrexia; pain in extremity; and neutropenia (3 subjects each [50.0%]), and (9) cough (3 subjects [50.0%]). Serious adverse events occurred in (1) 1 of 3 subjects (33.3%), (2) 2 of 3 subjects (66.7%), (3) 2 of 3 subjects (66.7%), (4) 3 of 3 subjects (100%), (6) 2 of 6 subjects (33.3%), (7) 3 of 6 subjects (50.0%), (8) 1 of 6 subjects (16.7%), and (9) 3 of 6 subjects (50.0%). No specific serious adverse events occurred in ≥2 subjects in any group.

There were no adverse events leading to study drug discontinuation.

7.3.1.2.2 Expansion part

Adverse events occurred in 68 of 71 subjects (95.8%), and those for which a causal relationship to study drug could not be ruled out occurred in 55 of 71 subjects (77.5%). Adverse events reported by ≥20% of subjects were fatigue (35 subjects [49.3%]); nausea (29 subjects [40.8%]); anaemia (28 subjects [39.4%]); constipation (17 subjects [23.9%]); thrombocytopenia (16 subjects [22.5%]); and insomnia (15 subjects [21.1%]).

Serious adverse events occurred in 25 of 71 subjects (35.2%). Those reported by ≥2 subjects were hyponatraemia (3 subjects [4.2%]); and device related infection; pleural effusion; dyspnoea; disease progression; small intestinal obstruction; and metastases to central nervous system (2 subjects each [2.8%]), and a causal relationship to study drug was denied for all those events.

There were no adverse events leading to study drug discontinuation.

7.3.1.3 Foreign phase II study (ABRAZO study)

7.3.1.3.1 Cohort 1

Adverse events occurred in 47 of 48 subjects (97.9%), and those for which a causal relationship to study drug could not be ruled out occurred in 46 of 48 subjects (95.8%). Adverse events reported by ≥20% of subjects were fatigue (29 subjects [60.4%]); anaemia (24 subjects [50.0%]); nausea (20 subjects [41.7%]); diarrhoea and thrombocytopenia (18 subjects each [37.5%]); back pain; and decreased appetite (12 subjects each [25.0%]); viral upper respiratory tract infection; dyspnoea; and alopecia (11 subjects each [22.9%]), and vomiting; and neutropenia (10 subjects each [20.8%]).

Serious adverse events occurred in 16 of 48 subjects (33.3%). Those reported by ≥2 subjects were anaemia (5 subjects [10.4%]); pleural effusion; and neoplasm progression (3 subjects each [6.3%]); and breast cancer metastatic; thrombocytopenia; dyspnoea; and pneumonia (2 subjects each [4.2%]), and a causal relationship to study drug could not be ruled out for anaemia (4 subjects); and thrombocytopenia (2 subjects).

Adverse events leading to study drug discontinuation occurred in 4 of 48 subjects (8.3%). The reported adverse events leading to study drug discontinuation were ALT increased; breast cancer metastatic; dyspnoea; and anaemia (1 subject each [2.1%]), and a causal relationship to study drug could not be ruled out for ALT increased; and anaemia (1 subject each).

7.3.1.3.2 Cohort 2

Adverse events occurred in 34 of 35 subjects (97.1%), and those for which a causal relationship to study drug could not be ruled out occurred in 33 of 35 subjects (94.3%). Adverse events reported by ≥20% of subjects were anaemia (19 subjects [54.3%]); nausea (15 subjects [42.9%]); neutropenia (12 subjects [34.3%]); headache (11 subjects [31.4%]); diarrhoea; asthenia; and decreased appetite (10 subjects each [28.6%]); arthralgia; thrombocytopenia; and dyspnoea (9 subjects each [25.7%]); vomiting; fatigue; and back pain (8 subjects each [22.9%]); and abdominal pain; and cough (7 subjects each [20.0%]).

Serious adverse events occurred in 7 of 35 subjects (20.0%). Those reported by ≥2 subjects were pleural effusion; and dyspnoea (2 subjects each [5.7%]), and a causal relationship to study drug could not be ruled out for dyspnoea (1 subject).

Adverse events leading to study drug discontinuation occurred in 1 of 35 subjects (2.9%). The reported adverse events leading to study drug discontinuation were AST increased; and blood ALP increased (1 subject each [2.9%]), and a causal relationship to study drug could not be ruled out for both events.

7.3.1.4 Foreign phase III study (EMBRACA study)

Adverse events occurred in 282 of 286 subjects (98.6%) in the talazoparib group and 123 of 126 subjects (97.6%) in the chemotherapy group, and those for which a causal relationship to study drug could not be

ruled out occurred in 256 of 286 subjects (89.5%) in the talazoparib group and 112 of 126 subjects (88.9%) in the chemotherapy group. Adverse events reported by ≥15% of subjects in either group are shown in Table 72.

Table 72. Adverse events reported by ≥15% of subjects in either group

SOC PT (MedDRA ver.20.0)	n (%)			
	Talazoparib N = 286		Chemotherapy N = 126	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	282 (98.6)	201 (70.3)	123 (97.6)	81 (64.3)
Gastrointestinal disorders				
Nausea	142 (49.7)	1 (0.3)	60 (47.6)	2 (1.6)
Vomiting	76 (26.6)	7 (2.4)	30 (23.8)	3 (2.4)
Diarrhoea	68 (23.8)	2 (0.7)	34 (27.0)	7 (5.6)
Constipation	67 (23.4)	1 (0.3)	28 (22.2)	0
Abdominal pain	38 (13.3)	2 (0.7)	20 (15.9)	2 (1.6)
General disorders and administration site conditions				
Fatigue	147 (51.4)	7 (2.4)	54 (42.9)	4 (3.2)
Asthenia	45 (15.7)	5 (1.7)	12 (9.5)	2 (1.6)
Pyrexia	35 (12.2)	2 (0.7)	22 (17.5)	0
Musculoskeletal and connective tissue disorders				
Back pain	69 (24.1)	7 (2.4)	20 (15.9)	2 (1.6)
Arthralgia	55 (19.2)	1 (0.3)	15 (11.9)	0
Pain in extremity	45 (15.7)	2 (0.7)	14 (11.1)	0
Blood and lymphatic system disorders				
Anaemia	155 (54.2)	115 (40.2)	24 (19.0)	6 (4.8)
Neutropenia	78 (27.3)	54 (18.9)	38 (30.2)	31 (24.6)
Thrombocytopenia	50 (17.5)	23 (8.0)	7 (5.6)	2 (1.6)
Respiratory, thoracic and mediastinal disorders				
Cough	65 (22.7)	2 (0.7)	20 (15.9)	0
Dyspnoea	54 (18.9)	7 (2.4)	19 (15.1)	3 (2.4)
Nervous system disorders				
Headache	97 (33.9)	5 (1.7)	29 (23.0)	2 (1.6)
Dizziness	53 (18.5)	1 (0.3)	13 (10.3)	2 (1.6)
Metabolism and nutrition disorders				
Decreased appetite	62 (21.7)	1 (0.3)	28 (22.2)	1 (0.8)
Skin and subcutaneous tissue disorders				
Alopecia	78 (27.3)	0	35 (27.8)	0
Palmar-plantar erythrodysaesthesia syndrome	4 (1.4)	1 (0.3)	28 (22.2)	4 (3.2)

Serious adverse events occurred in 103 of 286 subjects (36.0%) in the talazoparib group and 39 of 126 subjects (31.0%) in the chemotherapy group. Those reported by ≥5 subjects in each group were anaemia (18 subjects [6.3%]); pyrexia (8 subjects [2.8%]); pulmonary embolism (6 subjects [2.1%]); and headache; back pain; and vomiting (5 subjects each [1.7%]) in the talazoparib group and pleural effusion (7 subjects [5.6%]) in the chemotherapy group, and a causal relationship to study drug could not be ruled out for anaemia (16 subjects); pyrexia (2 subjects); and headache; and pulmonary embolism (1 subject each) in the talazoparib group.

Adverse events leading to study drug discontinuation occurred in 15 of 286 subjects (5.2%) in the talazoparib group and 7 of 126 subjects (5.6%) in the chemotherapy group. Those reported by ≥2 subjects in each group were anaemia (3 subjects [1.0%]) in the talazoparib group, and a causal relationship to study drug could not be ruled out for all those events.

7.3.1.5 Foreign phase I study (Study 001)

Adverse events occurred in (1) 7 of 9 patients with normal renal function (77.8%), (2) 8 of 9 patients with mild renal impairment (88.9%), (3) 8 of 8 patients with moderate renal impairment (100%), and (4) 7 of 8 patients with severe renal impairment (87.5%), and those for which a causal relationship to study drug could not be ruled out occurred in (1) 6 of 9 patients (66.7%), (2) 6 of 9 patients (66.7%), (3) 4 of 8 patients (50.0%), and (4) 7 of 8 patients (87.5%). Adverse events reported by ≥30% of patients in each group were (1) nausea (4 patients [44.4%]); and dyspnoea (3 patients [33.3%]), (2) fatigue (4 patients [44.4%]); and constipation (3 patients [33.3%]), and (3) nausea (3 patients [37.5%]).

Serious adverse events occurred in (1) 1 of 9 patients (11.1%) and (4) 2 of 8 patients (25.0%). The reported serious adverse events were (1) condition aggravated (1 patient [11.1%]) and (4) dyspnoea; metabolic acidosis; dehydration; and pneumonia (1 patient each [12.5%]), and a causal relationship to study drug was denied for all those events.

Adverse events leading to study drug discontinuation occurred in (1) 1 of 9 patients (11.1%) and (4) 1 of 8 patients (12.5%). The reported adverse events leading to study drug discontinuation were (1) thrombocytopenia (1 patient [11.1%]) and (4) dehydration (1 patient [12.5%]), and a causal relationship to study drug could not be ruled out for (1) thrombocytopenia (1 patient).

7.3.1.6 Foreign phase I study (Study 002)

Adverse events occurred in (1) 6 of 7 patients with normal hepatic function (85.7%), (2) 8 of 10 patients with mild hepatic impairment (80.0%), (3) 3 of 5 patients with moderate hepatic impairment (60.0%), and (4) 14 of 16 patients with severe hepatic impairment (87.5%), and those for which a causal relationship to study drug could not be ruled out occurred in (1) 4 of 7 patients (57.1%), (2) 3 of 10 patients (30.0%), and (4) 2 of 16 patients (12.5%). Adverse events reported by ≥25% of patients in each group were (1) fatigue (4 patients [57.1%]); and nausea; diarrhoea; and constipation (2 patients each [28.6%]) and (4) disease progression; hyperbilirubinaemia; and hyponatraemia (4 patients each [25.0%]).

Serious adverse events occurred in (1) 1 of 7 patients (14.3%), (2) 3 of 10 patients (30.0%), (3) 2 of 5 patients (40.0%), and (4) 13 of 16 patients (81.3%). Those reported by ≥2 patients in each group were (4) disease progression (4 patients [25.0%]); hyponatraemia (3 patients [18.8%]); and hepatic encephalopathy; hyperkalaemia; hyperbilirubinaemia; neoplasm progression; and abdominal pain (2 patients each [12.5%]), and a causal relationship to study drug was denied for all those events.

Adverse events leading to study drug discontinuation occurred in (3) 2 of 5 patients (40.0%) and (4) 10 of 16 patients (62.5%). Those reported by ≥2 patients in each group were (4) hyponatraemia (3 patients [18.8%]); and hepatic encephalopathy; and disease progression (2 patients each [12.5%]), and a causal relationship to study drug was denied for all those events.

7.3.1.7 Foreign phase I study (Study 003)

Adverse events occurred in 4 of 6 subjects (66.7%), and those for which a causal relationship to study drug could not be ruled out occurred in 1 of 6 subjects (16.7%). Adverse events reported by ≥2 subjects were dizziness (2 subjects [33.3%]).

There were no serious adverse events or adverse events leading to study drug discontinuation.

7.3.1.8 Foreign phase I study (Study 004)

7.3.1.8.1 Part 1

Adverse events occurred in (1) 12 of 19 subjects (63.2%) following administration of talazoparib alone, (2) 3 of 16 subjects (18.8%) following administration of itraconazole alone, and (3) 5 of 15 subjects (33.3%) following coadministration of talazoparib with itraconazole, and those for which a causal relationship to study drug could not be ruled out occurred in (1) 3 of 19 subjects (15.8%) and (2) 1 of 16 subjects (6.3%). Adverse events reported by ≥10% of subjects who received talazoparib were (1) abdominal pain; constipation; and anaemia (3 subjects each [15.8%]); and dyspepsia; epistaxis, and neoplasm progression (2 subjects each [10.5%]) and (3) anaemia (2 subjects [13.3%]).

Serious adverse events occurred in (1) 3 of 19 subjects (15.8%) and (3) 1 of 15 subjects (6.7%). The reported serious adverse events were (1) neoplasm progression (2 subjects [10.5%]); and mouth haemorrhage (1 subject [5.3%]) and (3) neoplasm progression (1 subject [6.7%]), and a causal relationship to study drug could not be ruled out for (1) mouth haemorrhage (1 subject).

Adverse events leading to study drug discontinuation occurred in (1) 4 of 19 subjects (21.1%) and (3) 1 of 15 subjects (6.7%). The reported adverse events leading to study drug discontinuation were (1) anaemia (2 subjects [10.5%]); and neoplasm progression; and vomiting (1 subject each [5.3%]) and (3) neoplasm progression (1 subject [6.7%]), and a causal relationship to study drug was denied for all those events.

7.3.1.8.2 Part 2

Adverse events occurred in (1) 7 of 17 subjects (41.2%) following administration of talazoparib alone, (2) 8 of 16 subjects (50.0%) following administration of rifampicin alone, and (3) 5 of 15 subjects (33.3%) following coadministration of talazoparib with rifampicin, and those for which a causal relationship to study drug could not be ruled out occurred in (1) 4 of 17 subjects (23.5%), (2) 5 of 16 subjects (31.3%), and (3) 2 of 15 subjects (13.3%). Adverse events reported by ≥10% of subjects who received talazoparib (1)(3) were (1) anaemia (2 subjects [11.8%]).

Serious adverse events occurred in (1) 1 of 17 subjects (5.9%) and (2) 1 of 16 subjects (6.3%). The reported serious adverse events were (1) anastomotic stenosis (1 subject [5.9%]) and (2) hydrothorax (1 subject [6.3%]), and a causal relationship to study drug was denied for both events.

Adverse events leading to study drug discontinuation occurred in (1) 1 of 17 subjects (5.9%) and (2) 1 of 16 subjects (6.3%). The reported adverse events leading to study drug discontinuation were (1) anastomotic stenosis (1 subject [5.9%]) and (2) nausea; fatigue; and vomiting (1 subject each [6.3%]), and a causal relationship to study drug could not be ruled out for all those events.

7.3.1.9 Foreign phase I study (Study 005)

Adverse events occurred in 28 of 37 subjects (75.7%), and those for which a causal relationship to study drug could not be ruled out occurred in 17 of 37 subjects (45.9%). Adverse events reported by ≥10% of subjects were fatigue (9 subjects [24.3%]); nausea (8 subjects [21.6%]); diarrhoea (5 subjects [13.5%]); and vomiting and anaemia (4 subjects each [10.8%]).

Serious adverse events occurred in 3 of 37 subjects (8.1%). The reported serious adverse events were toxicity to various agents; syncope; large intestinal obstruction; spontaneous haemorrhage; and anaemia (1 subject each [2.7%]), and a causal relationship to study drug could not be ruled out for anaemia (1 subject).

There were no adverse events leading to study drug discontinuation.

7.3.1.10 Foreign phase I study (Study 022)

7.3.1.10.1 Arm 1

Adverse events occurred in all subjects, and those for which a causal relationship to study drug could not be ruled out occurred in 17 of 25 subjects (68.0%). Adverse events reported by ≥30% of subjects were fatigue (11 subjects [44.0%]); pyrexia; and febrile neutropenia (9 subjects each [36.0%]); and diarrhoea; vomiting; dyspnoea; and epistaxis (8 subjects each [32.0%]).

Serious adverse events occurred in 21 of 25 subjects (84.0%). Those reported by ≥3 subjects were febrile neutropenia (8 subjects [32.0%]); neutropenic sepsis (4 subjects [16.0%]); and acute myeloid leukaemia; pneumonia; and epistaxis (3 subjects each [12.0%]), and a causal relationship to study drug could not be ruled out for neutropenic sepsis (2 subjects); and febrile neutropenia (1 subject).

Adverse events leading to study drug discontinuation occurred in 3 of 25 subjects (12.0%). The reported adverse events leading to study drug discontinuation were mucosal inflammation; pneumonia; and peripheral sensory neuropathy (1 subject each [4.0%]), and a causal relationship to study drug could not be ruled out for peripheral sensory neuropathy.

7.3.1.10.2 Arm 2

Adverse events occurred in all subjects, and those for which a causal relationship to study drug could not be ruled out occurred in 6 of 8 subjects (75.0%). Adverse events reported by ≥30% of subjects were pain in extremity (4 subjects [50.0%]); and pyrexia; chills; thrombocytopenia; neutropenia; and cough (3 subjects each [37.5%]).

Serious adverse events occurred in 4 of 8 subjects (50.0%). No specific serious adverse events occurred in ≥2 subjects.

There were no adverse events leading to study drug discontinuation.

7.3.1.11 Foreign phase I study (Study 023)

Adverse events occurred (1) 3 of 18 subjects (16.7%) after administration of talazoparib under fasted conditions and (2) 4 of 18 subjects (22.2%) after administration of talazoparib under fed conditions, and those for which a causal relationship to study drug could not be ruled out occurred in (2) 1 of 18 subjects (5.6%). No specific adverse events occurred in ≥2 subjects in either group.

There were no serious adverse events or adverse events leading to study drug discontinuation.

7.3.1.12 Foreign phase II study (Study 020)

Adverse events occurred in 60 of 61 subjects (98.4%), and those for which a causal relationship to study drug could not be ruled out occurred in 58 of 61 subjects (95.1%). Adverse events reported by ≥20% of subjects were fatigue (48 subjects [78.7%]); nausea (42 subjects [68.9%]); alopecia (35 subjects [57.4%]); anaemia (30 subjects [49.2%]); headache (26 subjects [42.6%]); dizziness (20 subjects [32.8%]); constipation (19 subjects [31.1%]); and diarrhoea (13 subjects [21.3%]).

Serious adverse events occurred in 11 of 61 subjects (18.0%). Those reported by ≥2 subjects were anaemia (9 subjects [14.8%]), and a causal relationship to study drug could not be ruled out for all those events.

Adverse events leading to study drug discontinuation occurred in 3 of 61 subjects (4.9%). Those reported by ≥2 subjects were anaemia (2 subjects [3.3%]), and a causal relationship to study drug could not be ruled out for both events.

7.3.1.13 Foreign extension study (Study 010)

Adverse events occurred in (1) 2 of 2 subjects (100%) in the talazoparib 0.25 mg starting dose group, (2) 58 of 61 subjects (95.1%) in the talazoparib 0.5 mg starting dose group, (3) 3 of 3 subjects (100%) in the talazoparib 0.75 mg starting dose group, and (4) 47 of 52 subjects (90.4%) in the talazoparib 1 mg starting dose group, and those for which a causal relationship to study drug could not be ruled out occurred in (1) 1 of 2 subjects (50.0%), (2) 41 of 61 subjects (67.2%), (3) 3 of 3 subjects (100%), and (4) 31 of 52 subjects (59.6%). Adverse events reported by ≥2 subjects and ≥20% of subjects in each group were (2) anaemia (18 subjects [29.5%]); nausea (16 subjects [26.2%]); and fatigue (15 subjects [24.6%]), (3) anaemia; neutropenia; and white blood cell count decreased (2 subjects each [66.7%]), and (4) anaemia (19 subjects [36.5%]); and nausea; and fatigue (11 subjects each [21.2%]).

Serious adverse events occurred in (1) 1 of 2 subjects (50.0%), (2) 24 of 61 subjects (39.3%), (3) 2 of 3 subjects (66.7%), and (4) 18 of 52 subjects (34.6%). Those reported by ≥2 subjects in each group were (2) disease

progression (4 subjects [6.6%]); dyspnoea (3 subjects [4.9%]); and sepsis; and anaemia (2 subjects each [3.3%]) and (4) ovarian cancer (3 subjects [5.8%]); and breast cancer; and anaemia (2 subjects each [3.8%]), and a causal relationship to study drug could not be ruled out for (2) anaemia (2 subjects) and (4) anaemia (2 subjects).

Adverse events leading to study drug discontinuation occurred in (2) 3 of 61 subjects (4.9%), (3) 2 of 3 subjects (66.7%), and (4) 4 of 52 subjects (7.7%). No specific adverse events leading to study drug discontinuation occurred in ≥2 subjects in any group.

7.3.2 Adverse events etc. observed in clinical studies for prostate cancer

7.3.2.1 Global phase III study (TALAPRO-2 study)

7.3.2.1.1 Part 1

Adverse events and those for which a causal relationship to study drug could not be ruled out occurred in all subjects. Adverse events reported by ≥50% of subjects in each group were (1) fatigue (5 subjects [83.3%]); anaemia (4 subjects [66.7%]); and diarrhoea; influenza like illness; fall; and decreased appetite (3 subjects each [50.0%]) in the talazoparib 0.5 mg group and (2) anaemia (10 subjects [76.9%]); neutrophil count decreased (8 subjects [61.5%]); and nausea; and decreased appetite (7 subjects each [53.8%]) in the talazoparib 1 mg group.

Serious adverse events occurred in (1) 3 of 6 subjects (50.0%) and (2) 6 of 13 subjects (46.2%). No specific serious adverse events occurred in ≥2 subjects in either group.

Adverse events leading to study drug discontinuation occurred in (1) 3 of 6 subjects (50.0%) and (2) 8 of 13 subjects (61.5%). Those reported by ≥2 subjects in each group were (1) anaemia (2 subjects [33.3%]) and (2) anaemia (4 subjects [30.8%]), and a causal relationship to study drug could not be ruled out for all those events.

7.3.2.1.2 Part 2 (Cohort 1)

Adverse events occurred in 392 of 398 subjects (98.5%) in the talazoparib group and 379 of 401 subjects (94.5%) in the placebo group, and those for which a causal relationship to study drug could not be ruled out occurred in 357 of 398 subjects (89.7%) in the talazoparib group and 279 of 401 subjects (69.6%) in the placebo group. Adverse events reported by ≥10% of subjects in either group are shown in Table 73.

Table 73. Adverse events reported by ≥10% of subjects in either group

SOC PT (MedDRA ver.25.0)	n (%)			
	Talazoparib N = 398		Placebo N = 401	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	392 (98.5)	299 (75.1)	379 (94.5)	181 (45.1)
Gastrointestinal disorders				
Nausea	82 (20.6)	2 (0.5)	50 (12.5)	3 (0.7)
Constipation	72 (18.1)	1 (0.3)	68 (17.0)	2 (0.5)
Diarrhoea	57 (14.3)	1 (0.3)	55 (13.7)	0
General disorders and administration site conditions				
Fatigue	134 (33.7)	16 (4.0)	118 (29.4)	8 (2.0)
Asthenia	57 (14.3)	11 (2.8)	38 (9.5)	3 (0.7)
Oedema peripheral	42 (10.6)	0	24 (6.0)	0
Musculoskeletal and connective tissue disorders				
Back pain	88 (22.1)	10 (2.5)	72 (18.0)	4 (1.0)
Arthralgia	58 (14.6)	2 (0.5)	79 (19.7)	2 (0.5)
Blood and lymphatic system disorders				
Anaemia	262 (65.8)	185 (46.5)	70 (17.5)	17 (4.2)
Vascular disorders				
Hypertension	55 (13.8)	21 (5.3)	62 (15.5)	30 (7.5)
Hot flush	47 (11.8)	0	54 (13.5)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	41 (10.3)	2 (0.5)	25 (6.2)	1 (0.2)
Injury, poisoning and procedural complications				
Fall	71 (17.8)	9 (2.3)	59 (14.7)	8 (2.0)
Nervous system disorders				
Dizziness	48 (12.1)	4 (1.0)	24 (6.0)	2 (0.5)
Metabolism and nutrition disorders				
Decreased appetite	86 (21.6)	5 (1.3)	63 (15.7)	4 (1.0)
Investigations				
Neutrophil count decreased	142 (35.7)	73 (18.3)	28 (7.0)	6 (1.5)
Platelet count decreased	98 (24.6)	29 (7.3)	14 (3.5)	4 (1.0)
White blood cell count decreased	88 (22.1)	25 (6.3)	18 (4.5)	0
Lymphocyte count decreased	45 (11.3)	20 (5.0)	20 (5.0)	4 (1.0)
Weight decreased	40 (10.1)	2 (0.5)	33 (8.2)	3 (0.7)

Serious adverse events occurred in 157 of 398 subjects (39.4%) in the talazoparib group and 107 of 401 subjects (26.7%) in the placebo group. Those reported by ≥5 subjects in each group were anaemia (55 subjects [13.8%]); haematuria (10 subjects [2.5%]); urinary tract infection (9 subjects [2.3%]); fall; and pulmonary embolism (6 subjects each [1.5%]); and myocardial infarction (5 subjects [1.3%]) in the talazoparib group and SARS-CoV-2 test positive; disease progression; and urinary retention (5 subjects each [1.2%]) in the placebo group. A causal relationship to study drug could not be ruled out for anaemia (50 subjects); haematuria; myocardial infarction; and fall (3 subjects each); and pulmonary embolism (2 subjects) in the talazoparib group and SARS-CoV-2 test positive (1 subject) in the placebo group.

Adverse events leading to study drug discontinuation occurred in 75 of 398 subjects (18.8%) in the talazoparib group and 49 of 401 subjects (12.2%) in the placebo group. Those reported by ≥3 subjects in each group were anaemia (33 subjects [8.3%]); neutrophil count decreased (13 subjects [3.3%]); and myocardial infarction; and pneumonia (3 subjects each [0.8%]) in the talazoparib group and anaemia (6 subjects [1.5%]); and SARS-CoV-2 test positive (3 subjects [0.7%]) in the placebo group. A causal relationship to study drug could not be ruled out for anaemia (31 subjects); neutrophil count decreased (13 subjects);

and myocardial infarction (2 subjects) in the talazoparib group and anaemia (6 subjects); and SARS-CoV-2 test positive (1 subject) in the placebo group.

7.3.2.2 Foreign phase II study (TALAPRO-1 study)

Adverse events occurred in 121 of 127 subjects (95.3%), and those for which a causal relationship to study drug could not be ruled out occurred in 100 of 127 subjects (78.7%). Adverse events reported by ≥20% of subjects were anaemia (62 subjects [48.8%]); nausea (42 subjects [33.1%]); decreased appetite (36 subjects [28.3%]); and asthenia (30 subjects [23.6%]).

Serious adverse events occurred in 43 of 127 subjects (33.9%). Those reported by ≥2 subjects were pulmonary embolism (8 subjects [6.3%]); anaemia (5 subjects [3.9%]); disease progression (4 subjects [3.1%]); urinary tract infection; and pneumonia (3 subjects each [2.4%]); and platelet count decreased; subdural haematoma; general physical health deterioration; pyrexia; and pain (2 subjects each [1.6%]), and a causal relationship to study drug could not be ruled out for anaemia (5 subjects); platelet count decreased (2 subjects); and pulmonary embolism; and pyrexia (1 subject each).

Adverse events leading to study drug discontinuation occurred in 15 of 127 subjects (11.8%). Those reported by ≥2 subjects were platelet count decreased; and back pain (2 subjects each [1.6%]), and a causal relationship to study drug could not be ruled out for platelet count decreased (1 subject).

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 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 5.3.5.1.1.CRPC, CTD 5.3.5.2.4.BC) 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 (1) talazoparib has efficacy in the treatment of *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy and (2) talazoparib/enzalutamide has efficacy in the treatment of *BRCA*-mutated mCRPC, and that talazoparib has acceptable safety in view of its benefits. Talazoparib is a small molecule PARP inhibitor. It is a drug with

a new active ingredient, which is considered to show anti-tumor activity by inducing cell death due to the accumulation of DNA damage through the prevention of the dissociation of PARP from the DNA and PARylation inhibition. Talazoparib is clinically meaningful as a treatment option for patients with (1) *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy and (2) *BRCA*-mutated mCRPC. PMDA considers that its efficacy, indications, dosage and administration, etc., need to be further discussed.

PMDA has concluded that talazoparib may be approved if talazoparib is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 15, 2023

Product Submitted for Approval

Brand Name	Talzenna Capsules 0.1 mg, Talzenna Capsules 0.25 mg, Talzenna Capsules 1 mg
Non-proprietary Name	Talazoparib Tosilate
Applicant	Pfizer Japan Inc.
Date of Application	February 24, 2023

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

PMDA's conclusion:

On the basis of the considerations in Sections "7.1.R.3 Safety," "7.2.R.3 Safety," and "7.R.1 Safety (Events that require attention following administration of talazoparib, etc.)" in the Review Report (1), adverse events that require particular attention following administration of talazoparib in patients with *gBRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy and following administration of talazoparib/enzalutamide in patients with mCRPC who have received no prior systemic therapy for mCRPC are myelosuppression, ILD, thromboembolism, MDS/AML, and second primary malignancies (other than MDS/AML). Attention should be paid to the possible occurrence of these adverse events during treatment with talazoparib.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with talazoparib or talazoparib/enzalutamide, talazoparib and talazoparib/enzalutamide in their respective target populations are tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., monitoring for and management of adverse events and dose interruption of talazoparib and enzalutamide.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2 Efficacy, clinical positioning, and indications

1.2.1 Breast cancer

PMDA's conclusion:

On the basis of the considerations in Section "7.1.R.2 Efficacy" in the Review Report (1), since a foreign phase III study in patients with *gBRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy (the EMBRACA study) produced the following results etc., the efficacy of talazoparib was demonstrated in patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer previously treated with an anthracycline and a taxane. On the basis of the results of the expansion part of a Japanese phase I study (Study 030) with similar enrollment criteria with the EMBRACA study, etc., the efficacy of talazoparib is expected also in Japanese patients.

- The EMBRACA study demonstrated the superiority of talazoparib to chemotherapy in the primary endpoint of IRF-assessed PFS, and the PFS benefit derived from talazoparib was clinically meaningful.
- The EMBRACA study showed no trend towards shorter OS (a secondary endpoint) in the talazoparib group than in the chemotherapy group.

On the basis of the considerations in Section "7.1.R.4 Clinical positioning and indication" in the Review Report (1), the following statements should be included in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections for breast cancer.

Indications

BRCA-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy

Precautions Concerning Indications

- The efficacy and safety of talazoparib in the neoadjuvant or adjuvant setting have not been established.
- Talazoparib should be used in the following patients:
  - Patients previously treated with anthracycline- and taxane-containing chemotherapy
  - Patients previously treated with either anthracycline- or taxane-containing chemotherapy if the other agent is contraindicated
- Talazoparib should be used in patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

At the Expert Discussion, the expert advisors supported PMDA’s conclusion. In addition, 1 expert advisor made the following comment.

- The impact of censoring and subsequent therapy on efficacy outcomes should also be assessed in patients included in the EMBRACA study, and it is necessary to discuss the efficacy of talazoparib, given these effects.

On the basis of the above comment from the Expert Discussion, PMDA reviewed the following findings regarding the impact of censoring and subsequent therapy on efficacy outcomes and then concluded that

the EMBRACA study demonstrated the efficacy of talazoparib in patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer previously treated with an anthracycline and a taxane.

- At the primary analysis of PFS in the EMBRACA study (data cutoff date on September 15, 2017), 35.2% of subjects in the talazoparib group and 42.4% of subjects in the chemotherapy group were censored for PFS in the ITT population, including 0.3% of subjects in the talazoparib group and 11.1% of subjects in the chemotherapy group censored due to consent withdrawal and 9.8% of subjects in the talazoparib group and 20.1% of subjects in the chemotherapy group censored due to the initiation of new anti-neoplastic therapy prior to disease progression or death.
- After adjustment for the impact of censoring due to consent withdrawal, the IRF-assessed PFS hazard ratio for talazoparib vs. chemotherapy [95% CI][64] was 0.55 [0.42, 0.72]. According to a sensitivity analysis in which patients who started new anti-neoplastic therapy were considered as progressive disease events, the IRF-assessed PFS hazard ratio for talazoparib vs. chemotherapy [95% CI][65] was 0.46 [0.36, 0.59].
- At the final analysis of OS in the EMBRACA study (data cutoff date on September 30, 2019), the proportions of patients who received subsequent therapy in the ITT population were 81.2% in the talazoparib group and 76.4% in the chemotherapy group, including 4.5% of patients in the talazoparib group and 32.6% of patients in the chemotherapy group who received a subsequent PARP inhibitor and 46.3% of patients in the talazoparib group and 41.7% of patients in the chemotherapy group who received subsequent platinum therapy.
- According to a sensitivity analysis using the rank-preserving structural failure time model (RPSFTM) to assess the impact of subsequent treatment with platinum therapy and/or a PARP inhibitor on OS, the OS hazard ratio for talazoparib vs. chemotherapy [95% CI][66] was 0.76 [0.50, 1.03]. According to a sensitivity analysis to assess the impact of the subsequent use of PARP inhibitor only on OS, the OS hazard ratio for talazoparib vs. chemotherapy [95% CI][67] was 0.82 [0.62, 1.05].

On the basis of the above, PMDA instructed the applicant to include the above statements in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections, and the applicant agreed.

1.2.2 Prostate cancer

PMDA's conclusion:

On the basis of the considerations in Section "7.2.R.2 Efficacy" in the Review Report (1), a global phase III study in patients with mCRPC who had received no prior systemic therapy for mCRPC (Part 2 of the TALAPRO-2 study) demonstrated the superiority of talazoparib plus enzalutamide to placebo plus enzalutamide in the primary endpoint of BICR-assessed rPFS in Cohort 1. Then, based on the results of efficacy analyses by genetic mutation status in Part 2 of the TALAPRO-2 study etc., the efficacy of

[64] An inverse probability weighted (IPW) Cox proportional-hazards model stratified by the number of previous cytotoxic chemotherapy regimens for inoperable or recurrent breast cancer (0, 1/2/3), HR status (positive, negative), and history of CNS metastasis (yes, no)

[65] A Cox proportional-hazards model stratified by the number of previous cytotoxic chemotherapy regimens for inoperable or recurrent breast cancer (0, 1/2/3), HR status (positive, negative), and history of CNS metastasis (yes, no)

[66] OS analysis adjusted for switching to platinum therapy or PARP inhibitor using the RPSFTM. After the data cutoff date for the final analysis of OS (September 30, 2019), the method of sensitivity analyses of OS was changed from inverse probability of censoring weighting (IPCW) to RPSFTM in the Statistical Analysis Plan Version 5 (dated [redacted], 20[redacted]) prior to the release of dataset ([redacted], 20[redacted]).

[67] OS analysis adjusted for survival after switching to PARP inhibitor using the RPSFTM

talazoparib/enzalutamide is expected in patients with *BRCA*-mutated mCRPC who have received no prior systemic therapy for mCRPC.

On the basis of the considerations in Section "7.2.R.4 Clinical positioning and indication" in the Review Report (1), the following statements should be included in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections for prostate cancer.

Indications

BRCA-mutated metastatic castration-resistant prostate cancer

Precautions Concerning Indications

- The efficacy and safety of talazoparib in the adjuvant setting have not been established.
- Talazoparib should be used in patients with a *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

At the Expert Discussion, the expert advisors supported PMDA's conclusion, but 1 expert advisor made the following comments.

- In Part 2 of the TALAPRO-2 study, the prospectively defined efficacy populations were the overall population and the HRR-deficient population, and the efficacy of talazoparib/enzalutamide should be evaluated in these 2 populations. The results of analyses of subgroups not prospectively defined should not be employed as the basis for important decision-making because of large random error and uncontrollable subjective bias.
- The results of rPFS and OS in Part 2 of the TALAPRO-2 study seem to suggest the effectiveness of talazoparib/enzalutamide in some patients in the non-*BRCA*-mutated HRR-deficient and HRR gene mutation-negative subgroups. The results of this study should not be considered evidence to deny the possibility of exploring predictive markers for response to talazoparib other than *BRCA* mutations, etc.
- The clinical relevance of the expected magnitude of the effects of talazoparib/enzalutamide in the non-*BRCA*-mutated HRR-deficient and HRR gene mutation-negative subgroups should be determined, referring to the hazard ratios in clinical studies of the currently approved drugs for mCRPC.
- When discussing whether efficacy differs among the *BRCA*-mutated, non-*BRCA*-mutated HRR-deficient, and HRR gene mutation-negative subgroups based on the results of Part 2 of the TALAPRO-2 study, the justification should be based on the results of interaction tests of treatment-by-subgroup.
- On the basis of the above, the expert advisor cannot support PMDA's conclusion that the expected therapeutic benefits do not outweigh the possible risks in non-*BRCA*-mutated HRR-deficient patients or HRR gene mutation-negative patients.

On the basis of the above comments from the Expert Discussion, PMDA reviewed the strategy for evaluating the results of Part 2 of the TALAPRO-2 study. Then, given the following points etc., PMDA did not change its conclusion presented in the Review Report (1) and concluded that talazoparib/enzalutamide has been shown

to be clinically meaningful in patients with *BRCA*-mutated mCRPC who have received no prior systemic therapy for mCRPC.

- With regard to the results of Part 2 (Cohort 1) of the TALAPRO-2 study, as described in Section "7.2.R.2.1 Study population" in the Review Report (1), not only the results in the overall population but also the results in the *BRCA*-mutated, non-*BRCA*-mutated HRR-deficient, and HRR gene mutation-negative subgroups need to be evaluated, from the standpoint of the mechanism of action.
- Due to the limited number of subjects in each subgroup, PMDA decided to comprehensively evaluate the results of the final analysis of rPFS by genetic mutation status in Part 2 (Cohort 1) of the TALAPRO-2 study (Review Report (1) Table 45), taking account of imbalances in patient characteristics between the treatment groups [see Section 7.2.R.2.4 in the Review Report (1)] and the analyses of the pooled HRR-deficient population (patients with HRR gene mutations enrolled in Cohorts 1 and 2 in Part 2 of the TALAPRO-2 study) (Review Report (1) Table 50).
- Although talazoparib/enzalutamide may have been effective in some patients in the non-*BRCA*-mutated HRR-deficient subgroup, as the number of patients with a mutation in each HRR gene was very limited, and the degrees of contribution of non-BRCA HRR factors to homologous recombination repair are unknown [see Section 7.2.R.2.1 in the Review Report (1)], efficacy evaluation based on the results of Part 2 of the TALAPRO-2 study is difficult.
- As to the results of the final analysis of rPFS and the results of the first and second interim analyses of OS by genetic mutation status in Part 2 of the TALAPRO-2 study (Review Report (1) Tables 45 to 51), the results of interaction tests of treatment-by-subgroup are shown in Table 74.

Table 74. Results of interaction tests

Table number	*BRCA*-mutated subgroup, non-*BRCA*-mutated HRR-deficient subgroup, and HRR gene mutation-negative subgroup[*1]	*BRCA*-mutated subgroup and non-*BRCA*-mutated HRR-deficient subgroup[*2]	*BRCA*-mutated subgroup and HRR gene mutation-negative subgroup[*3]
45	*P* = 0.0390	*P* = 0.0215	*P* = 0.0127
46	*P* = 0.3601	*P* = 0.6266	*P* = 0.1962
47	*P* = 0.3681	*P* = 0.8998	*P* = 0.3004
48	*P* = 0.1129	*P* = 0.0732	*P* = 0.0382
49	*P* = 0.2565	*P* = 0.5074	*P* = 0.5598
50	—	*P* = 0.0002	—
51	—	*P* = 0.5967	—

—, Not applicable
*1 An unstratified Cox proportional-hazards model with (1) treatment, (2) subgroup (*BRCA*-mutated subgroup, non-*BRCA*-mutated HRR-deficient subgroup, HRR gene mutation-negative subgroup), and (3) treatment-by-subgroup interaction as covariates
*2 An unstratified Cox proportional-hazards model with (1) treatment, (2) subgroup (*BRCA*-mutated subgroup, non-*BRCA*-mutated HRR-deficient subgroup), and (3) treatment-by-subgroup interaction as covariates
*3 An unstratified Cox proportional-hazards model with (1) treatment, (2) subgroup (*BRCA*-mutated subgroup, HRR gene mutation-negative subgroup), and (3) treatment-by-subgroup interaction as covariates

- On the basis of the above considerations, taking account of the mechanism of action and the magnitude of observed effects in each subgroup, it cannot be concluded that Part 2 of the TALAPRO-2 study showed that the expected benefits of talazoparib/enzalutamide outweigh the possible risks in the non-*BRCA*-mutated HRR-deficient and HRR gene mutation-negative subgroups.

On the basis of the above, PMDA instructed the applicant to include the above statements in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections, and the applicant agreed.

1.3 Dosage and administration

PMDA's conclusion:

On the basis of the considerations in Sections "7.1.R.5 Dosage and administration," "7.2.R.5 Dosage and administration," and "7.R.2 Recommended dosage modifications for talazoparib" in the Review Report (1), the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for (1) breast cancer and (2) prostate cancer.

(1) Breast cancer

Dosage and Administration

The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.
- For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the recommended starting dose of talazoparib is 0.75 mg once daily.
- Do not use the 0.25-mg capsule to administer a 1 mg dose of talazoparib because the bioequivalence between the 1-mg and 0.25-mg capsules has not been demonstrated.
- In the event of adverse reactions to talazoparib, withhold talazoparib, reduce the dose of talazoparib, or discontinue talazoparib, as per the tables below.

Dose reduction levels

Usual dose	1 mg once daily
First dose reduction	0.75 mg once daily
Second dose reduction	0.5 mg once daily
Third dose reduction	0.25 mg once daily
Fourth dose reduction	Discontinue

Recommended dosage modifications for adverse reactions

Adverse reactions	Severity*	Dosage modifications
Anemia	Hemoglobin <8 g/dL	Withhold talazoparib until levels resolve to ≥9 g/dL. After resolution, talazoparib may be resumed at the next lower dose level.
Thrombocytopenia	Platelet count <50,000/μL	Withhold talazoparib until levels resolve to ≥75,000/μL. After resolution, talazoparib may be resumed at the next lower dose level.
Neutropenia	Neutrophil count <1,000/μL	Withhold talazoparib until levels resolve to ≥1,500/μL. After resolution, talazoparib may be resumed at the next lower dose level.
Other adverse reactions	Grade 3 or 4	Withhold talazoparib until levels resolve to Grade ≤1. After resolution, talazoparib may be resumed at the next lower dose level.

* Severity grade based on NCI-CTCAE ver.4.03

(2) Prostate cancer

Dosage and Administration

The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of talazoparib in combination with other anti-neoplastic drugs have not been established.
- The efficacy and safety of talazoparib in patients not surgically or medically castrated have not been established.
- For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the recommended starting dose of talazoparib is 0.35 mg once daily.
- Do not use the 0.1-mg capsule to administer a 0.5 mg dose of talazoparib because the bioequivalence between the 0.1-mg and 0.25-mg capsules has not been demonstrated.
- In the event of adverse reactions to talazoparib, withhold talazoparib, reduce the dose of talazoparib, or discontinue talazoparib, as per the tables below.

Dose reduction levels

Usual dose	0.5 mg once daily
First dose reduction	0.35 mg once daily
Second dose reduction	0.25 mg once daily
Third dose reduction	0.1 mg once daily
Fourth dose reduction	Discontinue

Recommended dosage modifications for adverse reactions

Adverse reactions	Severity*	Dosage modifications
Anemia	Hemoglobin <8 g/dL	Withhold talazoparib until levels resolve to ≥9 g/dL. After resolution, talazoparib may be resumed at the next lower dose level.
Thrombocytopenia	Platelet count <50,000/μL	• For 1st occurrence, withhold talazoparib until levels resolve to ≥50,000/μL. After resolution, talazoparib may be resumed at the next lower dose level. • For recurrence, withhold talazoparib until levels resolve to ≥75,000/μL. After resolution, talazoparib may be resumed at the next lower dose level.
Neutropenia	Neutrophil count <1,000/μL	Withhold talazoparib until levels resolve to ≥1,500/μL. After resolution, talazoparib may be resumed at the next lower dose level.
Other adverse reactions	Grade 3 or 4	Withhold talazoparib until levels resolve to Grade ≤1. After resolution, talazoparib may be resumed at the next lower dose level.

* Severity grade based on NCI-CTCAE ver.4.03

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

On the basis of the above, PMDA instructed the applicant to include 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 plans to conduct post-marketing surveillance in patients with *BRCA*-mutated HER2-negatie inoperable or recurrent breast cancer and patients with CRPC to evaluate the safety etc. of talazoparib in clinical practice after marketing. The planned sample sizes are 84 patients and 104 patients, respectively, and the observation period is 24 weeks for both surveys.

On the basis of the considerations in Section "7.R.3 Post-marketing investigations" in the Review Report (1), PMDA concluded that it is necessary to conduct post-marketing surveillance in (1) patients with

BRCA-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy and (2) patients with *BRCA*-mutated mCRPC.

PMDA also made the following conclusions concerning the post-marketing surveillance plans for the above patients (1) and (2).

- Myelosuppression, ILD, thromboembolism, and second primary malignancies should be included in the safety specification, and then the information on the safety of talazoparib in patients with renal impairment should also be collected.
- The planned sample size and observation period need to be reviewed, taking account of the incidences of the events that are included in the safety specification for the surveillance, in clinical studies.

At the Expert Discussion, the expert advisors supported the above conclusions by PMDA.

On the basis of the above considerations, PMDA instructed the applicant to review the post-marketing surveillance plans for the above (1) and (2).

The applicant's response:

- For both surveys, myelosuppression, ILD, thromboembolism, and second primary malignancies will be included in the safety specification, and then the information on the safety of talazoparib in patients with renal impairment will also be collected.
- Taking account of the incidences etc. of the events that are included in the safety specification in clinical studies, the planned sample size and observation period will be determined as follows.
  (1) Post-marketing surveillance in patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy: a planned sample size of 37 patients, an observation period of 52 weeks
  (2) Post-marketing surveillance in patients with *BRCA*-mutated mCRPC: a planned sample size of 104 patients, an observation period of 52 weeks

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for talazoparib should include the safety specification presented in Table 75, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 76 to Table 78.

Table 75. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Myelosuppression • ILD • Thromboembolism	• Second primary malignancies • Embryo-fetal toxicity • Use in patients with renal impairment	None
Efficacy specification		
None		

Table 76. 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 • Use-results survey (BRCA-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy) • Use-results survey (BRCA-mutated mCRPC)	None	• Disseminate data gathered during early post-marketing phase vigilance • Develop information materials to be distributed to healthcare professionals • Develop information materials to be distributed to patients

Table 77. Outline of use-results survey in patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy (draft)

Objective	To evaluate the safety etc. of talazoparib in clinical practice after marketing.
Survey method	Central registry system
Population	Patients with *BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy
Observation period	52 weeks from the start of treatment with talazoparib
Planned sample size	37 patients as the safety analysis population
Main survey items	Safety specification: myelosuppression, ILD, thromboembolism, second primary malignancies Other main survey items: patient characteristics (sex, age, prior treatment, medical history, ECOG PS, renal impairment status, etc.), the use of talazoparib, adverse events, etc.

Table 78. Outline of use-results survey in patients with *BRCA*-mutated mCRPC (draft)

Objective	To evaluate the safety etc. of talazoparib in clinical practice after marketing.
Survey method	Central registry system
Population	Patients with *BRCA*-mutated mCRPC
Observation period	52 weeks from the start of treatment with talazoparib
Planned sample size	104 patients as the safety analysis population
Main survey items	Safety specification: myelosuppression, ILD, thromboembolism, second primary malignancies Other main survey items: patient characteristics (age, prior treatment, medical history, ECOG PS, renal impairment status, etc.), the use of talazoparib, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and dosage and administration as shown below, with the following condition, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and provided that the proper use of the product is ensured under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. As 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 classified as a powerful drug and a poisonous drug, respectively.

Indications

(1) Talzenna Capsules 0.1 mg

BRCA-mutated metastatic castration-resistant prostate cancer

(2) Talzenna Capsules 0.25 mg

BRCA-mutated metastatic castration-resistant prostate cancer

BRCA-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy

(3) Talzenna Capsules 1 mg

BRCA-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy

Dosage and Administration

(1) Talzenna Capsules 0.1 mg

The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition.

(2) Talzenna Capsules 0.25 mg

[*BRCA*-mutated metastatic castration-resistant prostate cancer]

The usual adult dosage is 0.5 mg of talazoparib taken orally once daily in combination with enzalutamide. The dosage should be reduced, as appropriate, according to the patient's condition.

[*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy]

The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

(3) Talzenna Capsules 1 mg

The usual adult dosage is 1 mg of talazoparib taken orally once daily. The dosage 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.

Warnings

Talzenna should be administered only to patients eligible for Talzenna therapy, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.

Contraindications

Patients with a history of hypersensitivity to any of the components of Talzenna

Precautions Concerning Indications

[*BRCA*-mutated metastatic castration-resistant prostate cancer]

1. The efficacy and safety of Talzenna in the adjuvant setting have not been established.
2. Talzenna should be used in patients with a *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

[*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy]

3. The efficacy and safety of Talzenna in the neoadjuvant or adjuvant setting have not been established.
4. Talzenna should be used in the following patients:
   - Patients previously treated with anthracycline- and taxane-containing chemotherapy
   - Patients previously treated with either anthracycline- or taxane-containing chemotherapy if the other agent is contraindicated
5. Talzenna should be used in patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by testing with the approved *in vitro* diagnostic or medical device.

Precautions Concerning Dosage and Administration

[*BRCA*-mutated metastatic castration-resistant prostate cancer]

1. The efficacy and safety of Talzenna in combination with other anti-neoplastic drugs have not been established.
2. The efficacy and safety of Talzenna in patients not surgically or medically castrated have not been established.
3. For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the recommended starting dose of Talzenna is 0.35 mg once daily.
4. Do not use the 0.1-mg capsule to administer a 0.5 mg dose of Talzenna because the bioequivalence between the 0.1-mg and 0.25-mg capsules has not been demonstrated.
5. In the event of adverse reactions to Talzenna, withhold Talzenna, reduce the dose of Talzenna, or discontinue Talzenna, as per the tables below.

Dose reduction levels

Usual dose	0.5 mg once daily
First dose reduction	0.35 mg once daily
Second dose reduction	0.25 mg once daily
Third dose reduction	0.1 mg once daily
Fourth dose reduction	Discontinue

Recommended dosage modifications for adverse reactions

Adverse reactions	Severity*	Dosage modifications
Anemia	Hemoglobin <8 g/dL	Withhold Talzenna until levels resolve to ≥9 g/dL. After resolution, Talzenna may be resumed at the next lower dose level.
Thrombocytopenia	Platelet count <50,000/μL	• For 1st occurrence, withhold Talzenna until levels resolve to ≥50,000/μL. After resolution, Talzenna may be resumed at the next lower dose level. • For recurrence, withhold Talzenna until levels resolve to ≥75,000/μL. After resolution, Talzenna may be resumed at the next lower dose level.
Neutropenia	Neutrophil count <1,000/μL	Withhold Talzenna until levels resolve to ≥1,500/μL. After resolution, Talzenna may be resumed at the next lower dose level.
Other adverse reactions	Grade 3 or 4	Withhold Talzenna until levels resolve to Grade ≤1. After resolution, Talzenna may be resumed at the next lower dose level.

* Severity grade based on NCI-CTCAE ver.4.03

[*BRCA*-mutated HER2-negative inoperable or recurrent breast cancer after prior chemotherapy]

6. The efficacy and safety of Talzenna in combination with other anti-neoplastic drugs have not been established.
7. For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), the recommended starting dose of Talzenna is 0.75 mg once daily.
8. Do not use the 0.25-mg capsule to administer a 1 mg dose of Talzenna because the bioequivalence between the 1-mg and 0.25-mg capsules has not been demonstrated.
9. In the event of adverse reactions to Talzenna, withhold Talzenna, reduce the dose of Talzenna, or discontinue Talzenna, as per the tables below.

Dose reduction levels

Usual dose	1 mg once daily
First dose reduction	0.75 mg once daily
Second dose reduction	0.5 mg once daily
Third dose reduction	0.25 mg once daily
Fourth dose reduction	Discontinue

Recommended dosage modifications for adverse reactions

Adverse reactions	Severity*	Dosage modifications
Anemia	Hemoglobin <8 g/dL	Withhold Talzenna until levels resolve to ≥9 g/dL. After resolution, Talzenna may be resumed at the next lower dose level.
Thrombocytopenia	Platelet count <50,000/μL	Withhold Talzenna until levels resolve to ≥75,000/μL. After resolution, Talzenna may be resumed at the next lower dose level.
Neutropenia	Neutrophil count <1,000/μL	Withhold Talzenna until levels resolve to ≥1,500/μL. After resolution, Talzenna may be resumed at the next lower dose level.
Other adverse reactions	Grade 3 or 4	Withhold Talzenna until levels resolve to Grade ≤1. After resolution, Talzenna may be resumed at the next lower dose level.

* Severity grade based on NCI-CTCAE ver.4.03

Appendix

List of Abbreviations

Abiraterone	abiraterone acetate
ABRAZO study	Study C3441008
ADT	androgen deprivation therapy
A/G ratio	albumin/globulin ratio
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
application	marketing application
AR	androgen receptor
AST	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
ATP	adenosine triphosphate
ATR	ataxia telangiectasia and Rad3 related
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BID	bis in die
BRCA1	BRCA1 DNA repair associated
BRCA2	BRCA2 DNA repair associated
BRCA gene	breast cancer susceptibility gene
BSEP	bile salt export pump
CDK12	cyclin dependent kinase 12
CHEK1	checkpoint kinase 1
CHEK2	checkpoint kinase 2
CI	confidence interval
CLcr	creatinine clearance
CL/F	apparent oral clearance
CLL	chronic lymphocytic leukemia
CMC	carboxymethylcellulose
CPP	critical process parameter
CPS	combined positive score: the number of PD-L1 stained cells (tumor cells, macrophages, and lymphocytes) divided by the total number of viable tumor cells, multiplied by 100
CQA	critical quality attribute
CR	complete response
CRPC	castration-resistant prostate cancer
CTC	circulating tumor cells
CYP	cytochrome P450
^{14}C-talazoparib	^{14}C-talazoparib tosilate
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
docetaxel	docetaxel hydrate
DSB	double strand break

ECOG	Eastern Cooperative Oncology Group
efflux ratio	The ratio of apparent permeability coefficient in the secretory direction to the absorptive direction
eGFR	estimated glomerular filtration rate
EMBRACA study	Study C3441009
F	absolute bioavailability
F1	relative bioavailability
FANCA	fanconi anemia, complementation group A
FAS	full analysis set
g*BRCA* mutation	germline *BRCA* mutation
GC	gas chromatography
γ-GTP	γ-glutamyl transferase
HER2	human epidermal growth factor receptor 2
hERG	human *ether-a-go-go* related gene
HLGT	high level group term
HR	hormone receptor
HRR	homologous recombination repair
ICH Q1E guideline	Guideline on Evaluation of Stability Data (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ILD	interstitial lung disease
IR	infrared absorption spectroscopy
IRF	independent radiology facility
ITT	intention-to-treat
Japanese clinical practice guidelines (Breast cancer)	Clinical practice guidelines for breast cancer, edited by the Japanese Breast Cancer Society
Japanese clinical practice guidelines (Prostate cancer)	Clinical practice guidelines for prostate cancer, edited by the Japanese Urological Association
ka	first-order absorption rate constant
KLK3	kallikrein 3
LC	liquid chromatography
LSD	least significant difference
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCL	mantle cell lymphoma
mCRPC	metastatic castration-resistant prostate cancer
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
M/E ratio	myeloid/erythroid ratio
MedDRA	Medical Dictionary for Regulatory Activities
MLH-1	mutL homolog 1
MMS	methyl methanesulfonate
MRE11A	meiotic recombination 11 homolog A
mRNA	messenger ribonucleic acid
MS	mass spectrometry
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NBN	nibrin

NCCN guidelines (Breast cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Breast Cancer
NCCN guidelines (Prostate cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Prostate Cancer
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	not evaluable
NMR	nuclear magnetic resonance spectroscopy
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
PALB2	partner and localizer of BRCA2
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basal direction
PAR	poly (ADP-ribose)
PARP	poly (ADP-ribose) polymerase
PD	progressive disease
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
placebo/enzalutamide	the combination of placebo and enzalutamide
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PSA	prostate-specific antigen
PT	preferred term
PTEN	phosphatase and tensin homolog
QD	quaque die
QOL	quality of life
ΔQTcF	change from baseline in QT interval corrected using the Fridericia formula
QW	quaque a week
RAD51C	RAD51 paralog C
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RPSFTM	rank-preserving structural failure time model
rPFS	radiographic progression free survival
S-1	a combination formulation of tegafur, gimeracil, and oteracil potassium
SD	stable disease
SMQ	standardized MedDRA queries
SOC	system organ class
SSB	single strand break
Study 001	Study C3441001
Study 002	Study C3441002
Study 003	Study C3441003
Study 004	Study C3441004

Study 005	Study C3441005
Study 007	Study C3441007
Study 010	Study C3441010
Study 022	Study C3441022
Study 023	Study C3441023
Study 030	Study C3441030
TALAPRO-1 study	Study C3441006
TALAPRO-2 study	Study C3441021
talazoparib	talazoparib tosilate
talazoparib/enzalutamide	the combination of talazoparib and enzalutamide
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
ULN	upper limit of normal
UV-VIS	ultraviolet-visible spectroscopy
V_2/F	apparent central volume of distribution