Review Report

July 5, 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	Lynparza Tablets 100 mg, Lynparza Tablets 150 mg
Non-proprietary Name	Olaparib (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	February 10, 2022
Dosage Form/Strength	Tablets, each containing 100 mg or 150 mg of olaparib
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
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, in combination with abiraterone, has efficacy in the treatment of metastatic castration-resistant prostate cancer in *BRCA* mutation-positive patients who have not received prior chemotherapy for metastatic castration-resistant prostate cancer, 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 conditions.

Indications

Maintenance treatment of recurrent ovarian cancer responding to platinum-based chemotherapy
Maintenance treatment of *BRCA* mutation-positive ovarian cancer after first-line chemotherapy
Maintenance treatment of homologous recombination deficiency-positive ovarian cancer after first-line chemotherapy including bevacizumab (genetical recombination)
Treatment of inoperable or recurrent *BRCA* mutation-positive HER2-negative breast cancer previously treated with chemotherapy
Adjuvant pharmacotherapy for *BRCA* mutation-positive HER2-negative breast cancer with a high risk of recurrence
Treatment of *BRCA* mutation-positive metastatic castration-resistant prostate cancer

Maintenance treatment of incurable, unresectable *BRCA* mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs

(No change is made in the present partial change application. Double-line denotes additions made as of August 24, 2022, after submission of the present application.)

Dosage and Administration

Maintenance treatment of recurrent ovarian cancer responding to platinum-based chemotherapy, maintenance treatment of BRCA mutation-positive ovarian cancer after first-line chemotherapy, ~~treatment of BRCA mutation-positive metastatic castration-resistant prostate cancer,~~ maintenance treatment of incurable, unresectable BRCA mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs

The usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.

Maintenance treatment of homologous recombination deficiency-positive ovarian cancer after first-line chemotherapy including bevacizumab (genetical recombination)

When administered in combination with bevacizumab (genetical recombination) ~~for the maintenance treatment of homologous recombination deficiency-positive ovarian cancer in patients who have received first chemotherapy including bevacizumab (genetical recombination)~~, the usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.

Treatment of inoperable or recurrent BRCA mutation-positive HER2-negative breast cancer previously treated with chemotherapy, adjuvant pharmacotherapy for BRCA mutation-positive HER2-negative breast cancer with a high risk of recurrence

The usual adult dosage is 300 mg of olaparib administered orally twice daily. For adjuvant pharmacotherapy, the treatment duration must not exceed 1 year. The dose may be adjusted according to the patient's condition.

Treatment of BRCA mutation-positive metastatic castration-resistant prostate cancer

The usual adult dosage is 300 mg of olaparib administered orally twice daily. When administered in combination with other drugs, abiraterone acetate and prednisolone should be selected. The dose may be adjusted according to the patient's condition.

(Underline denotes additions. Strikethrough denotes deletions. Double-line denotes additions made as of August 24, 2022, after submission of the present application.)

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

August 23, 2022

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	Lynparza Tablets 100 mg, Lynparza Tablets 150 mg
Non-proprietary Name	Olaparib
Applicant	AstraZeneca K.K.
Date of Application	February 10, 2022
Dosage Form/Strength	Tablets, each containing 100 mg or 150 mg of olaparib
Proposed Indications	Maintenance treatment of recurrent ovarian cancer responding to platinum-based chemotherapy Maintenance treatment of *BRCA* mutation-positive ovarian cancer after first-line chemotherapy Maintenance treatment of homologous recombination deficiency-positive ovarian cancer after first-line chemotherapy including bevacizumab (genetical recombination) Treatment of inoperable or recurrent *BRCA* mutation-positive HER2-negative breast cancer previously treated with chemotherapy Treatment of ~~*BRCA* mutation-positive~~ metastatic castration-resistant prostate cancer Maintenance treatment of incurable, unresectable *BRCA* mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs (Strikethrough denotes deletions.)
Proposed Dosage and Administration	The usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition. When administered in combination with bevacizumab (genetical recombination) for the maintenance treatment of homologous recombination deficiency-positive ovarian cancer in patients after

first-line chemotherapy including bevacizumab (genetical recombination), the usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.

When administered in combination with abiraterone acetate and prednisolone for the treatment of metastatic castration-resistant prostate cancer, the usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.

(Underline denotes additions.)

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

Olaparib, discovered by KuDOS Pharmaceuticals (UK), is a low-molecular-weight inhibitor of poly (ADP-ribose) polymerase (PARP). Olaparib inhibits the dissociation of PARP from DNA and blocks the formation of a poly (ADP-ribose) polymerase (PAR) chain, inducing the generation of a double-strand break (DSB). In tumors where homologous recombination repair (HRR) pathway-mediated DNA repair system has been damaged by *BRCA* mutations, etc., olaparib is expected to inhibit the repair of the generated DSB (*Cell.* 2002;108:171-82) and accumulate DNA damage and induces apoptosis (*Sci Transl Med.* 2016;8:362ps17), thereby inhibiting tumor growth.

In Japan, olaparib was approved for the maintenance treatment of recurrent ovarian cancer in patients who are in response to platinum-based chemotherapy in January 2018, the treatment of inoperable or recurrent *BRCA* mutation-positive HER2-negative breast cancer in patients who have previously been treated with chemotherapy in July 2018, maintenance treatment of *BRCA* mutation-positive ovarian cancer in patients who have received first-line chemotherapy in June 2019, and maintenance treatment of homologous recombination deficiency-positive ovarian cancer in patients who have received first-line chemotherapy including bevacizumab (genetical recombination), the treatment of metastatic *BRCA* mutation-positive castration-resistant prostate cancer, and maintenance treatment of incurable, unresectable *BRCA* mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs in December 2020.

1.2 Development history, etc.

During the development of olaparib/abiraterone therapy for metastatic castration-resistant prostate cancer (mCRPC), the applicant initiated a foreign phase II study primarily in patients with mCRPC who had previously been treated with docetaxel-based chemotherapy (Study 08) in April 2014, and a global phase III study in patients with pharmacotherapy-naïve mCRPC (PROpel study) in October 2018.

Applications with pivotal data from the PROpel study were filed in June 2022 in the US and December 2021 in EU, and are currently under review.

As of July 2022, olaparib/abiraterone therapy has not been approved for the treatment of pharmacotherapy-naïve mCRPC in any country or region.

In Japan, patient enrollment in the PROpel study began in December 2018.
Recently, with pivotal data from the study, a partial change application has been filed to add a new indication and dosage regimen of olaparib/abiraterone therapy for pharmacotherapy-naïve mCRPC.

2. Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication and a new dosage, no data relating to quality have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacology data were previously evaluated for the initial approval of olaparib, and no new study data have been submitted.

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

Although the present application is intended for a new indication and new dosage, the non-clinical pharmacokinetics data were previously evaluated for the initial approval of olaparib, and no new study data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication and a new dosage, no data relating to toxicity have been submitted.

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

Although the present application is intended for a new indication and new dosage, the biopharmaceutic data and associated analytical methods were previously evaluated for the initial approval of olaparib, and no new study data have been submitted.

6.2 Clinical pharmacology

The pharmacokinetics (PK) of olaparib and abiraterone were evaluated in patients with cancer who were receiving olaparib/abiraterone therapy.

6.2.1 Global clinical phase III study (CTD 5.3.5.1.1, PROpel study, October 2018 to ongoing [data cutoff on July 30, 2021])

A randomized, double-blind, comparative study was conducted to evaluate the efficacy and safety of olaparib versus placebo administered in combination with abiraterone in 796 patients with mCRPC who have not received prior chemotherapy for mCRPC (124 patients were included in the PK analysis).

Patients received olaparib 300 mg or placebo administered orally twice daily (BID) and abiraterone 1,000 mg administered orally once daily (QD). Plasma concentrations of olaparib, abiraterone, and Δ4-abiraterone (the active metabolite of abiraterone) were assessed.

Table 1 shows steady-state PK parameters of olaparib, abiraterone, and Δ4-abiraterone.

Table 1. PK parameters of olaparib, abiraterone, and Δ4-abiraterone

Treatment	Analyte	N	C_{max} (ng/mL)	t_{max}*1 (h)	AUC*2 (ng·h/mL)
Olaparib	Olaparib	66	6,280 (33.7)	2.00 (0.25, 5.08)	39,300 (42.2)*3
	Abiraterone	64	113 (137)	2.04 (0, 8.00)	394 (108)*4
	Δ4-abiraterone	65	3.02 (102)	2.58 (0, 8.00)	11.7 (80.3)*4
Placebo	Abiraterone	56	105 (106)	2.00 (0, 8.00)	340 (78.0)*5
	Δ4-abiraterone	58	3.90 (100)	2.01 (0, 7.00)	14.7 (71.0)*5

Geometric mean (geometric coefficient of variation [%]); *1, Median (minimum, maximum); *2, AUC_{tau} for olaparib, $AUC_{0\text{-}8h}$ for abiraterone and Δ4-abiraterone; *3, N = 52; *4, N = 54; *5, N = 44

The applicant's explanation:

The above results, along with the steady-state C_{max} and AUC_{tau} values of olaparib monotherapy in the PROfound study,[1)] 7,510 ng/mL and 39,200 ng·h/mL, respectively, are suggestive of no pharmacokinetic interaction between olaparib and abiraterone.

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the clinical pharmacology of olaparib was acceptable.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 2 studies, i.e., the global phase III study and the foreign phase II study, shown in Table 2.

1) A global phase III study conducted to compare the efficacy and safety of olaparib 300 mg BID versus the investigator's choice of abiraterone or enzalutamide, administered in combination with androgen deprivation therapy (ADT), in patients with HRR-related gene mutation-positive mCRPC who had previously been treated with abiraterone, enzalutamide, or both drugs

Table 2. Clinical studies on efficacy and safety

Data category	Geographical location	Study identifier	Phase	Study population	N	Dosage regimen*	Main endpoints
Evaluation data	Global	PROpel study	III	Patients with pharmacotherapy-naïve mCRPC	796 (a) 399 (b) 397	Abiraterone 1,000 mg administered orally QD in combination with (a) olaparib 300 mg or (b) placebo administered orally BID	Efficacy Safety
	Foreign	Study 08	II	Part A: Patients with mCRPC Part B: Patients with mCRPC treated with docetaxel	Part A (a) 3 (b) 7 (c) 6 Part B (d) 71 (e) 71	Part A (a) Olaparib 200 mg administered orally BID in combination with abiraterone 1,000 mg administered orally QD (b) Olaparib 300 mg administered orally BID for 3 to 7 days, followed by olaparib 300 mg administered orally BID in combination with abiraterone 1,000 mg administered orally QD (c) Abiraterone 1,000 mg orally administered QD for 5 to 7 days, followed by olaparib 300 mg administered orally BID in combination with abiraterone 1,000 mg administered orally QD Part B (d) Olaparib 300 mg or (e) placebo administered orally BID in combination with abiraterone 1,000 mg administered orally QD	Efficacy Safety

* Abiraterone was administered in combination with prednisolone or prednisone (unapproved in Japan) 5 mg administered orally BID.

The following section summarizes the clinical studies. Common adverse events other than deaths reported in each study are detailed in Section "7.2 Adverse events reported in clinical studies."

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1.1, PROpel study, October 2018 to ongoing [data cutoff on July 30, 2021])

A randomized, double-blind, comparative study was conducted at 126 sites in 17 countries including Japan to evaluate the efficacy and safety of olaparib versus placebo administered in combination with abiraterone in patients with mCRPC who had not received prior chemotherapy for mCRPC (target sample size, 720 patients). The criteria pertaining to prior chemotherapies of target population were as follows.

- Patients must not have received medication for mCRPC previously, except prior ADT use and antiandrogen agents such as bicalutamide, flutamide, or nilutamide used ≥4 weeks before the start of the study treatment.
- Treatment with enzalutamide, apalutamide, or darolutamide prior to the diagnosis of mCRPC must have been completed ≥12 months before enrollment.
- There was no disease progression of localized prostate cancer after local treatment, or during or shortly after docetaxel therapy prior to the diagnosis of mCRPC.

Olaparib 300 mg or placebo was administered orally BID in combination with oral abiraterone 1,000 mg QD. The treatment was continued until disease progression or any withdrawal criterion was met. Abiraterone was used in combination with either prednisolone or prednisone (5 mg, orally BID). Patients who were on ADT at the time of enrollment continued ADT throughout the study period.

A total of 796 enrolled and randomized patients (399 in the olaparib group and 397 in the placebo group, including 36 and 41 Japanese patients, respectively) were included in the intention-to-treat (ITT) population for the efficacy analyses. In the ITT population, the study drug was not administered to 1 patient each in the olaparib group and the placebo group, thus 794 patients (398 in the olaparib group and 396 in the placebo group, including 36 and 41 Japanese patients, respectively) were included in the safety analysis set.

The primary endpoint was radiological progression-free survival (rPFS) as assessed by the investigator.[2)] For the efficacy evaluation, an interim analysis and the final analysis were scheduled to be conducted when the number of rPFS events observed reached approximately 379 and 453, respectively. A Lan-DeMets α spending function of the O'Brien-Fleming type was used to control the probability of a type I error associated with the interim analysis.

Table 3 and Figure 1 show the results of the interim rPFS analysis (data cutoff on July 30, 2021) and their Kaplan-Meier curves, respectively. The results demonstrated the superiority of olaparib over placebo.

Table 3. Results of the interim rPFS analysis (Investigator's assessment, ITT population, data cutoff on July 30, 2021)

	Olaparib	Placebo
N	399	397
Number of events (%)	168 (42.1)	226 (56.9)
Median [95% CI] (months)	24.8 [20.5, 27.6]	16.6 [13.9, 19.2]
Hazard ratio [95% CI][*1]	0.66 [0.54, 0.81]	
P-value (two-sided)[*2]	<0.0001	

*1, Cox proportional hazards model, stratified by location of the metastasis (bone only, visceral, vs. other) and prior docetaxel treatment for prostate cancer before the diagnosis of mCRPC (with vs. without); *2, Stratified log-rank test with a two-sided significance level of 0.0324 (with the same stratification factors as those used in the Cox proportional hazards model)

2) rPFS was defined as the time from the day of randomization to the day of the first documentation of (a), (b), or (c).
(a) Progression on a bone scintigraphy (*i.e.*, when either of the following (i) or (ii) was met)
(i) When scintigraphy at the post-randomization Week 8 identified ≥2 new lesions as compared with baseline, and a confirmatory scan at ≥6 weeks later identified ≥2 additional new lesions as compared with the post-randomization Week 8. (The time point when ≥2 new lesions were identified as compared with baseline was defined as the day of the event.)
(ii) The post-randomization Week 8 bone scintigraphy showing no ≥2 new lesions as compared with baseline the post-randomization Week 8 scintigraphy served as a new baseline. When ≥2 new lesions were identified after the post-randomization Week 8 scintigraphy as compared with the new baseline, and a confirmatory scan performed at ≥6 weeks later identified ≥2 additional new lesions as compared with the new baseline. (The time point when ≥2 new lesions were identified as compared with the new baseline was defined as the day of event.)
(b) Progression of soft tissue lesions confirmed on CT or MRI, according to RECIST ver. 1.1
(c) Death from any cause

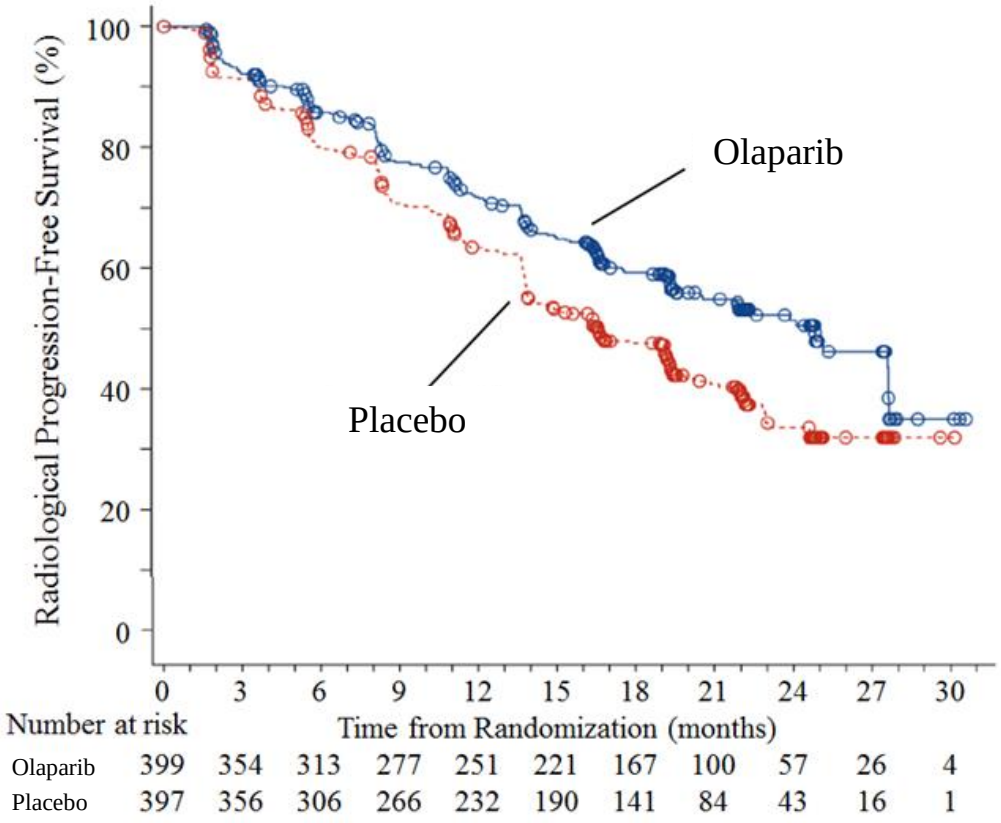

Figure 1. Kaplan-Meier curves for rPFS
(Investigator's assessment, ITT population, data cutoff on July 30, 2021)

The safety analysis revealed deaths in 24 of 398 patients (6.0%) in the olaparib group and 22 of 396 patients (5.6%) in the placebo group during the treatment period or within 30 days after the last dose (including 0 of 36 Japanese patients in the olaparib group and 2 of 41 Japanese patients in the placebo group). Except for disease progression (8 patients in the olaparib group, 10 patients in the placebo group), the causes of death were death in 3 patients, COVID-19 in 2 patients, and acute respiratory failure/COVID-19, COVID-19 pneumonia, craniocerebral injury/acute respiratory failure, mitral valve disease, myocardial ischaemia/pneumonia, pneumonia bacterial/prostate cancer, pneumonia/COVID-19, pneumonia/dyspnoea, respiratory failure/COVID-19, septic shock/COVID-19, and subdural haematoma in 1 patient each in the olaparib group, and death in 2 patients, and acute kidney injury/colitis ulcerative, acute pulmonary oedema, acute respiratory failure/COVID-19, COVID-19, cardio-respiratory arrest/coronary artery disease, cardio-respiratory arrest/infection, haemorrhagic stroke, ischaemic stroke, pneumonia aspiration/ischaemic stroke, and sepsis/unevaluable event in 1 patient each in the placebo group. For all of the events, a causal relationship to olaparib, placebo, or abiraterone was ruled out.

7.1.2 Foreign study

7.1.2.1 Foreign phase II study (CTD 5.3.5.1.2, Study 08, April 2014 to [redacted] 20[redacted] [data cutoff on September 22, 2017])

A foreign phase II study was conducted at 41 sites overseas to evaluate the efficacy and safety of olaparib/abiraterone therapy primarily in patients with mCRPC who had previously been treated with

docetaxel-based chemotherapy. The study was composed of Part A as an open-label, uncontrolled study and Part B as a randomized, open-label, comparative study (target sample size: 6 patients each in (a) Cohort 1, (b) Group 1 of Cohort 2, and (c) Group 2 of Cohort 2 in Part A; and (d) 140 patients in Part B).

The groups (a) to (d) were assigned to the following regimens. The treatment was continued until disease progression or any withdrawal criterion was met.

(a) Oral olaparib 200 mg BID in combination with oral abiraterone 1,000 mg QD
(b) Oral olaparib 300 mg BID for 3 to 7 days, followed by oral olaparib 300 mg BID in combination with oral abiraterone 1,000 mg QD
(c) Oral abiraterone 1,000 mg QD for 5 to 7 days, followed by oral olaparib 300 mg BID in combination with oral abiraterone 1,000 mg QD
(d) Oral olaparib 300 mg or placebo BID in combination with oral abiraterone 1,000 mg QD

All 158 patients enrolled in the study (3 in (a), 7 in (b), 6 in (c), 71 in the olaparib group in (d), and 71 in the placebo group in (d)) were treated with the study drug in combination with abiraterone, and were included in the safety analysis set. A total of 142 patients in Part B (71 in the olaparib group and 71 in the placebo group) were included in the efficacy analyses.

In Part A, dose limiting toxicities (DLTs) were evaluated during the first 14 days of combination therapy with olaparib and abiraterone. As no DLT was found in any cohorts, the recommended dose of olaparib, when administered with abiraterone, was set at 300 mg BID for Part B.

The primary endpoint in Part B was investigator-assessed rPFS.[3)] The primary analysis was scheduled when the number of rPFS events observed reached approximately 100.

Table 4 and Figure 2 show the results from the primary rPFS analysis in Part B (data cutoff on September 22, 2017) and their Kaplan-Meier curves, respectively. The results met the prespecified efficacy criteria.

Table 4. Results of the primary rPFS analysis (Investigator's assessment, efficacy analysis set, data cutoff on September 22, 2017)

	Olaparib	Placebo
N	71	71
Number of events (%)	46 (64.8)	54 (76.1)
Median [95% CI] (months)	13.8 [10.8, 20.4]	8.2 [5.5, 9.7]
Hazard ratio [95% CI][*1]	0.65 [0.44, 0.97]	
P-value (one-sided)[*2]	0.017	

*1, Calculated from the unstratified log-rank statistics; *2, Unstratified log-rank test with a one-sided significance level of 0.10

3) rPFS was defined as the time from the day of randomization to the day of the first documentation of (a), (b), or (c).
(a) Progression of bone lesions confirmed by bone scintigraphy (as assessed according to the PCWG-2 criteria)
(b) Progression of soft tissue lesions confirmed by CT or MRI, according to RECIST ver. 1.1
(c) Death from any cause

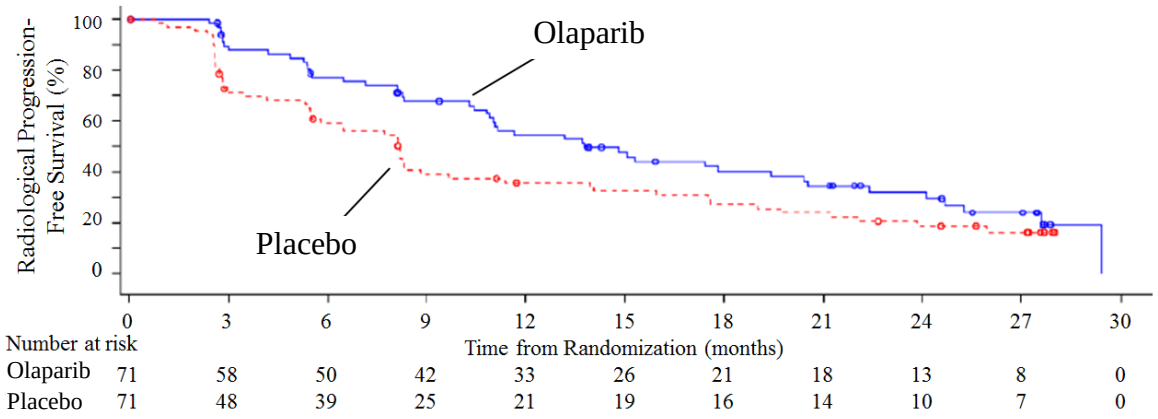

Figure 2. Kaplan-Meier curves for rPFS
(Investigator's assessment, efficacy analysis set, data cutoff on September 22, 2017)

The safety analysis revealed deaths in 1 of 7 patients (14.3%) in (b), 7 of 71 patients (9.9%) in the olaparib group in (d), and 9 of 71 patients (12.7%) in the placebo group in (d) during the treatment period or within 30 days after the last dose. Except for disease progression [1 patient in (b), 3 patients in the olaparib group in (d), and 7 patients in the placebo group in (d)], the causes of death were pneumonitis, cardiac failure, ischaemic stroke, and mediastinitis in 1 patient each in the olaparib group in (d), and death and sepsis in 1 patient each in the placebo group in (d). For the pneumonitis in 1 patient in the olaparib group in (d), a causal relationship to olaparib or abiraterone could not be ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Data for the review

PMDA's view:

The evaluation of efficacy and safety of olaparib/abiraterone therapy was designed to be based mainly on the results from the PROpel study, while the efficacy in Japanese patients was systematically evaluated based on the results from the PROpel study and other data, according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Amendment to '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), and other relevant regulations.

7.R.2 Efficacy

Based on the reviews in the following subsections, PMDA concluded that olaparib/abiraterone therapy would have a certain level of efficacy in the target population of the PROpel study, i.e., patients with *BRCA* mutation-positive pharmacotherapy-naïve mCRPC. The efficacy of olaparib/abiraterone therapy in patients with *BRCA* mutation-negative mCRPC will be finalized, taking into account the comments from the Expert Discussion.

7.R.2.1 Target population

The PROpel study targeted patients with mCRPC who had not previously been treated for mCRPC. All approved indications of olaparib are intended for patients suspected to have homologous recombination deficiency due to *BRCA* gene mutation, etc. Based on this, PMDA asked the applicant to explain the mechanism of how olaparib/abiraterone therapy would inhibit the growth of prostate cancer independently from *BRCA* mutation status.

The applicant's explanation:

In the activation of gene transcription by nuclear receptors, poly ADP-ribose polymerase-1 (PARP-1) plays a role as a positive coregulator of the target genes (*Science.* 2006;312:1798-802). In human prostate cancer-derived LNCaP cells, veliparib, a PARP inhibitor like olaparib, suppressed the transcription of androgen receptor (AR) target genes such as KLK3/PSA, TMPRSS2, leading to the inhibition of tumor cell growth (*Cancer Discov.* 2012;2:1134-49). These reports indicate that olaparib reduces the transcription of AR target genes via PARP inhibition, thereby suppressing the growth of prostate cancer, regardless of *BRCA* mutation status.

Meanwhile, based on the following non-clinical study results, in the concomitant use of olaparib, AR inhibitor suppresses the production of HRR proteins, damages the HRR pathway, and prevents the repair of DSB induced by olaparib, consequently suppressing growth of prostate cancer.

- The inhibitory effects of olaparib or enzalutamide against the production of HRR proteins such as BRCA1, RAD51AP1, RAD51C, RAD54, and RMI2 were assessed in human prostate cancer-derived VCaP, LNCaP, and CWR22Rv1 cell lines. The combination of enzalutamide with olaparib reduced the production of some of these proteins as compared with the control, despite differences among the cell lines (*Sci Signal.* 2017;10:eaam7479).
- The inhibitory effects of olaparib or enzalutamide on HRR function were assessed based on the homologous recombination ratio in human prostate cancer-derived LNCap cell line transfected with 2 different plasmids that carried a homologous region. The relative activity of enzalutamide or olaparib alone versus control was approximately 60%, while that of the combination of enzalutamide with olaparib was approximately 45% (*Sci Signal.* 2017;10:eaam7479).
- The inhibitory effects of bicalutamide, olaparib, and the combination of these drugs were assessed against tumor growth in NSG mice[4)] subcutaneously implanted with human prostate cancer-derived C4-2 cell lines. While the changes over time in tumor volume with bicalutamide alone and olaparib alone were similar to that with the control, the combination of olaparib with bicalutamide achieved a significantly higher tumor growth inhibition than the control *(Nature Communications.* 2017;8:374).

Abiraterone, an inhibitor of androgen synthesis, is also expected to inhibit the activation of AR signaling by reducing the expression of androgen. Therefore, the combination of olaparib and abiraterone, as with the

4) NSG mice are derived from the NOD/SCID background strain, and are deficient in the IL-2 receptor γ-chain.

combination of olaparib and an AR inhibitor, is considered to inhibit the growth of prostate cancer, regardless of *BRCA* mutation status.

Thus, olaparib/abiraterone therapy is expected to inhibit the growth of prostate cancer, regardless of *BRCA* mutation status, via the following action mechanisms.

(i) Olaparib inhibits PARP-1, and impairs the function of PARP-1 as an AR transcriptional regulator Consequently, PARP-1-dependent transcription of AR target genes is suppressed.

(ii) Abiraterone inhibits androgen synthesis and suppresses the AR-dependent transcription of HRR-related genes. This reduces the production of proteins essential for HRR, damaging the HRR pathway. DSBs induced by olaparib are left unrepaired, and consequently increased DNA damage triggers cell death.

PMDA's view:

BRCA mutation-positive patients in the PROpel study are considered to have homologous recombination deficiency. The applicant's expectation of the add-on effect of olaparib to abiraterone in this population is therefore understandable based on the action mechanism as observed for the approved indications [see Section 1.1]. Meanwhile, the following are anticipated action mechanisms of olaparib/abiraterone therapy primarily in *BRCA* mutation-negative patients:

- In terms of the mechanism (i) mentioned earlier, the PROfound study involving patients with HRR-related gene mutation-positive mCRPC failed to suggest possible efficacy of olaparib monotherapy in patients carrying mutations in HRR-related genes other than *BRCA* genes (see "Review Report for Lymparza Tablets 100 mg, Lymparza Tablets 150 mg dated November 24, 2020"). Because the analysis results from the PROfound study were not available when the PROpel study began, this action mechanism seemed understandably promising at the planning stage of the PROpel study. However, the results from the PROfound study suggested uncertainty about whether olaparib would provide an add-on effect to abiraterone by inhibiting the transcription of PARP-1-dependent AR target genes in *BRCA* mutation-negative patients.
- Concerning the mechanism (ii), the lack of non-clinical data of olaparib/abiraterone limited the investigation. Furthermore, available non-clinical data were insufficient to conclude that AR inhibitors reduce the expression of HRR-related proteins. The report by Li, et al. revealed varied inhibitory effect of olaparib/abiraterone on tumor growth by cell line. Another study in CB17 SCID mice implanted with human prostate cancer-derived CWR22Rv1 cell line found no clear difference between the olaparib/enzalutamide combination and each drug used alone in change over time in tumor volume (*Sci Signal.* 2017; 10: eaam7479). These findings indicate uncertainty about whether AR inhibition can trigger functional HRR deficiency and suppress tumor growth.

As stated, the anticipated primary action mechanism of olaparib/abiraterone therapy in *BRCA* mutation-positive patients differs from that anticipated in *BRCA* mutation-negative patients, and it remains inconclusive whether the non-clinical study results support the *BRCA* mutation-independent action mechanisms. In this view, the appropriateness of assessing the efficacy of olaparib/abiraterone therapy in patients with mCRPC collectively

as a single population, regardless of their *BRCA* mutation status, is uncertain. Therefore, PMDA has concluded that the efficacy of olaparib/abiraterone therapy in patients with pharmacotherapy-naïve mCRPC should be assessed carefully, based on the results not only from the entire population of the PROpel study but also from subgroup analyses by *BRCA* mutation status.

7.R.2.2 Setting of the control group

The applicant's explanation about the rationale for selecting placebo as the control in the PROpel study for the evaluation of the efficacy and safety of olaparib administered in combination with abiraterone:

When the planning of PROpel study was underway, the NCCN guidelines (v2.2018) and other guidelines strongly recommended abiraterone therapy as a treatment option for the target population of the PROpel study, based on the results from foreign clinical studies (*e.g.*, *N Engl J Med.* 2013;368:138-48). Therefore, placebo was selected as the control in the PROpel study.

PMDA accepted the applicant's explanation.

7.R.2.3 Efficacy endpoint

The applicant's explanation about the appropriateness of the primary endpoint of the PROpel study, i.e., investigator-assessed rPFS:

The primary endpoint of rPFS prolongation contributes to the alleviation of symptoms associated with disease progression and delaying the start of treatment with antineoplastic cytotoxic agents that increases the physical burden on patients. Therefore, selecting rPFS as the primary endpoint in the PROpel study was appropriate. Prolonged rPFS will lead to the preservation of patients' physical functions and QOL, and is thus clinically meaningful for the target population of the PROpel study.

PMDA's view:

The primary endpoint of the PROpel study should have been overall survival (OS), because the treatment for the target population of the PROpel study was aimed to prolong their survival. Nevertheless, the applicant's view on a certain level of clinical significance in prolonged rPFS in the patient population is understandable. Therefore, it is acceptable to evaluate the efficacy of olaparib/abiraterone therapy based on the results of rPFS, the selected primary endpoint, while also checking the OS results in the PROpel study.

7.R.2.4 Results of the efficacy evaluation

The PROpel study demonstrated the superiority of olaparib/abiraterone over placebo/abiraterone in investigator-assessed rPFS, the primary endpoint [see Section 7.1.1.1]. The hazard ratio [95% confidence interval (CI)] of rPFS, as assessed by blinded independent central review (BICR) for the olaparib group versus the placebo group was 0.61 [0.49, 0.74].

In the PROpel study, if a statistically significant difference was observed in rPFS, a hypothesis testing for OS, the secondary endpoint, was to be conducted according to a hierarchical procedure. In particular, 2 interim OS analyses were scheduled for efficacy evaluation at the time points of interim and final rPFS analyses, and the final OS analysis was scheduled when the number of OS events reached 360. To adjust the probability of a type I error associated with the interim analysis, a conservative significance level of 0.0005 (one-sided) was allocated to the first interim analysis, while a combined significance level of 0.0245 (one-sided) was allocated to the second interim analysis and the final analysis, based on the Bonferroni method. The significance level for the second interim analysis was to be calculated from the combined significance level (0.0245 [one-sided]) using the O'Brien-Fleming α spending function. The significance level for the final analysis was to be calculated so that the type I error probability for the entire study would be 0.025 (one-sided), taking account of the correlation among the estimated test statistics for all analyses.

The results of the first interim OS analysis (data cutoff on July 30, 2021) and their Kaplan-Meier curves are shown in Table 5 and Figure 3, respectively. These results failed to demonstrate the superiority of olaparib/abiraterone over placebo/abiraterone.

Table 5. Results of the first interim OS analysis (ITT population, data cutoff on July 30, 2021)

	Olaparib	Placebo
N	399	397
Number of events (%)	107 (26.8)	121 (30.5)
Median [95% CI] (months)	- [-, -]	- [-, -]
Hazard ratio [95% CI][*1]	0.86 [0.66, 1.12]	
P-value (two-sided)[*2]	0.2923	

-, Not reached; *1, Cox proportional hazards model stratified by location of the metastasis (bone only, visceral, vs. other) and prior docetaxel treatment for prostate cancer before the diagnosis of mCRPC (with vs. without); *2, Stratified log-rank test with a two-sided significance level of 0.001 (with the same stratification factors as those used in the Cox proportional hazards model)

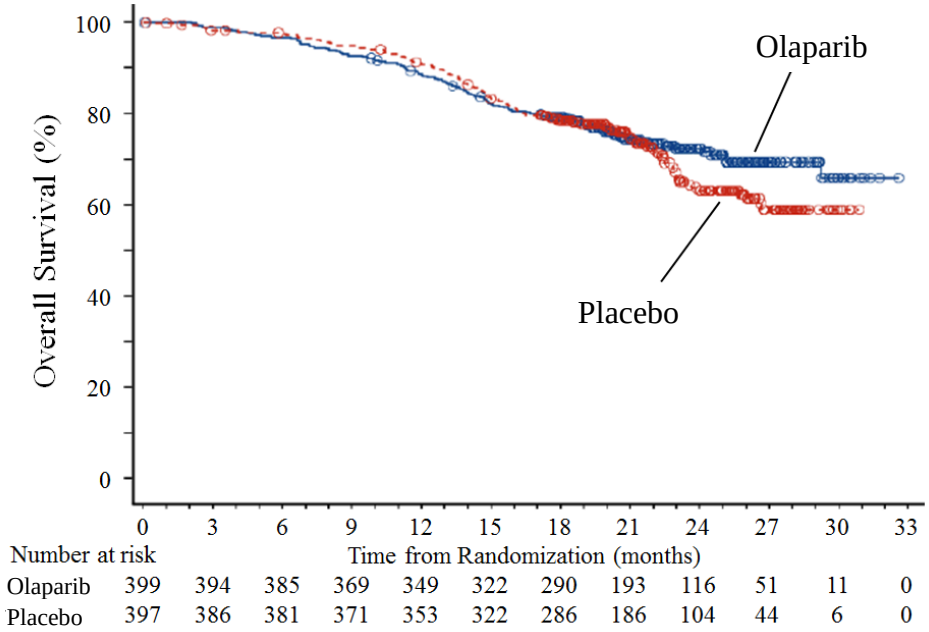

Figure 3. Kaplan Meier curves for the first interim OS analysis (ITT population, data cutoff on July 30, 2021)

Table 6 and Figure 4 show the results of the interim rPFS analysis in the Japanese population in the PROpel study and their Kaplan-Meier curves, respectively.

Table 6. Results of the interim rPFS analysis in the Japanese population (Investigator's assessment, ITT population, data cutoff on July 30, 2021)

	Olaparib	Placebo
N	36	41
Number of events (%)	12 (33.3)	21 (51.2)
Median [95% CI] (months)	27.6 [23.9, -]	19.3 [10.4, -]
Hazard ratio [95% CI]*	0.55 [0.26, 1.14]	

-, Not reached; * Cox proportional hazards model stratified by location of the metastasis (bone only, visceral, vs. other) and prior docetaxel treatment for prostate cancer before the diagnosis of mCRPC (with vs. without)

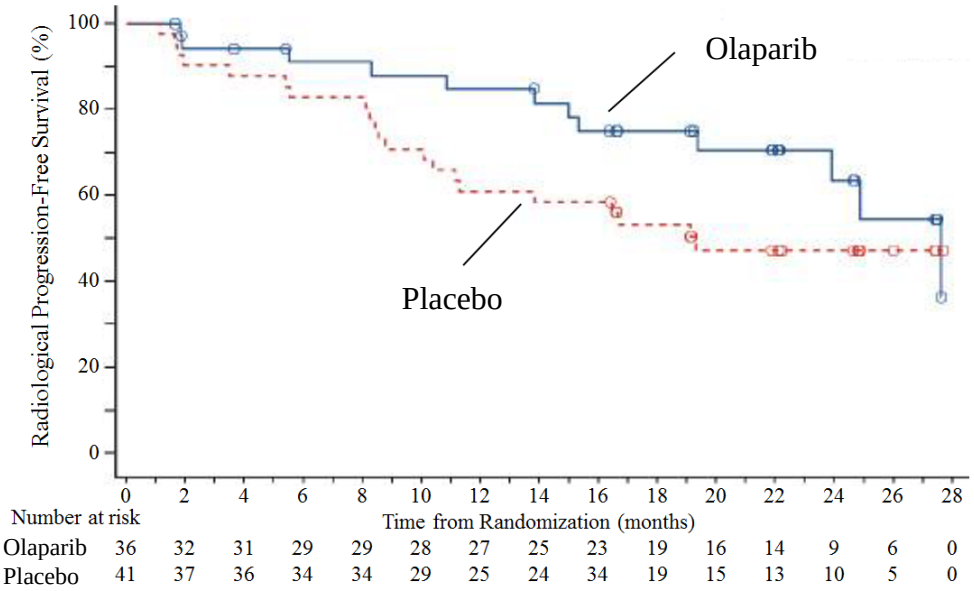

Figure 4. Kaplan-Meier curves for the interim rPFS analysis in the Japanese population (Investigator's assessment, ITT population, data cutoff on July 30, 2021)

Based on the discussion in Section "7.R.2.1 Target population," PMDA asked the applicant to explain the efficacy of olaparib/abiraterone therapy by BRCA mutation status in (a) the ITT population and (b) the HRR-related gene mutation-positive population.

The applicant's explanation:

In the PROpel study, patients with HRR-related gene mutations were identified by tumor tissue-based testing using FoundationOne CDx and plasma-based testing using FoundationOne Liquid CDx. The efficacy of olaparib/abiraterone therapy by *BRCA* mutation status in (a) the ITT population and (b) the HRR-related gene mutation-positive population is described below. The HRR-related genes defined in the PROpel study included *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* genes.

(a) Efficacy by *BRCA* mutation status in the ITT population

The efficacy by *BRCA* (*BRCA1* or *BRCA2*) mutation status in the ITT population was assessed in patients who had BRCA testing data in the PROpel study. Table 7 and Figure 5, and Table 8 and Figure 6, respectively, are rPFS and OS results by *BRCA* mutation status in this population.

Table 7. Results of the interim rPFS analysis by *BRCA* mutation status (Investigator's assessment, ITT population, data cutoff on July 30, 2021)

Sample	Gene mutation	Treatment	N	Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction*
Tumor tissue	*BRCA* mutation-positive	Olaparib	26	- [-, -]	0.30 [0.13, 0.65]	0.0246
		Placebo	24	9.9 [5.5, 17.8]		
	BRCA mutation-negative	Olaparib	243	23.9 [19.3, 27.6]	0.78 [0.60, 1.00]	
		Placebo	242	16.7 [13.9, 19.4]		
Plasma	*BRCA* mutation-positive	Olaparib	39	- [-, -]	0.18 [0.08, 0.34]	0.0001
		Placebo	30	8.2 [5.3, 11.1]		
	BRCA mutation-negative	Olaparib	328	23.9 [19.3, 27.6]	0.78 [0.63, 0.97]	
		Placebo	337	16.8 [14.3, 19.4]		

-, Not reached; *, Unstratified Cox proportional hazards model including (a) treatment, (b) *BRCA* mutation status, and (c) treatment-by-*BRCA* mutation status interaction as covariates

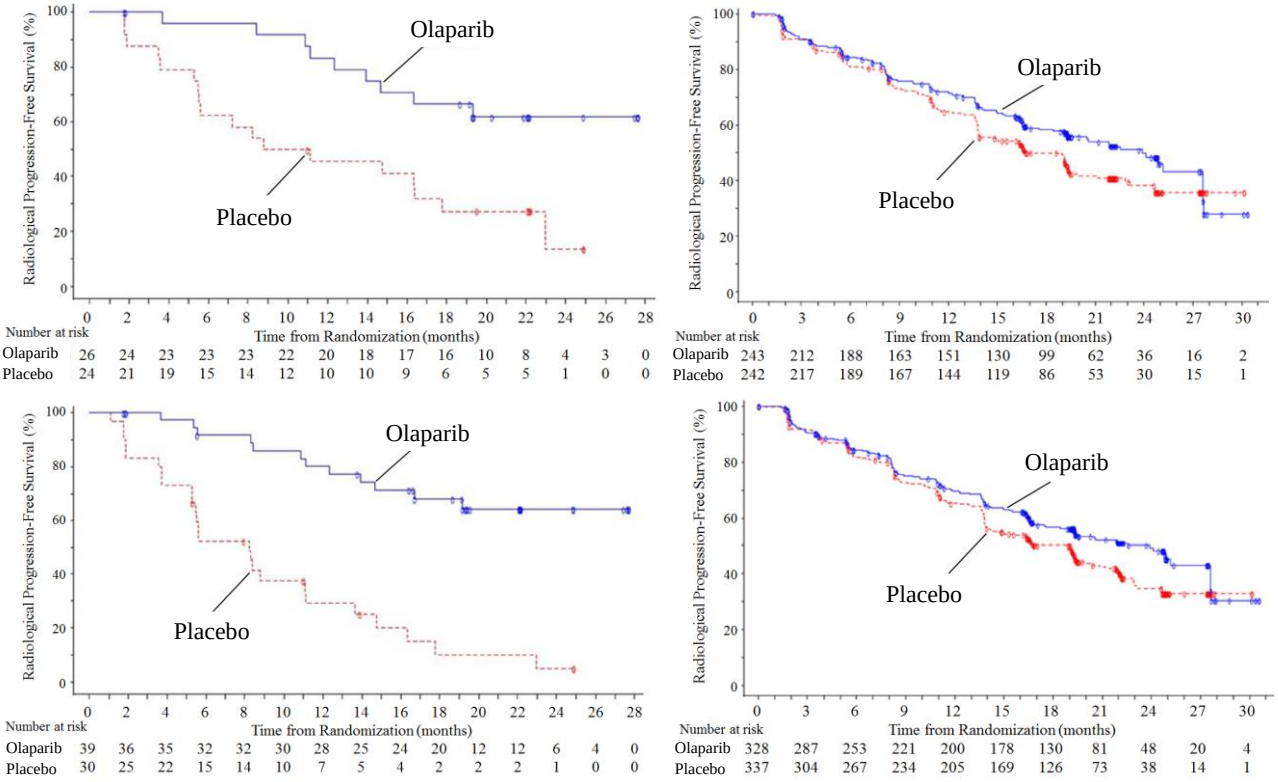

Figure 5. Kaplan-Meier curves for the interim rPFS analysis by *BRCA* mutation status (Investigator's assessment, ITT population, data cutoff on July 30, 2021)
(Top left, tumor tissue-based *BRCA* mutation-positive; top right, tumor tissue-based *BRCA* mutation-negative; bottom left, plasma-based *BRCA* mutation-positive; bottom right, plasma-based *BRCA* mutation-negative)

Table 8. Results of the first interim OS analysis by *BRCA* mutation status (ITT population, data cutoff on July 30, 2021)

Sample	Gene mutation	Treatment	N	Number of events (%)	Hazard ratio* [95% CI]	*P*-value for interaction*
Tumor tissue	*BRCA* mutation-positive	Olaparib	26	5 (19.2)	0.30 [0.10, 0.82]	0.0205
		Placebo	24	12 (50.0)		
	BRCA mutation-negative	Olaparib	243	71 (29.2)	1.11 [0.79, 1.56]	
		Placebo	242	64 (26.4)		
Plasma	*BRCA* mutation-positive	Olaparib	39	9 (23.1)	0.42 [0.17, 0.96]	0.0779
		Placebo	30	14 (46.7)		
	BRCA mutation-negative	Olaparib	328	93 (28.4)	0.93 [0.70, 1.23]	
		Placebo	337	103 (30.6)		

* Unstratified Cox proportional hazards model including (a) treatment, (b) *BRCA* mutation status, and (c) treatment-by-*BRCA* mutation status interaction as covariates

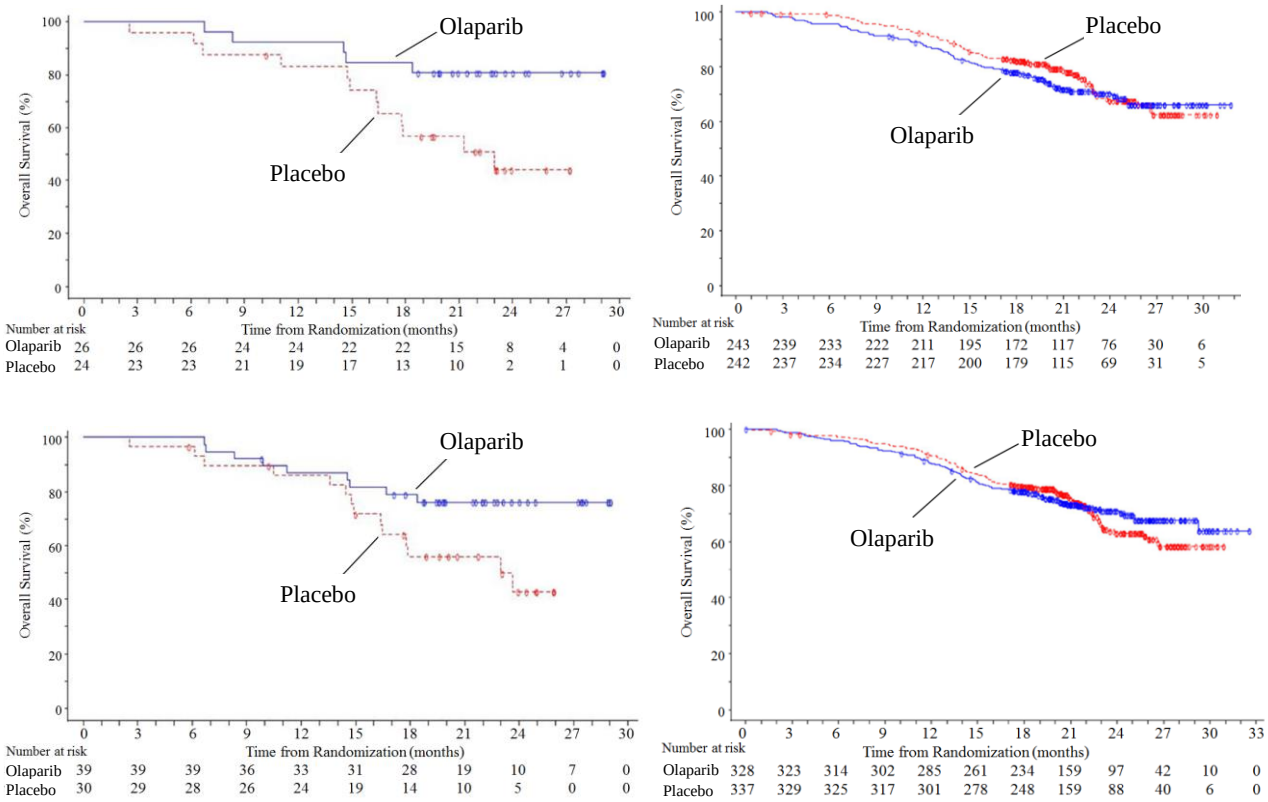

Figure 6. Kaplan-Meier curves for the first interim OS analysis by *BRCA* mutation status (ITT population, data cutoff on July 30, 2021)
(Top left, tumor tissue-based *BRCA* mutation-positive; top right, tumor tissue-based *BRCA* mutation-negative; bottom left, plasma-based *BRCA* mutation-positive; bottom right, plasma-based *BRCA* mutation-negative)

The above rPFS and OS results in the ITT population, despite some different tendencies depending on *BRCA* mutation status, suggest promising efficacy of olaparib/abiraterone therapy in *BRCA* mutation-negative patients as well, based on the following views.

- The rPFS results in the *BRCA* mutation-negative population did not tend to differ from those in the overall population, and showed a clinically significant rPFS prolongation.
- The OS results showed the hazard ratio [95% CI] of 1.11 [0.79, 1.56] for the olaparib group to the placebo group in the tumor tissue-based *BRCA* mutation-negative population. However, in view of the limited number of OS events and the hazard ratio [95% CI] of 0.93 [0.70, 1.23] for the olaparib group

versus the placebo group in the plasma-based *BRCA* mutation-negative population, olaparib/abiraterone therapy did not tend to shorten the OS in the *BRCA* mutation-negative population compared with the *BRCA* mutation-positive population.

(b) Efficacy by *BRCA* mutation status in the HRR-related gene mutation-positive population

The efficacy by *BRCA* (*BRCA1* or *BRCA2*) mutation status in the HRR-related gene mutation-positive population was assessed in patients who had an HRR-related gene mutation testing result in the PROpel study. Table 9 and Figure 7, and Table 10 and Figure 8, respectively, are rPFS and OS results by *BRCA* mutation status in this population (data cutoff on July 30, 2021).

Table 9. Results of the interim rPFS analysis by *BRCA* mutation status (Investigator's assessment, HRR-related gene mutation-positive population, data cutoff on July 30, 2021)

Sample	Gene mutation	Treatment	N	Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction*
Tumor tissue	*BRCA* mutation-positive	Olaparib	26	- [-, -]	0.30 [0.13, 0.66]	0.1905
		Placebo	24	9.9 [5.5, 17.8]		
	BRCA mutation-negative	Olaparib	36	- [-, -]	0.61 [0.30, 1.23]	
		Placebo	32	19.4 [11.1 24.6]		
Plasma	*BRCA* mutation-positive	Olaparib	39	- [-, -]	0.19 [0.09, 0.37]	0.0002
		Placebo	30	8.2 [5.3, 11.1]		
	BRCA mutation-negative	Olaparib	59	16.5 [9.4, -]	0.93 [0.57, 1.48]	
		Placebo	70	16.6 [11.1, 19.9]		

-, Not reached; * Unstratified Cox proportional hazards model including (a) treatment, (b) *BRCA* mutation status, and (c) treatment-by-*BRCA* mutation status interaction as covariates

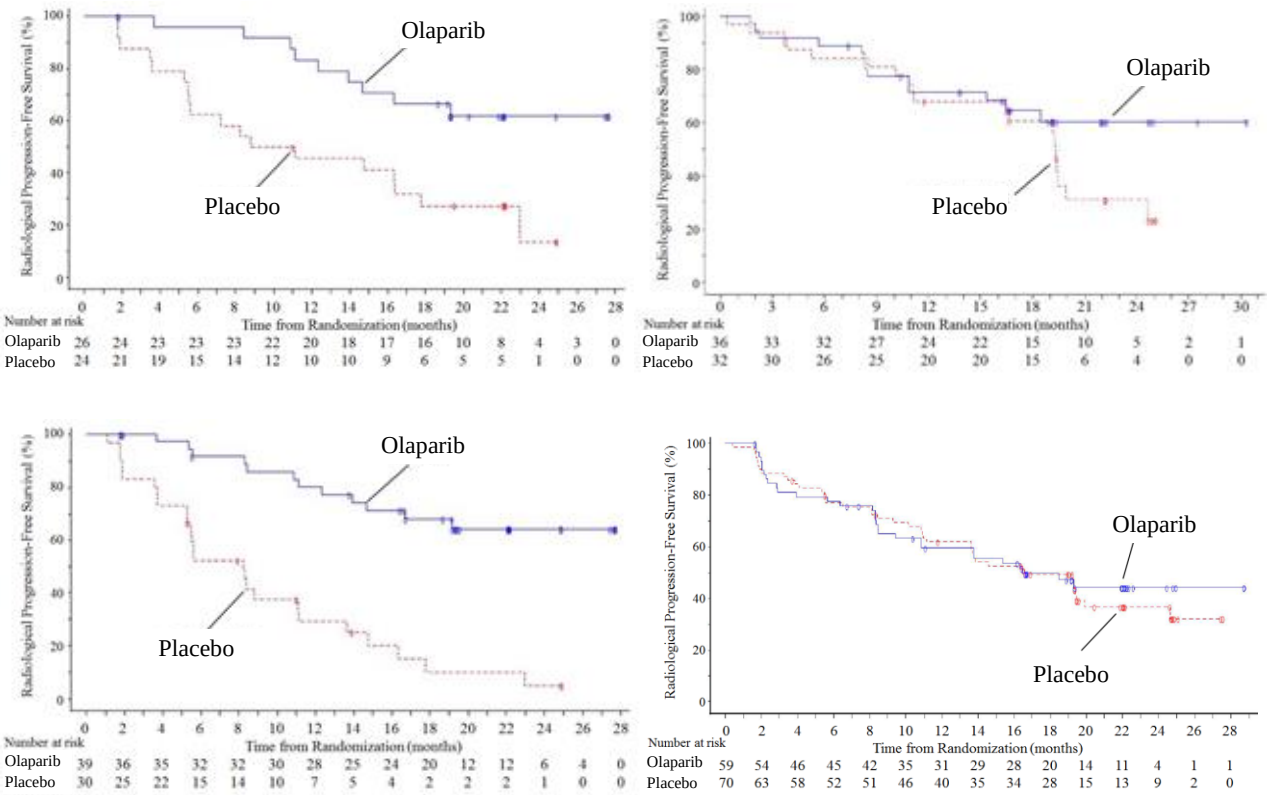

Figure 7. Kaplan-Meier curves for the interim rPFS analysis by *BRCA* mutation status (Investigator's assessment, HRR-related gene mutation-positive population, data cutoff on July 30, 2021) (Top left, tumor tissue-based *BRCA* mutation-positive; top right, tumor tissue-based *BRCA* mutation-negative; bottom left, plasma-based *BRCA* mutation-positive; bottom right, plasma-based *BRCA* mutation-negative)

Table 10. Results of the first interim OS analysis by *BRCA* mutation status (HRR-related gene mutation-positive population, data cutoff on July 30, 2021)

Sample	Gene mutation	Treatment	N	Number of events (%)	Hazard ratio* [95% CI]	*P*-value for interaction*
Tumor tissue	*BRCA* mutation-positive	Olaparib	26	5 (19.2)	0.31 [0.10, 0.85]	0.0643
		Placebo	24	12 (50.0)		
	BRCA mutation-negative	Olaparib	36	8 (22.2)	1.28 [0.44, 3.90]	
		Placebo	32	6 (18.8)		
Plasma	*BRCA* mutation-positive	Olaparib	39	9 (23.1)	0.42 [0.18, 0.97]	0.0481
		Placebo	30	14 (46.7)		
	BRCA mutation-negative	Olaparib	59	19 (32.2)	1.22 [0.65, 2.31]	
		Placebo	70	20 (28.6)		

* Unstratified Cox proportional hazards model including (a) treatment, (b) *BRCA* mutation status, and (c) treatment-by-*BRCA* mutation status interaction as covariates

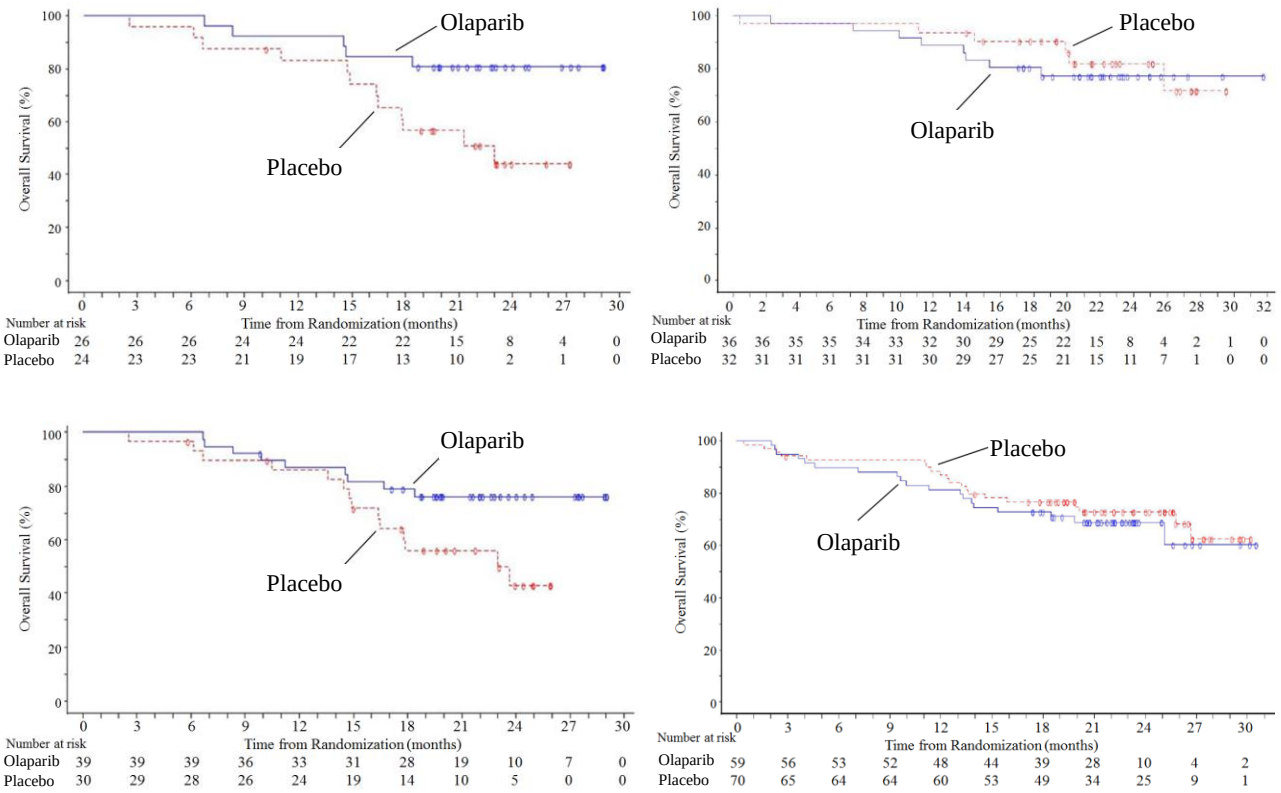

Figure 8. Kaplan-Meier curves for the first interim OS analysis by *BRCA* mutation status (HRR-related gene mutation-positive population, data cutoff on July 30, 2021) (Top left, tumor tissue-based *BRCA* mutation-positive; top right, tumor tissue-based *BRCA* mutation-negative; bottom left, plasma-based *BRCA* mutation-positive; bottom right, plasma-based *BRCA* mutation-negative)

The above rPFS and OS results in the HRR-related gene mutation-positive population, despite some different tendencies by *BRCA* mutation status, suggest promising the efficacy of olaparib/abiraterone therapy in HRR-related gene mutation-positive *BRCA* mutation-negative patients as well, based on the following views.

- These results were obtained from exploratory analyses in limited number of patients, and were thus potentially affected by imbalances in patient characteristics.
- The limited number of OS events precluded a precise evaluation.

PMDA's view:

Based on the discussion in Section "7.R.2.1 Target population," the efficacy of olaparib/abiraterone therapy was reviewed in the overall population and by *BRCA* mutation status in the PROpel study as follows.

The efficacy of olaparib/abiraterone therapy is considered to have been demonstrated in the overall population of the PROpel study including the Japanese population, based on the following views.

- Olaparib was demonstrated to be superior to placebo in rPFS, the primary endpoint, and had a clinically significant magnitude of effect.
- OS, the secondary endpoint, did not clearly tended to be short in the olaparib group as compared with the placebo group.

- Despite the limited number of Japanese patients that allowed limited evaluation, the tendencies in the rPFS and OS results in the Japanese population did not clearly differ from those in the overall population.

Nevertheless, olaparib is expected to act through different primary mechanisms in *BRCA* mutation-positive and -negative patients eligible for the PROpel study [see Section 7.R.2.1]. Therefore, the efficacy of olaparib/abiraterone therapy in *BRCA* mutation-positive and -negative patients should be assessed separately, based on the non-clinical and clinical study data, taking into account the limitations in the evaluation based on the exploratory subgroup analyses conducted.

In terms of *BRCA* mutation-positive patients, olaparib/abiraterone therapy clinically significantly prolonged rPFS and tended to prolong OS as well in both the ITT population and the HRR-related gene mutation-positive population. In addition, taking into account the results from the PROfound study, olaparib/abiraterone therapy is expected to have a certain level of efficacy through its action mechanism based on *BRCA* mutation-induced homologous recombination deficiency.

In the *BRCA* mutation-negative patients, in contrast, olaparib/abiraterone therapy was less effective in rPFS prolongation than the placebo/abiraterone therapy and showed no trend toward prolonged OS in either the ITT population or the HRR-related gene mutation-positive population. The hazard ratio of OS for the olaparib group versus the placebo group was lower in plasma-based *BRCA* mutation-negative patients than in tumor tissue-based *BRCA* mutation negative patients. This is likely because some patients who tested positive for *BRCA* mutation by tumor tissue-based testing were found negative by plasma-based testing, in view of the positive agreement rate of 73.9% (34 of 46 patients) between the plasma-based testing and the tissue-based testing for prostate cancer in the PROpel study, and of the magnitude of the therapeutic effect of olaparib/abiraterone therapy in the *BRCA* mutation-positive population.

Furthermore, the *BRCA* mutation-independent action mechanism of olaparib/abiraterone therapy has yet to be fully supported by non-clinical data. The clinical significance of the trend toward prolonged rPFS in the *BRCA* mutation-negative patients in the ITT population will be finalized taking into account the comments from the Expert Discussion.

Based on the above discussion, it remains inconclusive whether olaparib/abiraterone therapy has promising efficacy in the target population of the PROpel study, regardless of their *BRCA* mutation status. PMDA therefore concluded that the outcomes of efficacy analysis by *BRCA* mutation status should be communicated via the package insert, etc., and healthcare professionals should be advised to select patients eligible olaparib/abiraterone therapy [see Section 7.R.4.1].

7.R.3 Safety [For adverse events, see Section "7.2 Adverse events reported in clinical studies."]

PMDA's view:

According to the discussions in the following subsections, olaparib/abiraterone therapy in patients with

pharmacotherapy-naïve mCRPC requires special attention particularly for venous thromboembolism and infections, in addition to the adverse events specified as such at the approval for the approved indications (myelosuppression, interstitial lung disease [ILD], and secondary malignancy) (see "Review Report for Lynparza Tablets 100 mg, Lynparza Tablets 150 mg dated November 24, 2020").

Although the use of olaparib/abiraterone warrants attention to the above-mentioned adverse events, the therapy is tolerable in patients with pharmacotherapy-naïve mCRPC, where treating physicians with sufficient knowledge and experience in cancer chemotherapy continue to take appropriate measures such as adverse event monitoring and management and the interruption of olaparib or abiraterone.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of olaparib/abiraterone therapy based on the safety data from the PROpel study:

Table 11 is a summary of the safety data from the PROpel study.

Table 11. Safety summary (PROpel study, data cutoff on July 30, 2021)

	n (%)	
	Olaparib N = 398	Placebo N = 396
All adverse events	387 (97.2)	376 (94.9)
Grade ≥3 adverse events	188 (47.2)	152 (38.4)
Adverse events resulting in death	16 (4.0)	17 (4.3)
Serious adverse events	135 (33.9)	107 (27.0)
Adverse events leading to drug discontinuation*	57 (14.3)	39 (9.8)
Olaparib or placebo	55 (13.8)	31 (7.8)
Abiraterone	34 (8.5)	35 (8.8)
Adverse events leading to drug interruption*	187 (47.0)	114 (28.8)
Olaparib or placebo	178 (44.7)	100 (25.3)
Abiraterone	131 (32.9)	87 (22.0)
Adverse events leading to dose reduction*	83 (20.9)	35 (8.8)
Olaparib or placebo	80 (20.1)	22 (5.6)
Abiraterone	10 (2.5)	17 (4.3)

* Adverse events leading to the discontinuation, interruption, or dose reduction of olaparib, placebo, or abiraterone

In the PROpel study, adverse events of any grade reported with a ≥5% higher incidence in the olaparib group than in the placebo group were anaemia (181 patients [45.5%] in the olaparib group, 64 patients [16.2%] in the placebo group), nausea (112 patients [28.1%], 50 patients [12.6%]), fatigue (111 patients [27.9%], 75 patients [18.9%]), diarrhoea (69 patients [17.3%], 37 patients [9.3%]), and decreased appetite (58 patients [14.6%], 23 patients [5.8%]). Grade ≥3 adverse events reported with a ≥2% higher incidence in the olaparib group than in the placebo group were anaemia (60 patients [15.1%], 13 patients [3.3%]), pulmonary embolism (26 patients [6.5%], 7 patients [1.8%]), and lymphocyte count decreased (13 patients [3.3%], 5 patients [1.3%]). Serious adverse events reported with a ≥2% higher incidence in the olaparib group than in the placebo group were anaemia (23 patients [5.8%], 2 patients [0.5%]) and pulmonary embolism (13 patients [3.3%], 3 patients

[0.8%]). The adverse event leading to the discontinuation of any study drug[5)] with a ≥2% higher incidence in the olaparib group than in the placebo group was anaemia (15 patients [3.8%], 3 patients [0.8%]). The adverse event leading to the interruption of any study drug[5)] with a ≥2% higher incidence in the olaparib group than in the placebo group was anaemia (61 patients [15.3%], 7 patients [1.8%]). The adverse event leading to the dose reduction of any study drug[5)] with a ≥2% higher incidence in the olaparib group than in the placebo group was anaemia (41 patients [10.3%], 2 patients [0.5%]).

There were no adverse events that resulted in death with a ≥2% higher incidence in the olaparib group than in the placebo group.

The applicant's explanation about the differences in the safety profiles between patients with pharmacotherapy-naïve mCRPC and patients with *BRCA* mutation-positive mCRPC, the approved indication:

Table 12 is a safety summary of patients receiving olaparib in (a) the PROpel study and (b) in the PROfound study involving patients with HRR-related gene mutation-positive mCRPC who had previously been treated with abiraterone, enzalutamide, or both drugs.[1)]

Table 12. Safety summary from the PROpel study and the PROfound study

	n (%)	
	PROpel (Olaparib/abiraterone)	PROfound (Olaparib)
	N = 398	N = 256
All adverse events	387 (97.2)	246 (96.1)
Grade ≥3 adverse events	188 (47.2)	136 (53.1)
Adverse events resulting in death	16 (4.0)	10 (3.9)
Serious adverse events	135 (33.9)	94 (36.7)
Adverse events leading to drug discontinuation*	55 (13.8)	51 (19.9)
Adverse events leading to drug interruption*	178 (44.7)	119 (46.5)
Adverse events leading to dose reduction*	80 (20.1)	60 (23.4)

* Adverse events leading to the discontinuation, interruption, or dose reduction of olaparib

Grade ≥3 adverse events reported with a ≥2% higher incidence in the PROpel study than in the PROfound study were pulmonary embolism (26 patients [6.5%] in the PROpel study, 7 patients [2.7%] in the PROfound study), hypertension (14 patients [3.5%], 3 patients [1.2%]), lymphocyte count decreased (13 patients [3.3%], 1 patient [0.4%]), and COVID-19 (12 patients [3.0%], 0 patients). The serious adverse event reported with a ≥2% higher incidence in the PROpel study than in the PROfound study was COVID-19 (12 patients [3.0%], 0 patients). The adverse event leading to drug discontinuation with a ≥2% higher incidence in the PROpel study than in the PROfound study was COVID-19 (10 patients [2.5%], 0 patients).

There were no adverse events of any grade reported with a ≥10% higher incidence in the PROpel study than in the PROfound study. There were no adverse events resulting in death with a ≥2% higher incidence in the

5) Olaparib, placebo, or abiraterone

PROpel study than in the PROfound study. No adverse events led to the discontinuation or dose reduction of olaparib in these studies.

PMDA's view:

Although the incidences of some Grade ≥3 adverse events, etc. were higher in the olaparib group than in the placebo group in the PROpel study, most of the events were known adverse events of olaparib. [For the events with incidences that tended to be higher in the olaparib group than in the placebo group (i.e., pulmonary embolism and COVID-19), see Sections 7.R.3.3 and 7.R.3.4, respectively.] Despite some adverse events observed more frequently in the olaparib group than in the placebo group, olaparib/abiraterone therapy is considered tolerable in patients with pharmacotherapy-naïve mCRPC, where treating physicians with sufficient knowledge and experience in cancer chemotherapy continue to take appropriate measures such as adverse event monitoring and the interruption of olaparib or abiraterone.

7.R.3.2 Differences in safety between Japanese and non-Japanese patients

The applicant's explanation about the differences in the safety of olaparib/abiraterone therapy between Japanese patients and non-Japanese patients, based on the safety information from the PROpel study:

Table 13 is a safety summary from the Japanese and non-Japanese populations in the olaparib group of the PROpel study.

Table 13. Safety summary from the Japanese and non-Japanese populations (Olaparib group of the PROpel study, data cutoff on July 30, 2021)

	n (%)	
	Japanese N = 36	Non-Japanese N = 362
All adverse events	36 (100)	351 (97.0)
Grade ≥3 adverse events	20 (55.6)	168 (46.4)
Adverse events resulting in death	0	16(4.4)
Serious adverse events	12 (33.3)	123 (34.0)
Adverse events leading to drug discontinuation*	7 (19.4)	50 (13.8)
Adverse events leading to drug interruption*	26 (72.2)	161 (44.5)
Adverse events leading to dose reduction*	13 (36.1)	70 (19.3)

* Adverse events leading to the discontinuation, interruption, or dose reduction of olaparib or abiraterone

Adverse events of any grade reported with a ≥10% higher incidence in the Japanese population than in the non-Japanese population were lymphocyte count decreased (8 patients [22.2%] in the Japanese population, 23 patients [6.4%] in the non-Japanese population), malaise (7 patients [19.4%], 6 patients [1.7%]), hepatic function abnormal (6 patients [16.7%], 0 patients), dry skin (5 patients [13.9%], 13 patients [3.6%]), and dental caries (5 patients [13.9%], 2 patients [0.6%]).[6)] Grade ≥3 adverse events reported with a ≥5% higher incidence in the Japanese population than in the non-Japanese population were lymphocyte count decreased (6 patients

6) Dental caries was not reported in the placebo group.

[16.7%], 7 patients [1.9%]),[7)] neutrophil count decreased (3 patients [8.3%], 6 patients [1.7%]), amylase increased (2 patients [5.6%], 1 patient [0.3%]), pneumocystis jirovecii pneumonia (2 patients [5.6%], 0 patients), dental caries (2 patients [5.6%], 0 patients), and hepatic function disorder (2 patients [5.6%], 0 patients). The serious adverse event reported with a ≥5% higher incidence in the Japanese population than in the non-Japanese population was pneumocystis jirovecii pneumonia (2 patients [5.6%], 1 patient [0.3%]). The adverse event leading to the discontinuation of any study drug with a ≥5% higher incidence in the Japanese population than in the non-Japanese population was lymphocyte count decreased (2 patients [5.6%], 0 patients). Adverse events leading to the interruption of any study drug with a ≥5% higher incidence in the Japanese population than in the non-Japanese population were anaemia (9 patients [25.0%], 53 patients [14.6%]), lymphocyte count decreased (3 patients [8.3%], 3 patients [0.8%]), amylase increased (2 patients [5.6%], 2 patients [0.6%]), pneumocystis jirovecii pneumonia (2 patients [5.6%], 1 patient [0.3%]), and hepatic function abnormal (2 patients [5.6%], 0 patients). Adverse events leading to the dose reduction of any study drug with a ≥5% higher incidence in the Japanese population than in the non-Japanese population were anaemia (8 patients [22.2%], 33 patients [9.1%]) and hepatic function abnormal (3 patients [8.3%], 0 patients).

No adverse event resulted in death with a ≥5% higher incidence in the Japanese population than in the non-Japanese population.

PMDA's view:

Although the limited number of Japanese patients in the PROpel study precluded a precise comparison of the safety of olaparib/abiraterone therapy between Japanese and non-Japanese patients, based on the following views, etc., olaparib/abiraterone therapy is considered tolerable in Japanese patients when it is appropriately managed through the interruption of olaparib or abiraterone, etc.

- All of the adverse events reported with a higher incidence in the Japanese population than in the non-Japanese population were known adverse events of olaparib or its concomitant drugs, i.e., abiraterone or corticosteroids.
- There was no clear trend toward a higher incidence of adverse events resulting in death or serious adverse events in the Japanese population compared with the non-Japanese population.

The following subsections describe PMDA's review with a focus on the events that were frequently reported in the olaparib group (i.e., venous thromboembolism and infection), based on the safety results from the PROpel study.

7.R.3.3 Venous thromboembolism

The applicant's explanation about the occurrence of venous thromboembolism during treatment with olaparib:

[7)] In the placebo group, Grade ≥3 lymphocyte count decreased was reported in 3 patients (7.3%) in the Japanese population and 2 patients (0.6%) in the non-Japanese population.

Events falling under a standardized MedDRA query (SMQ) of "Embolic and thrombotic events, venous" were counted as venous thromboembolism.

Table 14 shows the incidences of venous thromboembolism in the PROpel study.

Table 14. Incidences of venous thromboembolism (PROpel study)

PT (MedDRA ver. 24.0)	n (%)			
	Olaparib N = 398		Placebo N = 396	
	All grades	Grade ≥3	All grades	Grade ≥3
Venous thromboembolism	29 (7.3)	27 (6.8)	13 (3.3)	8 (2.0)
Pulmonary embolism	26 (6.5)	26 (6.5)	7 (1.8)	7 (1.8)
Deep vein thrombosis	7(1.8)	1 (0.3)	3 (0.8)	0
Thrombophlebitis superficial	0	0	2 (0.5)	0
Portal vein thrombosis	0	0	1 (0.3)	1 (0.3)

In the PROpel study, venous thromboembolism resulted in death in 1 of 398 patients (0.3%; pulmonary embolism in 1 patient) in the olaparib group, and none in the placebo group. For the death in the olaparib group, a causal relationship to olaparib was ruled out. Serious venous thromboembolism was reported in 14 of 398 patients (3.5%; pulmonary embolism in 13 patients and deep vein thrombosis in 1 patient) in the olaparib group and 4 of 396 patients (1.0%; pulmonary embolism in 3 patients and portal vein thrombosis in 1 patient) in the placebo group. A causal relationship to the study drug could not be ruled out for the pulmonary embolism in 4 patients in the olaparib group, and the pulmonary embolism and portal vein thrombosis in 1 patient each in the placebo group. Venous thromboembolism led to the discontinuation of olaparib or placebo in none in the olaparib group and 1 of 396 patients (0.3%; pulmonary embolism in 1 patient) in the placebo group. Venous thromboembolism led to the interruption of olaparib or placebo in 8 of 398 patients (2.0%; pulmonary embolism in 8 patients and deep vein thrombosis in 1 patient [some patients had more than one event]) in the olaparib group and 2 of 396 patients (0.5%; pulmonary embolism and deep vein thrombosis in 1 patient each) in the placebo group. No venous thromboembolism led to the dose reduction of olaparib or placebo.

The median (minimum, maximum) time to the first onset of venous thromboembolism in the PROpel study was 172 (12, 681) days in the olaparib group and 244 (10, 706) days in the placebo group.

Table 15 details patients who experienced serious venous thromboembolism for which a causal relationship to olaparib could not be ruled out in clinical studies[8)] of olaparib, including the PROpel study.

8) Included the following clinical studies, other than those submitted for this partial change application;
Study 19, a foreign phase III study in patients with platinum-sensitive recurrent ovarian cancer responding to a recent platinum-based chemotherapy
The PAOLA-1 study, a global phase III study in patients with ovarian cancer responding to a platinum- and bevacizumab (genetical recombination) -based first-line chemotherapy
The SOLO1 study, a global phase III study in patients with *BRCA* mutation-positive ovarian cancer responding to a platinum-based first-line chemotherapy
The PROfound study, a global phase III study in patients with HRR-related gene mutation-positive mCRPC who have previously been treated with abiraterone, enzalutamide, or both drugs

Table 15. Patients reporting serious venous thromboembolism (for which a causal relationship to Olaparib could not be ruled out)

Study	Age	Sex	Race	Cancer type	Concomitant drug	PT*	Grade	Time of onset (onset date)	Duration of the event (days)	Actions against olaparib	Outcome
PROpel	7[redacted]	Man	Non-Japanese	Prostate cancer	Abiraterone	Pulmonary embolism	3	117	53	None	Resolved
	7[redacted]	Man	Non-Japanese	Prostate cancer	Abiraterone	Pulmonary embolism	3	681	Unknown	Interrupted	Unresolved
	8[redacted]	Man	Japanese	Prostate cancer	Abiraterone	Pulmonary embolism	3	166	255	None	Resolved
	8[redacted]	Man	Non-Japanese	Prostate cancer	Abiraterone	Pulmonary embolism	3	333	8	Interrupted	Resolved
Study 19	4[redacted]	Woman	Non-Japanese	Ovarian cancer	None	Pulmonary embolism	4	6	2	Reduced	Resolved
					None	Pulmonary embolism	4	1,485	78	Interrupted	Resolved
PAOLA-1	7[redacted]	Woman	Non-Japanese	Ovarian cancer	BV	Pulmonary embolism	3	436	25	Interrupted	Resolved
SOLO1	5[redacted]	Woman	Non-Japanese	Ovarian cancer	None	Pulmonary embolism	3	1,254	180	None	Resolved
PROfound	7[redacted]	Woman	Non-Japanese	Prostate cancer	None	Pulmonary embolism	3	107	7	Interrupted	Resolved
	6[redacted]	Woman	Non-Japanese	Prostate cancer	None	Pulmonary embolism	3	161	2	None	Resolved

* MedDRA ver. 22.0 for Study PAOLA-1, MedDRA ver. 24.0 for other clinical studies

PMDA asked the applicant to explain the risk factors for venous thromboembolism.

The applicant's explanation:

Table 16 shows the incidences of venous thromboembolism during treatment with olaparib in comparative studies using olaparib in patients with advanced solid tumors.

Table 16. Incidences of venous thromboembolism in comparative studies using olaparib

Study	Cancer type	Treatment	N	Number of patients reporting venous thromboembolism (%)
PROpel	Prostate cancer	Olaparib/abiraterone*1	398	29 (7.3)
		Placebo/abiraterone*1	396	13 (3.3)
PROfound	Prostate cancer	Olaparib	256	17 (6.6)
		Abiraterone*1 or enzalutamide	130	3 (2.3)
PAOLA-1	Ovarian cancer	Olaparib/BV	535	19 (3.6)
		Placebo/BV	267	5 (1.9)
SOLO1	Ovarian cancer	Olaparib	260	8 (3.1)
		Placebo	130	2 (1.5)
SOLO2	Ovarian cancer	Olaparib	195	10 (5.1)
		Placebo	99	1 (1.0)
SOLO3	Ovarian cancer	Olaparib	178	12 (6.7)
		Chemotherapy*2	76	4 (5.3)
OlympiAD	Breast cancer	Olaparib	205	6 (2.9)
		Chemotherapy*3	91	3 (3.3)
POLO	Pancreatic cancer	Olaparib	90	2 (2.2)
		Placebo	61	1 (1.6)

*1, Prednisolone or prednisone was concomitantly used; *2, Paclitaxel, liposomal doxorubicin hydrochloride, nogitecan hydrochloride, or gemcitabine hydrochloride; *3, Capecitabine, eribulin mesilate, or vinorelbine ditartrate

The studies involving patients with prostate cancer and a study using BV as the concomitant drug tended to show a higher incidence of venous thromboembolism in the olaparib group than in the control group. Prostate cancer tends to be common in the elderly as compared with other types of cancer. Given these facts, a multivariate logistic analysis using explanatory variables,[9] including age (≥50 or <50 years), the concomitant BV (with or without), and cancer type (prostate cancer, ovarian cancer, breast cancer, or pancreatic cancer), was conducted in the combined population from patients receiving olaparib in the 8 studies listed in Table 16. The lower 95% CI of the adjusted odds ratio of the incidence of venous thromboembolism was >1 only in patients aged ≥50 years (adjusted odds ratio [95% CI] in patients aged ≥50 years to those aged <50 years: 3.56 [1.57, 9.67]),[10] indicating that being elderly was a possible risk factor for venous thromboembolism associated with olaparib therapy.

PMDA's view:

Taking into account that (a) the olaparib group tended to have higher incidences of Grade ≥3 venous thromboembolism and serious venous thromboembolism than the placebo group, and that (b) multiple patients experienced serious venous thromboembolism for which a causal relationship could not be ruled out in the clinical studies of olaparib, the occurrence of venous thromboembolism requires attention. Thus, the occurrence of venous thromboembolism and the management practices in the clinical studies should be appropriately communicated to healthcare professionals through the package insert, etc.

7.R.3.4 Infections

The applicant's explanation about the occurrence of infections during treatment with olaparib:

Events falling under the MedDRA's system organ class (SOC) of "infections and infestations" were counted as infections.

Table 17 shows the incidences of infections in the PROpel study.

Table 17. Incidences of infections reported with a ≥2% incidence in either treatment group (PROpel study)

PT (MedDRA ver. 24.0)	n (%)			
	Olaparib N = 398		Placebo N = 396	
	All grades	Grade ≥3	All grades	Grade ≥3
Infections	173 (43.5)	47 (11.8)	146 (36.9)	35 (8.8)
Urinary tract infection	41 (10.3)	8 (2.0)	31 (7.8)	4 (1.0)
COVID-19	24 (6.0)	12 (3.0)	17 (4.3)	7 (1.8)
Upper respiratory tract infection	18 (4.5)	0	20 (5.1)	0
Pneumonia	16 (4.0)	7 (1.8)	10 (2.5)	3 (0.8)
Nasopharyngitis	14 (3.5)	0	9 (2.3)	0
Gastroenteritis	9 (2.3)	1 (0.3)	3 (0.8)	0
Influenza	9 (2.3)	0	7 (1.8)	0
Bronchitis	9 (2.3)	0	4 (1.0)	0

9) Although concomitant ADT was considered a possible risk factor, most patients with prostate cancer received ADT, and concomitant ADT was thus not included in the exploratory variables.

10) The adjusted odds ratio [95% CI] for prostate cancer to pancreatic cancer was 2.82 [0.85, 17.48], the ratio for prostate cancer to ovarian cancer was 1.53 [0.99, 2.36], the ratio for prostate cancer to breast cancer was 1.32 [0.55, 3.73], and the ratio for the concomitant use of BV to no concomitant use of BV was 1.37 [0.59, 2.82].

In the PROpel study, infections resulted in death in 9 of 398 patients (2.3%; COVID-19 in 5 patients, COVID-19 pneumonia in 2 patients, and pneumonia and pneumonia bacterial in 1 patient each) in the olaparib group and 7 of 396 patients (1.8%; COVID-19 in 3 patients, and infection, pneumococcal sepsis, sepsis, and staphylococcal sepsis in 1 patient each) in the placebo group. A causal relationship to olaparib or placebo was ruled out for all the events.

Serious infections were reported in 52 of 398 patients (13.1%; COVID-19 in 12 patients, pneumonia and urinary tract infection in 8 patients each, urosepsis in 5 patients, COVID-19 pneumonia and pneumocystis jirovecii pneumonia in 3 patients each, lower respiratory tract infection, sepsis, and suspected COVID-19 in 2 patients each, and anal abscess, atypical pneumonia, bacterial sepsis, cellulitis, gastroenteritis, hepatitis B reactivation, infection, pneumonia bacterial, pneumonia viral, skin infection, and wound infection staphylococcal in 1 patient each [some patients had more than one event.]) in the olaparib group, and 37 of 396 patients (9.3%; COVID-19 in 9 patients, pneumonia in 4 patients, sepsis and urinary tract infection in 3 patients each, appendicitis, osteomyelitis, and urosepsis in 2 patients each, and acute sinusitis, bacterial sepsis, COVID-19 pneumonia, diverticulitis, gastroenteritis viral, infection, lung abscess, oral infection, perirectal abscess, pneumococcal sepsis, pneumonia bacterial, pneumonia viral, pyelonephritis, staphylococcal sepsis, and urinary tract infection pseudomonal in 1 patient each [some patients had more than one event.]) in the placebo group. A causal relationship to olaparib could not be ruled out for the pneumocystis jirovecii pneumonia and pneumonia in 2 patients each and the sepsis in 1 patient in the olaparib group, while a causal relationship to placebo was ruled out for all the events in the placebo group.

Infections led to the discontinuation of olaparib or placebo in 10 of 398 patients (2.5%; COVID-19, pneumocystis jirovecii pneumonia, and pneumonia in 2 patients each, and bacterial sepsis, pneumonia bacterial, suspected COVID-19, and urinary tract infection in 1 patient each) in the olaparib group, but no patients in the placebo group.

Infections led to the interruption of olaparib or placebo in 38 of 398 patients (9.5%; COVID-19 in 10 patients, upper respiratory tract infection in 4 patients, COVID-19 pneumonia and pneumocystis jirovecii pneumonia in 3 patients each, gastroenteritis, lower respiratory tract infection, pneumonia, suspected COVID-19, and urinary tract infection in 2 patients each, and bronchitis, cellulitis, hepatitis B reactivation, influenza, oral candidiasis, rash pustular, sinusitis fungal, skin infection, and urosepsis in 1 patient each [some patients reported more than one event.]) in the olaparib group, and 27 of 396 patients (6.8%; COVID-19 in 8 patients, lower respiratory tract infection and urinary tract infection in 3 patients each, and acute sinusitis, COVID-19 pneumonia, dacryocanaliculitis, influenza, oral candidiasis, oral infection, osteomyelitis, perirectal abscess, pneumonia, pyelonephritis, respiratory tract infection, sepsis, upper respiratory tract infection, and viral infection in 1 patient each [some patients reported more than one event.]) in the placebo group.

Infections led to the dose reduction of olaparib or placebo in 2 of 398 patients (0.5%; pneumonia cryptococcal and urinary tract infection in 1 patient each) in the olaparib group and 1 of 396 patients (0.3%; diverticulitis in 1 patient) in the placebo group.
The median (minimum, maximum) time to the first onset of infection in the PROpel study was 167 (1, 811) days in the olaparib group and 162 (1, 726) days in the placebo group.

Table 18 details patients reporting serious infections for which a causal relationship to olaparib could not be ruled out in clinical studies[11)] of olaparib, including the PROpel study.

11) Include the following clinical studies other than those submitted for this partial change application;
The SOLO2 study, a global phase III study in patients with recurrent, platinum-sensitive, *BRCA* mutation-positive ovarian cancer responding to a recent platinum-based chemotherapy
The SOLO3 study, a foreign phase III study in patients with recurrent, platinum-sensitive, *gBRCA* mutation-positive ovarian cancer who had previously been treated with ≥2 platinum-based chemotherapies
The PAOLA-1 study, a global phase III study in patients with ovarian cancer responding to a platinum- and bevacizumab (genetical recombination) -based first-line chemotherapy
The SOLO1 study, a global phase III study in patients with *BRCA* mutation-positive ovarian cancer responding to a platinum-based first-line chemotherapy
The OlympiA study, a global phase III study in patients with *gBRCA* mutation-positive HER2-negative breast cancer with a high risk of recurrence, who had previously been treated with neoadjuvant or adjuvant chemotherapy
The PROfound study, a global phase III study in patients with HRR-related gene mutation-positive mCRPC who had previously been treated with abiraterone, enzalutamide, or both drugs

Table 18. Patients reporting serious infections (for which a causal relationship to olaparib could not be ruled out)

Study	Age	Sex	Cancer type	Concomitant drug	PT*	Grade	Time of onset (onset date)	Duration of the event (days)	Actions against olaparib	Outcome
PROpel	7[redacted]	Man	Prostate cancer	Abiraterone	Pneumocystis jirovecii pneumonia	3	73	43	Interrupted	Resolved
	6[redacted]	Man	Prostate cancer	Abiraterone	Pneumocystis jirovecii pneumonia	2	138	Unknown	Discontinued	Improved
	7[redacted]	Man	Prostate cancer	Abiraterone	Pneumonia	3	77	23	Not applicable	Resolved
					Sepsis	4	103	15	Not applicable	Resolved
	6[redacted]	Man	Prostate cancer	Abiraterone	Pneumonia	4	89	13	Interrupted	Resolved
SOLO2	5[redacted]	Woman	Ovarian cancer	None	Neutropenic sepsis	2	70	2	Interrupted	Resolved
SOLO3	5[redacted]	Woman	Ovarian cancer	None	Urinary tract infection	3	943	12	Interrupted	Resolved
PAOLA-1	5[redacted]	Woman	Ovarian cancer	BV	Infection	3	446	9	Unknown	Resolved
	5[redacted]	Woman	Ovarian cancer	BV	Eye infection	3	12	76	Discontinued	Unresolved
	8[redacted]	Woman	Ovarian cancer	BV	Pneumonia	3	263	11	Discontinued	Resolved
	4[redacted]	Woman	Ovarian cancer	BV	Pneumonia	5	613	7	Unknown	Died
	3[redacted]	Woman	Ovarian cancer	BV	Erysipelas	3	361	3	Unknown	Resolved
	5[redacted]	Woman	Ovarian cancer	BV	Cytomegalovirus infection	2	331	48	Discontinued	Resolved
	4[redacted]	Woman	Ovarian cancer	BV	Cytomegalovirus infection	4	547	36	Discontinued	Resolved
SOLO1	5[redacted]	Woman	Ovarian cancer	None	Upper respiratory tract infection	2	34	19	None	Resolved
					Urinary tract infection	2	50	14	None	Resolved
	5[redacted]	Woman	Ovarian cancer	None	Medical device site cellulitis	3	703	8	Not applicable	Resolved
OlympiA	6[redacted]	Woman	Breast cancer	None	Gastroenteritis	3	297	8	Interrupted	Resolved
	5[redacted]	Woman	Breast cancer	None	Pneumonia	3	24	8	Interrupted	Resolved
PROfound	6[redacted]	Man	Prostate cancer	None	Pneumonia	2	43	43	Interrupted	Resolved
	5[redacted]	Man	Prostate cancer	None	Pneumonia	5	3	7	Discontinued	Died

* MedDRA ver. 22.0 for Study PAOLA-1, MedDRA ver. 24.0 for other clinical studies

PMDA asked the applicant to explain causative factors of the higher incidences of infections in the olaparib group and their risk factors.

The applicant's explanation:

Among patients in the olaparib group of the PROpel study, those with Grade ≥3 myelosuppression[12)] who experienced infection and those who did not accounted for 12.7% and 4.9%, respectively, indicating that the incidence of Grade ≥3 myelosuppression tended to be higher in patients who had experienced infection than in those who did not. However, only a small number (12.7%) of patients with infection reported Grade ≥3 myelosuppression.[12)] Thus, a relationship between myelosuppression and infections occurring during treatment with olaparib remained unclear.

12) Leukopenia, lymphopenia, and neutropenia

The following suggest that the concomitant use of prednisolone or prednisone and being elderly are the possible risk factors for infections during treatment with olaparib.

- A pooled analysis was conducted including patients with prostate cancer receiving olaparib in clinical studies.[13)] The incidence of infections of any grade was 44.3% in patients who received concomitant prednisolone or prednisone and 31.6% in patients who did not, and that the incidence of Grade ≥3 infections was 11.9% and 7.8%, respectively.
- A pooled analysis was conducted including patients with prostate cancer receiving olaparib/abiraterone therapy in clinical studies.[14)] The incidence of Grade ≥3 infections was 8.8% in the olaparib group and 9.2% in the placebo group of patients aged <65 years, and 13.4% in the olaparib group and 8.9% in the placebo group of patients aged ≥65 years.

PMDA's view:

The olaparib group tended to have higher incidences of Grade ≥3 infections and serious infections than the placebo group in the PROpel study. Multiple patients in the clinical studies died from infections for which a causal relationship to olaparib could not be ruled out and experienced serious infections for which a causal relationship to olaparib could not be ruled out. These outcomes indicate that infections requires attention. Therefore, the occurrence of infections and the management practices in the clinical studies should be appropriately communicated to healthcare professionals through the package insert, etc.

7.R.4 Clinical positioning and indication

In the present partial change application, the applicant proposed "Indication" and the "Precautions Concerning Indication" for prostate cancer as shown in the following table.

13) The PROpel study, Study 08, and the PROfound study (a global phase III study in patients with HRR-related gene mutation-positive mCRPC who had previously been treated with abiraterone, enzalutamide, or both drugs)

14) PROpel study and Study 08

Indication (Strikethrough denotes deletions.)	Precautions concerning indication (Underline denotes additions.)
Treatment of metastatic, ~~*BRCA* mutation-positive~~ castration-resistant prostate cancer	• The efficacy and safety of olaparib adjuvant therapy have not been established. • When used alone, olaparib should be administered to patients who have been confirmed to have *BRCA* mutation via testing using an approved *in vitro* diagnostic or medical device. • Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the treatment history (e.g., endocrine therapy history) of patients enrolled in the clinical studies and the efficacy and safety of olaparib, before selecting eligible patients.

PMDA's view:

Based on the discussion in Sections "7.R.2 Efficacy" and "7.R.3 Safety," and the subsections below, the "Indication" and the "Precautions Concerning Indication" sections for prostate cancer should be described as per the following table.

Indication (Strikethrough denotes deletions.)	Precautions concerning indication (Underline denotes additions. Strikethrough denotes deletions.)
Treatment of metastatic, ~~*BRCA* mutation-positive~~ castration-resistant prostate cancer	• The efficacy and safety of olaparib adjuvant therapy have not been established. • Patients must be tested for ~~"Testing~~ *BRCA* mutation using an approved *in vitro* diagnostic or medical device. Olaparib monotherapy should be administered to patients who have been confirmed to have *BRCA* mutation. • The efficacy of olaparib administered in combination with abiraterone acetate is suggested to differ by *BRCA* mutation status. Other treatment options should also be carefully considered for *BRCA* mutation-negative patients. • Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the ~~endocrine therapy~~ treatment history of patients enrolled in the clinical studies and the efficacy and safety of olaparib, before selecting eligible patients.

7.R.4.1 Clinical positioning and indication of olaparib

Latest clinical practice guidelines and major clinical oncology textbooks published in and outside Japan do not refer to olaparib/abiraterone therapy for pharmacotherapy-naïve mCRPC.

The applicant's explanation about the clinical positioning and indication of olaparib/abiraterone therapy:

The results of the PROpel study involving patients with pharmacotherapy-naïve mCRPC demonstrated the clinical usefulness of olaparib/abiraterone therapy [see Sections 7.R.2 and 7.R.3], and thus olaparib/abiraterone therapy is considered a promising treatment option for this patient population. Because of no clinical study data comparing the efficacy and safety of olaparib/abiraterone therapy with approved enzalutamide and docetaxel at present, there is no clear standard for choices among olaparib/abiraterone and these approved drugs for patients with pharmacotherapy-naïve mCRPC. The choice will be made case by case based on the efficacy and safety of each drug.

The "Precautions Concerning Indications" section of the current package insert recommends the use of olaparib in patients who have been confirmed to have *BRCA* mutation by testing with an approved *in vitro* diagnostic or medical device. It should be clearly highlighted that this advice refers to the approved use of olaparib monotherapy in patients with *BRCA* mutation-positive mCRPC. Meanwhile, olaparib/abiraterone therapy is recommended for patients with pharmacotherapy-naïve mCRPC, i.e., the target population of the

PROpel study [see Section 7.1.1.1], which should be mentioned in the "Clinical Studies" section. In addition, the "Precautions Concerning Indications" section should advise that treating physicians must fully understand the treatment history of the patients treated in the clinical studies and the efficacy and safety of olaparib, before selecting patients eligible for the therapy.

Accordingly, the indication of olaparib was proposed as "metastatic castration-resistant prostate cancer," with the following descriptions in the "Precautions Concerning Indications" section.

- The efficacy and safety of olaparib adjuvant therapy have not been established.
- When used alone, olaparib should be administered to patients who have been confirmed to have *BRCA* mutation via testing using an approved *in vitro* diagnostic or medical device.
- Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the treatment history (e.g., endocrine therapy history) of patients enrolled in the clinical studies and the efficacy and safety of olaparib, before selecting eligible patients.

PMDA's view:

The discussion in Section "7.R.2.4 Results of efficacy evaluation" suggests that the efficacy of olaparib/abiraterone therapy tended to differ by *BRCA* mutation status, and that the olaparib group tended to show higher incidences of Grade ≥3 adverse events and serious adverse events [see Section 7.R.3.1]. Taking into account these findings, etc., the use of olaparib/abiraterone therapy for *BRCA* mutation-negative patients should be carefully decided, while carefully examining other treatment options such as abiraterone monotherapy. Therefore, patients with pharmacotherapy-naïve mCRPC should also be tested for *BRCA* before receiving olaparib/abiraterone therapy.

Based on the above and the comments from the Expert Discussion, etc., PMDA has concluded that the indication should be defined as "metastatic castration-resistant prostate cancer" as proposed by the applicant, with the following modified descriptions in the "Precautions Concerning Indications" section, if clinical significance of the trend toward prolonged rPFS in the *BRCA* mutation-negative population is demonstrated.

- The efficacy and safety of olaparib adjuvant therapy have not been established.
- Patients must be tested for *BRCA* mutation using an approved *in vitro* diagnostic or medical device. Olaparib monotherapy should be administered to patients who have been confirmed to have *BRCA* mutation.
- The efficacy of olaparib administered in combination with abiraterone acetate is suggested to differ by *BRCA* mutation status. Other treatment options should also be carefully examined for *BRCA* mutation-negative patients.
- Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the treatment history of patients enrolled in the clinical studies and the efficacy and safety of olaparib, before selecting eligible patients.

7.R.5 Dosage and administration

In the present partial change application, the "Dosage and Administration" and cautionary advice to be offered in the "Precautions Concerning Dosage and Administration" section for prostate cancer were proposed as per the following table.

Dosage and administration (Underline denotes additions.)	Precautions concerning dosage and administration (Strikethrough denotes deletions.)
The usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition. When administered in combination with abiraterone acetate and prednisolone for the treatment of metastatic castration-resistant prostate cancer, the usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.	• Bioequivalence between the 150-mg tablets and the 100-mg tablets has not been demonstrated. The 100-mg tablets must not be used when administered at 300 mg. • Drug interruption and dose reduction criteria due to adverse drug reactions (same as the criteria for the approved indications.) • ~~The efficacy and safety of olaparib have not been established in combination use with other antineoplastic drugs.~~ • The efficacy and safety of olaparib have not been established in the absence of surgical or medical castration.

As a result of the discussion in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the subsection below, PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be described as per the following table.

Dosage and administration (Underline denotes additions.)	Precautions concerning dosage and administration (Underline denotes additions.)
In combination with abiraterone acetate and prednisolone, the usual adult dosage is 300 mg of olaparib administered orally twice daily. In *BRCA* mutation-positive patients, olaparib may be administered alone. The dose may be adjusted according to the patient's condition.	• Bioequivalence between the 150-mg tablets and the 100-mg tablets has not been demonstrated. The 100-mg tablets must not be used when administered at 300 mg. • Criteria for dose interruption and reduction due to adverse drug reactions (same as the criteria for the approved indications.) • The efficacy and safety of olaparib alone have not been established in patients with no history of treatment with abiraterone acetate or enzalutamide. • The efficacy and safety of olaparib have not been established in combination use with other antineoplastic drugs. • The efficacy and safety of olaparib have not been established in the absence of surgical or medical castration.

7.R.5.1 Dosage and administration of olaparib

The applicant's explanation about the dosage and administration of olaparib in patients with pharmacotherapy -naïve mCRPC:

In Study 08, the olaparib group showed a trend toward prolonged rPFS compared with the placebo group, with tolerable safety [see Section 7.1.2.1]. Therefore, olaparib 300 mg BID with abiraterone 1,000 mg QD was selected for the PROpel study based on the dosing regimen used in Study 08. The PROpel study successfully demonstrated the clinical usefulness of olaparib/abiraterone therapy in patients with pharmacotherapy-naïve mCRPC. Therefore, the dosage and administration of olaparib/abiraterone therapy for prostate cancer was determined based on the dosing regimen used in the PROpel study.

There are no clinical study data that assessed the clinical usefulness of olaparib administered in combination with antineoplastic drugs (including endocrine drugs) other than abiraterone in patients with mCRPC. The "Dosage and Administration" section will clearly state that olaparib be used with abiraterone, and the caution

about unestablished efficacy and safety of olaparib in combination use with other antineoplastic drugs will be deleted.

In the PROpel study, dose adjustment criteria to address adverse drug reactions followed those used in the clinical studies on the approved indications, and the clinical usefulness of olaparib was successfully demonstrated in the target population of the PROpel study. Therefore, no change is necessary in the dose adjustment criteria in the "Precautions for Dosage and Administration" section.

Based on the above, the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections were described as follows.

Dosage and administration
The usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.

When administered in combination with abiraterone acetate and prednisolone for the treatment of metastatic castration-resistant prostate cancer, the usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.

Precautions concerning dosage and administration
- Bioequivalence between the 150-mg tablets and the 100-mg tablets has not been demonstrated. The 100-mg tablets must not be used when olaparib is administered at 300 mg.
- Criteria for drug interruption and dose reduction to address adverse drug reactions
- The efficacy and safety of olaparib have not been established in the absence of surgical or medical castration.

PMDA's view:
In accordance with the change from the approved indication of "*BRCA* mutation-positive, metastatic castration-resistant prostate cancer" to "metastatic castration-resistant prostate cancer" [see Section 7.R.4.1], the "Dosage and Administration" section should make clear that the intended population for olaparib monotherapy is *BRCA* mutation-positive patients. In addition, the PROfound study that demonstrated the clinical usefulness of olaparib monotherapy were conducted in patients who had previously been treated with abiraterone, enzalutamide, or both drugs, and there are no clinical study data demonstrating the clinical usefulness of olaparib monotherapy in patients with pharmacotherapy-naïve mCRPC. Therefore, the treatment history of patients potentially eligible for olaparib monotherapy should be specifically defined in the package insert. The caution in the current package insert on unestablished efficacy and safety in use with other antineoplastic drugs is intended for the concomitant use with antineoplastic drugs without endocrine drugs. In view that the PROpel study demonstrated the efficacy and safety of olaparib only in the concomitant use with an endocrine drug, the deletion of this cautionary advice is inappropriate.

Accordingly, taking into account comments from the Expert Discussion, etc., PMDA has concluded that "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be described as follows when the clinical significance of the trend toward prolonged rPFS in the *BRCA* mutation-negative population is demonstrated.

Dosage and administration

In combination with abiraterone acetate and prednisolone, the usual adult dosage is 300 mg of olaparib administered orally twice daily. In *BRCA* mutation-positive patients, olaparib may be administered alone. The dose may be adjusted according to the patient's condition.

Precautions concerning dosage and administration

- Bioequivalence between the 150-mg tablets and the 100-mg tablets has not been demonstrated. The 100-mg tablets must not be used when administered at 300 mg.
- Criteria for dose interruption and reduction due to adverse drug reactions
- The efficacy and safety of olaparib alone have not been established in patients with no history of treatment with abiraterone acetate or enzalutamide.
- The efficacy and safety of olaparib have not been established in combination use with other antineoplastic drugs.
- The efficacy and safety of olaparib have not been established in the absence of surgical or medical castration.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan for the new indication:

Based on the following observations, there are no new safety concerns in the present partial change application, and new post-marketing surveillance targeting patients with pharmacotherapy-naïve mCRPC will not be necessary immediately after approval.

- The results of the PROpel study showed no clear difference in the safety profiles of olaparib between patients receiving olaparib/abiraterone therapy in the PROpel study and patients receiving olaparib for the approved indications [see Section 7.R.3.1].
- In the PROpel study, no safety concerns specific to Japanese patients were identified [see Section 7.R.3.2].
- A certain amount of safety data of olaparib are available from Japanese patients through the post-marketing surveillance for the approved indications, which have not raised new safety concerns of olaparib.

PMDA's view:

Taking into account the following observation, in addition to the applicant's explanation above, there is little necessity to conduct new post-marketing surveillance covering patients with pharmacotherapy-naïve mCRPC

immediately after approval to assess the safety of olaparib/abiraterone therapy. Routine pharmacovigilance activities will serve the purpose to collect safety data.

- The olaparib group had higher incidences of Grade ≥3 venous thromboembolism and infections than the placebo group, with some cases of serious venous thromboembolism and infections. However, most of the events resolved. Therefore, venous thromboembolism and infections are considered manageable as long as caution is advised about the occurrence of these events in the package insert.

7.2 Adverse events reported in clinical studies

Among the clinical study results submitted for the safety evaluation, death-related results are presented in Section "7.1 Evaluation data." The following summarizes major adverse events other than death.

7.2.1 Global phase III study (PROpel study)

Adverse events were reported in 387 of 398 patients (97.2%) in the olaparib group and 376 of 396 patients (94.9%) in the placebo group. Adverse events for which a causal relationship to the study drug[15)] could not be ruled out were reported in 321 of 398 patients (80.7%) in the olaparib group and 252 of 396 patients (63.6%) in the placebo group. Table 19 shows adverse events reported with a ≥10% incidence in either treatment group.

Table 19. Adverse events reported with a ≥10% incidence in either treatment group

SOC PT (MedDRA ver. 24.0)	n (%)			
	Olaparib N = 398		Placebo N = 396	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	387 (97.2)	188 (47.2)	376 (94.9)	152 (38.4)
Infections and infestations				
Urinary tract infection	41 (10.3)	8 (2.0)	31 (7.8)	4 (1.0)
Blood and lymphatic system disorders				
Anaemia	181 (45.5)	60 (15.1)	64 (16.2)	13 (3.3)
Metabolism and nutrition disorders				
Decreased appetite	58 (14.6)	4 (1.0)	23 (5.8)	0
Nervous system disorder				
Dizziness	43 (10.8)	0	25 (6.3)	0
Vascular disorders				
Hypertension	50 (12.6)	14 (3.5)	65 (16.4)	13 (3.3)
Hot flush	35 (8.8)	0	49 (12.4)	0
Gastrointestinal disorders				
Nausea	112 (28.1)	1 (0.3)	50 (12.6)	1 (0.3)
Constipation	69 (17.3)	0	55 (13.9)	1 (0.3)
Diarrhoea	69 (17.3)	3 (0.8)	37 (9.3)	1 (0.3)
Vomiting	52 (13.1)	4 (1.0)	36 (9.1)	1 (0.3)
Musculoskeletal and connective tissue disorders				
Back pain	68 (17.1)	3 (0.8)	73 (18.4)	4 (1.0)
Arthralgia	51 (12.8)	0	70 (17.7)	2 (0.5)
General disorders and administration site conditions				
Fatigue	111 (27.9)	4 (1.0)	75 (18.9)	3 (0.8)
Asthenia	44 (11.1)	5 (1.3)	38 (9.6)	3 (0.8)
Oedema peripheral	41 (10.3)	0	45 (11.4)	1 (0.3)

15) Olaparib, placebo, or abiraterone

Serious adverse events were reported in 135 of 398 patients (33.9%) in the olaparib group and 107 of 396 patients (27.0%) in the placebo group. Serious adverse events reported by ≥2 patients in each group were anaemia in 23 patients (5.8%), pulmonary embolism in 13 patients (3.3%), COVID-19 in 12 patients (3.0%), urinary tract infection and pneumonia in 8 patients (2.0%) each, urosepsis in 5 patients (1.3%), back pain, syncope, and febrile neutropenia in 4 patients (1.0%) each, fatigue, pyrexia, white blood cell count decreased, atrial fibrillation, acute kidney injury, COVID-19 pneumonia, acute myocardial infarction, and pneumocystis jirovecii pneumonia in 3 patients (0.8%) each, and diarrhoea, vomiting, asthenia, neutropenia, dehydration, osteonecrosis of jaw, suspected COVID-19, lower respiratory tract infection, bladder cancer, colitis, pneumonitis, and sepsis in 2 patients (0.5%) each in the olaparib group, and COVID-19 in 9 patients (2.3%), acute kidney injury, ischaemic stroke, atrial fibrillation, and pneumonia in 4 patients (1.0%) each, sepsis, urinary tract infection, pulmonary embolism, and acute myocardial infarction in 3 patients (0.8%) each, and death, back pain, anaemia, pyrexia, syncope, bone pain, loss of consciousness, drug-induced liver injury, febrile neutropenia, appendicitis, osteomyelitis, and urosepsis in 2 patients (0.5%) each in the placebo group. A causal relationship to the study drug[15)] could not be ruled out for the anaemia in 21 patients, pulmonary embolism in 4 patients, fatigue, white blood cell count decreased, pneumonia, and febrile neutropenia in 3 patients each, atrial fibrillation and pneumocystis jirovecii pneumonia in 2 patients each, and asthenia, neutropenia, acute kidney injury, pyrexia, pneumonitis, and sepsis in 1 patient each in the olaparib group, and acute myocardial infarction in 3 patients, drug-induced liver injury in 2 patients, and anaemia, atrial fibrillation, pulmonary embolism, and ischaemic stroke in 1 patient each in the placebo group.

Adverse events led to the discontinuation of the study drug[15)] in 57 of 398 patients (14.3%) in the olaparib group and 39 of 396 patients (9.8%) in the placebo group. Adverse events leading to the discontinuation of the study drug[15)] in ≥2 patients in each group were anaemia in 15 patients (3.8%), COVID-19 and fatigue in 3 patients (0.8%) each, and pneumonia, atrial fibrillation, pneumocystis jirovecii pneumonia, pneumonitis, lymphocyte count decreased, and lymphopenia in 2 patients (0.5%) each in the olaparib group, and ALT increased in 4 patients (1.0%), arthralgia, AST increased and anaemia in 3 patients (0.8%) each, and acute myocardial infarction, asthenia, musculoskeletal chest pain, and decreased appetite in 2 patients (0.5%) each in the placebo group. A causal relationship to the study drug[15)] could not be ruled out for the anaemia in 12 patients, fatigue in 3 patients, atrial fibrillation and lymphopenia in 2 patients, and pneumocystis jirovecii pneumonia, pneumonitis, and lymphocyte count decreased in 1 patient each in the olaparib group, and ALT increased in 4 patients, AST increased and anaemia in 3 patients each, acute myocardial infarction in 2 patients, and asthenia and decreased appetite in 1 patient each in the placebo group.

7.2.2 Foreign phase II study (Study 08)

7.2.2.1 Part A (Cohort 1)

All patients experienced adverse events and adverse events for which a causal relationship to the study drug[16)] could not be ruled out. Adverse events reported by ≥2 patients were back pain in 3 patients (100%), and lower

16) Olaparib or abiraterone

respiratory tract infection, diarrhoea, nausea, rectal haemorrhage, musculoskeletal chest pain, fall, and humerus fracture in 2 patients (66.7%) each.

Serious adverse events were reported in 2 of 3 patients (66.7%). The serious adverse events included pneumonia, urinary tract infection, pyrexia, and humerus fracture in 1 patient each (33.3%). A causal relationship to the study drug[16)] was ruled out for all of the events.

No patients discontinued treatment with the study drug due to adverse events.

7.2.2.2 Part A (Cohort 2)

All patients experienced adverse events. Adverse events for which a causal relationship to the study drug[16)] could not be ruled out were reported in 9 of 13 patients (69.2%). Adverse events reported with a ≥20% incidence were diarrhoea, nausea, and vomiting in 4 patients (30.8%) each, and back pain and fatigue in 3 patients (23.1%) each.

Serious adverse events were reported in 3 of 13 patients (23.1%). The serious adverse events included cellulitis, eye haemorrhage, and intestinal obstruction in 1 patient (7.7%) each. A causal relationship to the study drug[16)] was ruled out for all of the events.

The adverse event led to the discontinuation of olaparib in 1 of 13 patients (7.7%). The event was arthritis infective, for which a causal relationship to the study drug[16)] was ruled out.

7.2.2.3 Part B

Adverse events were reported in 66 of 71 patients (93.0%) in the olaparib group and 57 of 71 patients (80.3%) in the placebo group. Adverse events for which a causal relationship to the study drug[15)] could not be ruled out were reported in 46 of 71 patients (64.8%) in the olaparib group and 21 of 71 patients (29.6%) in the placebo group. Table 20 shows adverse events reported with a ≥20% incidence in either treatment group.

Table 20. Adverse events reported with a ≥20% incidence in either treatment group

SOC PT (MedDRA ver. 24.0)	n (%)			
	Olaparib N = 71		Placebo N = 71	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	66 (93.0)	38 (53.5)	57 (80.3)	20 (28.2)
Blood and lymphatic system disorders				
Anaemia	22 (31.0)	15 (21.1)	1 (1.4)	0
Gastrointestinal disorders				
Nausea	27 (38.0)	1 (1.4)	15 (21.1)	2 (2.8)
Constipation	18 (25.4)	0	8 (11.3)	0
Vomiting	15 (21.1)	2 (2.8)	9 (12.7)	1 (1.4)
Musculoskeletal and connective tissue disorders				
Back pain	18 (25.4)	1 (1.4)	14 (19.7)	1 (1.4)
General disorders and administration site conditions				
Fatigue	15 (21.1)	1 (1.4)	9 (12.7)	2 (2.8)
Asthenia	16 (22.5)	3 (4.2)	10 (14.1)	0

Serious adverse events were reported in 24 of 71 patients (33.8%) in the olaparib group and 13 of 71 patients (18.3%) in the placebo group. Serious adverse events reported by ≥2 patients were anaemia in 5 patients (7.0%), pneumonia in 4 patients (5.6%), and bacteraemia, urinary tract infection, acute myocardial infarction, myocardial infarction, and respiratory failure in 2 patients (2.8%) each in the olaparib group, and pneumonia in 3 patients (4.2%) and urinary tract infection in 2 patients (2.8%) in the placebo group. A causal relationship to the study drug[16)] could not be ruled out for the anaemia in 3 patients in the olaparib group.

Adverse events led to the discontinuation of olaparib or placebo in 21 of 71 patients (29.6%) in the olaparib group and 7 of 71 patients (9.9%) in the placebo group. Adverse events leading to the discontinuation of olaparib or placebo in ≥2 patients were anaemia in 4 patients (5.6%), nausea in 3 patients (4.2%), and myocardial infarction and muscular weakness in 2 patients (2.8%) each in the olaparib group, and vomiting in 3 patients (4.2%) in the placebo group. A causal relationship to the study drug[15)] could not be ruled out for the anaemia in 4 patients, nausea in 2 patients, and muscular weakness in 1 patient in the olaparib group, and vomiting in 3 patients in the placebo group.

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 inspection is currently ongoing. The results and the conclusion of the PMDA will be reported in the Review Report (2).

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

The inspection is currently ongoing. The results and the conclusion of the PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that olaparib/abiraterone therapy has efficacy in the treatment of mCRPC in patients who have not received chemotherapy for mCRPC, and that olaparib/abiraterone therapy has acceptable safety in view of its benefits. Olaparib/abiraterone therapy is clinically meaningful because it offers a new treatment option for patients with pharmacotherapy-naïve mCRPC. The efficacy, indication, dosage and administration, and other aspects of olaparib/abiraterone therapy should be further evaluated.

PMDA has concluded that olaparib may be approved if olaparib is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 5, 2023

Product Submitted for Approval

Brand Name	Lynparza Tablets 100 mg, Lynparza Tablets 150 mg
Non-proprietary Name	Olaparib
Applicant	AstraZeneca K.K.
Date of Application	February 10, 2022

List of Abbreviations

See the 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 Efficacy

As a result of its review described in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that olaparib/abiraterone therapy is expected to have a certain level of efficacy in *BRCA* mutation-positive patients with pharmacotherapy-naïve mCRPC. Meanwhile, a final conclusion on the efficacy of olaparib/abiraterone therapy in patients with BRCA mutation-negative mCRPC will be reached with comments from the Expert Discussion taken into account.

During the review, the second interim analysis and the final analysis of OS were conducted, and the results from both analyses failed to demonstrate the superiority of olaparib/abiraterone over placebo/abiraterone. The results of the final OS analysis (data cutoff on October 12, 2022) are shown in Table 21 and Figure 9.

Table 21. Result of the final OS analysis (ITT population, data cutoff on October 12, 2022)

	Olaparib		Placebo
N	399		397
Number of events (%)	176 (44.1)		205 (51.6)
Median [95% CI] (months)	42.1 [38.4, -]		34.7 [30.9, 39.3]
Hazard ratio [95% CI]*1		0.81 [0.67, 1.00]	
P-value (two-sided)*2		0.0544	

-, Not reached; *1, Cox proportional hazards model stratified by location of the metastasis (bone only, visceral, vs. other) and prior docetaxel treatment for prostate cancer before the diagnosis of mCRPC (with vs. without); *2, Stratified log-rank test with a two-sided significance level of 0.0377 (with the same stratification factors as those used in the Cox proportional hazards model)

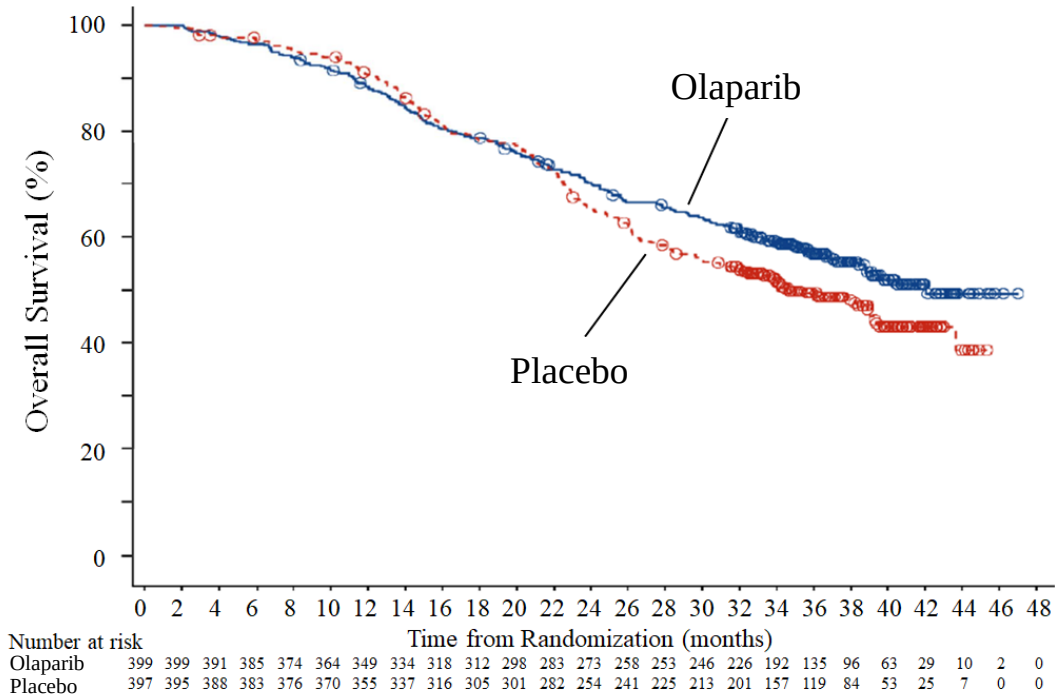

Figure 9. Kaplan-Meier curves for the final OS analysis (ITT population, data cutoff on October 12, 2022)

Tables 22 and 23 are the results from the final OS analysis (i) in patients with *BRCA* testing data in the ITT population, and (ii) by *BRCA* mutation status in the HRR-related gene mutation-positive population, respectively (data cutoff on October 12, 2022).

Table 22. Results of the final OS analysis by *BRCA* mutation status (ITT population, data cutoff on October 12, 2022)

Sample	Gene mutation	Treatment	N	Number of events (%)	Hazard ratio* [95% CI]	*P*-value for interaction*
Tumor tissue	*BRCA* mutation -positive	Olaparib	26	8 (30.8)	0.28 [0.11, 0.62]	0.0028
		Placebo	24	17 (70.8)		
	BRCA mutation -negative	Olaparib	243	115 (47.3)	1.06 [0.81, 1.37]	
		Placebo	242	110 (45.5)		
Plasma	*BRCA* mutation -positive	Olaparib	39	12 (30.8)	0.29 [0.14, 0.58]	0.0029
		Placebo	30	21 (70.0)		
	BRCA mutation -negative	Olaparib	328	154 (47.0)	0.89 [0.72, 1.11]	
		Placebo	337	175 (51.9)		

* Unstratified Cox proportional hazards model including (a) treatment, (b) *BRCA* mutation status, and (c) treatment-by-*BRCA* mutation status interaction as covariates

Table 23. Results of the final OS analysis by *BRCA* mutation status (HRR-related gene mutation-positive population, data cutoff on October 12, 2022)

Sample	Gene mutation	Treatment	N	Number of events (%)	Hazard ratio* [95% CI]	*P*-value for interaction*
Tumor tissue	*BRCA* mutation-positive	Olaparib	26	8 (30.8)	0.27 [0.11, 0.61]	0.0113
		Placebo	24	17 (70.8)		
	BRCA mutation-negative	Olaparib	36	17 (47.2)	1.13 [0.56, 2.33]	
		Placebo	32	14 (43.8)		
Plasma	*BRCA* mutation-positive	Olaparib	39	12 (30.8)	0.29 [0.14, 0.58]	0.0012
		Placebo	30	21 (70.0)		
	BRCA mutation-negative	Olaparib	59	36 (61.0)	1.17 [0.74, 1.84]	
		Placebo	70	39 (55.7)		

* Unstratified Cox proportional hazards model including (a) treatment, (b) *BRCA* mutation status, and (c) treatment-by-*BRCA* mutation status interaction as covariates

The expert advisors supported the PMDA's conclusion on a certain level of efficacy of olaparib/abiraterone therapy expected in patients with *BRCA* mutation-positive, pharmacotherapy-naïve mCRPC. At the same time, they expressed difficulty in reaching a conclusion that olaparib/abiraterone therapy would have a certain level of efficacy in *BRCA* mutation-negative patients based on the results from the PROpel study, with the following observations.

- The primary mechanism of action of olaparib/abiraterone therapy differs between *BRCA* mutation-positive patients and -negative patients [see Section 7.R.2.1]. The PROpel study showed a significantly different efficacy of olaparib/abiraterone therapy between the *BRCA* mutation-positive and -negative populations. Therefore, the efficacy of olaparib/abiraterone therapy should have been evaluated separately by *BRCA* mutation status.
- The contribution of olaparib/abiraterone therapy to rPFS prolongation was extremely limited in the *BRCA* mutation-negative population. The action mechanism of olaparib/abiraterone has yet to be supported by non-clinical study results. These factors preclude the conclusion that the benefits of olaparib/abiraterone therapy will outweigh its risks in *BRCA*-mutation negative patients.
- Patients eligible for the PROpel study had several treatment options other than olaparib/abiraterone therapy. The study results are not convincing enough to conclude that olaparib/abiraterone therapy will provide clinically sufficient benefits to the *BRCA* mutation-negative population as compared with those existing options.

Based on the above comments from the Expert Discussion, PMDA considers that it remains inconclusive whether the benefits of olaparib/abiraterone therapy outweigh its risks in patients with *BRCA* mutation-negative mCRPC.

Meanwhile, PMDA has concluded that the results of the final OS analysis, which was submitted in the middle of the review, did not affect the above PMDA's efficacy conclusion. This conclusion was supported by the expert advisors.

An approved *BRCA* testing method using tumor tissue or blood samples[17] is available to determine the eligibility for olaparib/abiraterone therapy. The rPFS and OS results from patients who were confirmed to have a *BRCA* (*BRCA1* or *BRCA2*) mutation via at least either one of tumor tissue-based or plasma-based testing in the PROpel study are shown in Table 24 and Figure 10, and Table 25 and Figure 11, respectively.

Table 24. Results of the interim rPFS analysis
(Investigator's assessment, *BRCA* mutation-positive population,*1 data cutoff on July 30, 2021)

	Olaparib	Placebo
N	47	38
Number of events (%)	14 (29.8)	28 (73.7)
Median [95% CI] (months)	- [-, -]	8.4 [5.5, 14.8]
Hazard ratio [95% CI]*2	0.23 [0.12, 0.43]	

-, Not reached; *1, Patients who were demonstrated to have a *BRCA* mutation by at least either tumor tissue-based or plasma-based testing; *2, Unstratified Cox proportional hazards model, including (a) treatment, (b) *BRCA* mutation status, and (c) treatment-by-*BRCA* mutation status interaction as covariates

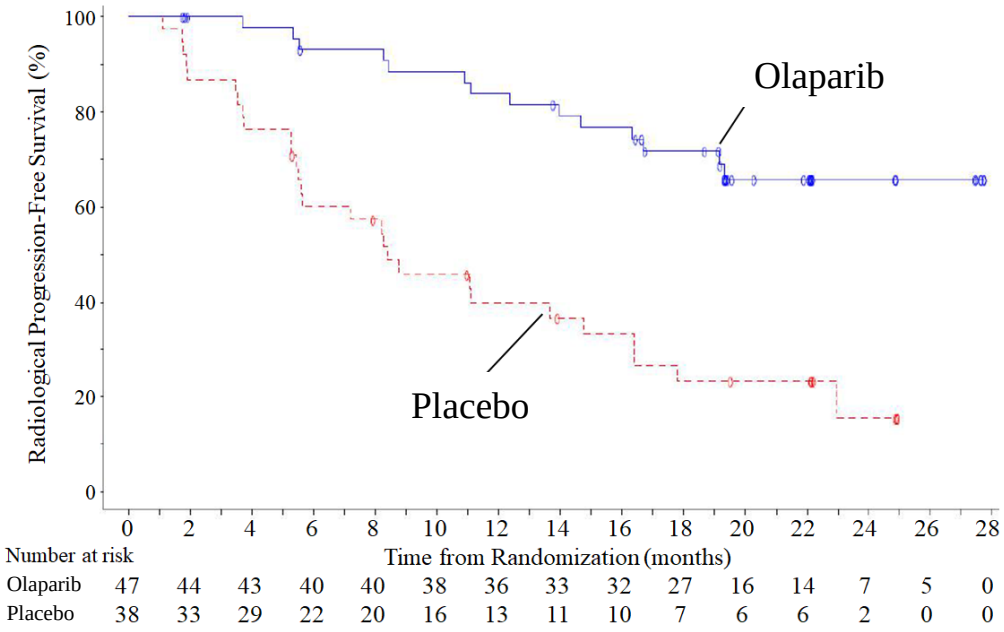

Figure 10. Kaplan-Meier curves for rPFS
(Investigator's assessment, *BRCA* mutation-positive population, data cutoff on July 30, 2021)

Table 25. Results of the first interim OS analysis (*BRCA* mutation-positive population,*1 data cutoff on July 30, 2021)

	Olaparib	Placebo
N	47	38
Number of events (%)	9 (19.1)	16 (42.1)
Median [95% CI] (months)	- [-, -]	23.6 [17.8, -]
Hazard ratio [95% CI]*2	0.39 [0.16, 0.86]	

-, Not reached; *1, Patients who were demonstrated to have a *BRCA* mutation by at least either tumor tissue-based or plasma-based testing; *2, Unstratified Cox proportional hazards model, including (a) treatment, (b) *BRCA* mutation status, and (c) treatment-by-*BRCA* mutation status interaction as covariates

17) The test was developed and approved, in conjunction with the partial change application for olaparib monotherapy for mCRPC in patients who have been treated with abiraterone or enzalutamide.

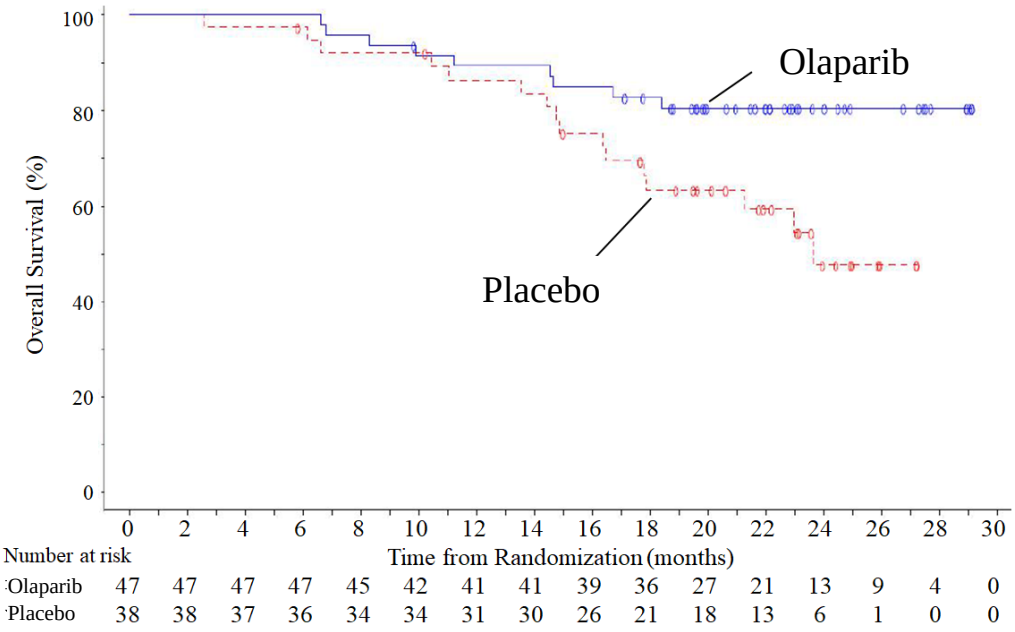

Figure 11. Kaplan-Meier curves for OS
(*BRCA* mutation-positive population, data cutoff on July 30, 2021)

1.2 Safety

PMDA's conclusion:

As a result of its review described in Section "7.R.3 Safety" of the Review Report (1), adverse events of particular attention in the use of olaparib/abiraterone therapy in patients with pharmacotherapy-naïve mCRPC are myelosuppression, interstitial lung disease (ILD), secondary malignancy, venous thromboembolism, and infections.

Although the use of olaparib warrants attention for the above-mentioned adverse events, olaparib/abiraterone therapy is tolerable in patients with pharmacotherapy-naïve mCRPC where appropriate measures, such as adverse event monitoring and management, olaparib interruption, are taken under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy.

At the Expert Discussion, the expert advisors supported the PMDA's conclusions.

1.3 Clinical positioning and indication

PMDA's conclusions:

As a result of its review in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), the choice of treatment for BRCA mutation-negative patients must be determined after careful examination of other therapeutic options including abiraterone monotherapy, and patients with pharmacotherapy-naïve mCRPC should be tested for *BRCA* mutation status prior to olaparib/abiraterone therapy. Appropriate cautionary advice on the use of olaparib for prostate cancer should be offered in the "Indications" and "Precautions Concerning Indications" sections, taking into account comments from the Expert Discussion on

the clinical significance of the trend toward prolonged rPFS observed in the *BRCA* mutation-negative population.

The expert advisors supported the PMDA's conclusion regarding the necessity of *BRCA* testing before olaparib/abiraterone therapy, making the following remark.

- It remains inconclusive whether the benefits of olaparib/abiraterone therapy in *BRCA*-mutation negative patients outweigh its risks. Therefore, the "Indications" section should make clear that olaparib/abiraterone therapy is intended for *BRCA* mutation-positive patients.

Based on the above comments from the Expert Discussion, PMDA instructed the applicant to offer the cautionary advice in the "Indications" and "Precautions Concerning Indications" sections as per the table below. The applicant agreed. (Underline denotes additions to and strikethrough denotes deletions from the statements for the approved indications.)

Indication	Precautions concerning indication
Treatment of *BRCA* mutation-positive, metastatic castration-resistant prostate cancer	• The efficacy and safety of olaparib adjuvant therapy have not been established. • Olaparib should be administered to patients who have been confirmed to have a *BRCA* mutation by testing using an approved *in vitro* diagnostic or medical device. • Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the ~~endocrine therapy~~ treatment history of patients enrolled in the clinical studies and the efficacy and safety of olaparib, before selecting eligible patients.

1.4 Dosage and administration

PMDA's conclusions based on the review in Section "7.R.5 Dosage and administration" of the Review Report (1):

The package insert should define the patient eligibility for olaparib monotherapy specifically by referring to treatment history, because the clinical usefulness of olaparib monotherapy has not been demonstrated by clinical study data for patients with pharmacotherapy-naïve mCRPC. Descriptions relevant to the use of olaparib for prostate cancer in "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be defined taking account of the discussion among the expert advisers on the clinical significance of the trend toward prolonged rPFS in the *BRCA* mutation-negative population.

The expert advisors commented that it remained inconclusive whether olaparib/abiraterone therapy has a certain level of efficacy in *BRCA* mutation-negative patients [see Section 1.1]. Accordingly, PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be described as per the table below, which was supported by the expert advisors.

Dosage and administration	Precautions concerning dosage and administration
The usual adult dosage is 300 mg of olaparib administered orally twice daily. When administered in combination with other drugs, abiraterone acetate and prednisolone should be selected. The dose may be adjusted according to the patient's condition.	• Bioequivalence between the 150-mg tablets and the 100-mg tablets has not been demonstrated. The 100-mg tablets must not be used when administered at 300 mg. • Criteria for dose interruption and reduction due to adverse drug reactions (same as the criteria for the approved indications.) • The efficacy and safety of olaparib administered alone have not been established in patients with no history of treatment with abiraterone acetate or enzalutamide. • The efficacy and safety of olaparib have not been established in combination use with other antineoplastic drugs. • The efficacy and safety of olaparib have not been established in the absence of surgical or medical castration.

Based on the above comments from the Expert Discussion, PMDA instructed the applicant to describe the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as above. The applicant agreed.

1.5 Risk management plan (draft)

As a result of its review in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA has concluded that there is little necessity to conduct post-marketing surveillance covering patients with pharmacotherapy-naïve mCRPC immediately after approval for safety assessment, etc. of olaparib/abiraterone therapy. Routine pharmacovigilance activities will adequately serve to collect safety data relevant to the new indication.

At the Expert Discussion, the expert advisors supported the PMDA's conclusions.

Based the above discussion, PMDA concluded that the risk management plan (draft) should include the safety specifications presented in Table 26, and that the applicant should conduct the additional pharmacovigilance activities presented in Table 27.

Table 26. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Myelosuppression • ILD • Venous thromboembolism • Infections	• Secondary malignancy • Embryo-fetal toxicity • Administration to patients with renal impairment	None
Efficacy specification		
None		

Underline denotes safety specifications to be added for the present application.

Table 27. 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
• Use-results survey in patients receiving olaparib for the maintenance treatment of incurable, unresectable *BRCA* mutation-positive pancreatic cancer after chemotherapy including that with platinum-based antineoplastic drugs • Use-results survey in patients receiving olaparib for the adjuvant pharmacotherapy for *BRCA* mutation-positive HER2-negative breast cancer with a high risk of recurrence • Post-marketing clinical studies (extension studies of the SOLO1 study and the OlympiA study)	None	None

No changes are made for the present partial change application. Wavy line denotes additions made after the submission of the present partial change application.

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

2.1 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.

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

The new drug application data (CTD 5.3.5.1.1) 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 and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the review above, PMDA has concluded that the product may be approved for the indications and the dosage and administration shown below, with the following conditions. The product will deserve the approval only where the fulfillment of requirements, i.e., necessary cautionary advice offered in the package insert; appropriate information provision about the proper use of the product in the post-marketing setting; and adherence to the proper use of the product under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy and at medical institutions fully prepared for emergencies, are assured. The re-examination period is the remainder of the re-examination period (until January 18, 2026).

Indications (No change is made in the present partial change application. Double-underline denotes additions made as of August 24, 2022, after the submission of the present application.)

Maintenance treatment of recurrent ovarian cancer responding to platinum-based chemotherapy

Maintenance treatment of *BRCA* mutation-positive ovarian cancer after first-line chemotherapy

Maintenance treatment of homologous recombination deficiency-positive ovarian cancer after first-line chemotherapy including bevacizumab (genetical recombination)

Treatment of inoperable or recurrent *BRCA* mutation-positive HER2-negative breast cancer previously treated with chemotherapy

Adjuvant pharmacotherapy for *BRCA* mutation-positive HER2-negative breast cancer with a high risk of recurrence

Treatment of *BRCA* mutation-positive metastatic castration-resistant prostate cancer

Maintenance treatment of incurable, unresectable *BRCA* mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs

Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of August 24, 2022, after the submission of the present application.)

*Maintenance treatment of recurrent ovarian cancer responding to platinum-based chemotherapy, maintenance treatment of BRCA mutation-positive ovarian cancer after first-line chemotherapy, ~~treatment of metastatic, BRCA mutation-positive castration-resistant prostate cancer,~~ maintenance treatment of incurable, u*nresectable *BRCA mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs*

The usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.

Maintenance treatment of homologous recombination deficiency-positive ovarian cancer after first-line chemotherapy including bevacizumab (genetical recombination)

When administered in combination with bevacizumab (genetical recombination) ~~for the maintenance treatment of homologous recombination deficiency-positive ovarian cancer in patients who have received first chemotherapy including bevacizumab (genetical recombination)~~, the usual adult dosage is 300 mg of olaparib administered orally twice daily. The dose may be adjusted according to the patient's condition.

Treatment of inoperable or recurrent BRCA mutation-positive HER2-negative breast cancer previously treated with chemotherapy, adjuvant pharmacotherapy for BRCA mutation-positive HER2-negative breast cancer with a high risk of recurrence

The usual adult dosage is 300 mg of olaparib administered orally twice daily. For adjuvant pharmacotherapy, the treatment duration must not exceed 1 year. The dose may be adjusted according to the patient's condition.

Treatment of BRCA mutation-positive metastatic castration-resistant prostate cancer

The usual adult dosage is 300 mg of olaparib administered orally twice daily. When administered in combination with other drugs, abiraterone acetate and prednisolone should be selected. The dose may be adjusted according to the patient's condition.

Approval Conditions

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

Warnings (No change)

Olaparib should be administered only to patients found eligible for the use of olaparib, under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy, at medical institutions fully prepared for emergencies. Prior to the treatment with olaparib, consent must be obtained from the patient or his/her family member who is fully explained about the efficacy and risks of the treatment.

Contraindications (No change)

Patients with a history of hypersensitivity to olaparib or any of its excipients.

Precautions Concerning Indications (Underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of August 24, 2022, after the submission of the present application.)

Maintenance treatment of recurrent ovarian cancer responding to platinum-based chemotherapy

1. Olaparib should be administered to patients responding to platinum-based chemotherapy after recurrence.
2. Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the progression free interval (PFI), i.e., time from the completion of the platinum-based chemotherapy to recurrence, of the patients enrolled in the clinical studies, etc. and the efficacy and safety of olaparib, before selecting eligible patients.

Maintenance treatment of BRCA mutation-positive ovarian cancer after first-line chemotherapy

3. Olaparib should be administered to patients diagnosed to have advanced ovarian cancer (The International Federation of Gynecology and Obstetrics [FIGO] stage III or IV) responding to first-line platinum-based chemotherapy.
4. Olaparib should be administered to patients who have been confirmed to have a *BRCA* mutation via testing using an approved *in vitro* diagnostic or medical device.
5. Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the treatment history of patients enrolled in the clinical studies and the efficacy and safety of olaparib, before selecting eligible patients.

Maintenance treatment of homologous recombination deficiency-positive ovarian cancer after first-line chemotherapy including bevacizumab (genetical recombination)

6. Olaparib should be administered to patients diagnosed as having advanced ovarian cancer (FIGO stage III or IV) responding to first-line chemotherapy including platinum-based and bevacizumab (genetical recombination) chemotherapies.

7. Olaparib should be administered to patients who have been confirmed to have homologous recombination deficiency via testing using an approved *in vitro* diagnostic or medical device.

Treatment of inoperable or recurrent BRCA mutation-positive HER2-negative breast cancer previously treated with chemotherapy

~~8. The efficacy and safety of olaparib as a neoadjuvant or adjuvant pharmacotherapy have not been established.~~

~~9~~8. Olaparib should be administered to patients who have previously been treated with chemotherapy including antineoplastic anthracyclines and taxanes.

~~10~~9. Olaparib should be administered to patients who have been confirmed to have a germline *BRCA* mutation (pathogenic/likely pathogenic) via testing using an approved *in vitro* diagnostic or medical device.

Adjuvant pharmacotherapy for BRCA mutation-positive HER2-negative breast cancer with a high risk of recurrence

10. The efficacy and safety of olaparib neoadjuvant pharmacotherapy have not been established.

11. Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the definition of "a high risk of recurrence," the treatment history of patients enrolled in the clinical studies, and the efficacy and safety of olaparib, before selecting eligible patients.

12. Olaparib should be administered to patients who have been confirmed to have a *BRCA* mutation via testing using an approved *in vitro* diagnostic or medical device.

Treatment of BRCA mutation-positive metastatic castration-resistant prostate cancer

~~11~~13. The efficacy and safety of olaparib adjuvant therapy have not been established.

~~12~~14. Olaparib should be administered to patients who have been confirmed to have a *BRCA* mutation by testing using an approved *in vitro* diagnostic or medical device.

~~13~~15. Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the ~~endocrine therapy~~ treatment history of patients enrolled in the clinical studies and the efficacy and safety of olaparib, before selecting eligible patients.

Maintenance treatment of incurable, unresectable BRCA mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs

~~14~~16. The efficacy and safety of olaparib as neoadjuvant or adjuvant therapy have not been established.

~~15~~17. Olaparib should be administered to patients with no disease progression after the completion of platinum-based chemotherapy.

~~16~~18. Treating physicians must have a full understanding of the information in the "Clinical Studies" section, including the disease stage and the duration of the platinum-based chemotherapy of the patients enrolled in the clinical studies and the efficacy and safety of olaparib, before selecting eligible patients.

~~17~~19. Olaparib should be administered to patients who have been confirmed to have a germline *BRCA* mutation (pathogenic/likely pathogenic) via testing using an approved *in vitro* diagnostic or medical device.

Precautions Concerning Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions. Double-line denotes additions made as of August 24, 2022, after the submission of the present application.)

All indications

1. Bioequivalence between the 150-mg tablets and the 100-mg tablets has not been demonstrated. The 100-mg tablets must not be used when administered at 300 mg.
2. If any adverse drug reaction associated with olaparib occurs, interrupt, reduce, or discontinue olaparib according to the criteria below.

Dose adjustment criteria due to adverse drug reactions

Adverse drug reaction	Severity*	Actions	Dose at resumption
Anaemia	Grade 3 or 4 hemoglobin decreased	Interrupt olaparib for ≤4 weeks until recovery of hemoglobin level to ≥9 g/dL.	• No dose reduction for the first resumption • 250 mg BID for the second resumption • 200 mg BID for the third resumption
Neutropenia	Grade 3 or 4	Interrupt olaparib until recovery to Grade ≤1.	
Thrombocytopenia	Grade 3 or 4	Interrupt olaparib for ≤4 weeks until recovery to Grade ≤1.	No dose reduction
Interstitial lung disease	Grade 2	Interrupt olaparib until recovery to Grade ≤1.	No dose reduction
	Grade 3 or 4	Discontinue olaparib.	No resumption
Other adverse drug reactions	Grade 3 or 4	Interrupt olaparib until recovery to Grade ≤1.	No dose reduction

* According the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver 4.0

Maintenance treatment of recurrent ovarian cancer in patients responding to platinum-based chemotherapy, treatment of inoperable or recurrent BRCA mutation-positive HER2-negative breast cancer previously treated with chemotherapy, maintenance treatment of incurable, unresectable BRCA mutation-positive pancreatic cancer after chemotherapy including platinum-based antineoplastic drugs

3. The efficacy and safety of olaparib have not been established in combination use with other antineoplastic drugs.

Maintenance treatment of BRCA mutation-positive ovarian cancer after first-line chemotherapy

4. The efficacy and safety of olaparib have not been established in combination use with other antineoplastic drugs.
5. Patients who have a complete response after 2 years of treatment with olaparib should discontinue the treatment.

Maintenance treatment of homologous recombination deficiency-positive ovarian cancer after first-line chemotherapy including bevacizumab (genetical recombination)

6. Patients who have a complete response after 2 years of treatment with olaparib should discontinue the treatment.
7. Treating physicians must have a full understanding of the information in the “Clinical Studies” section including the duration of treatment with bevacizumab (genetical recombination) as well as the efficacy and safety of olaparib before administration.

Adjuvant pharmacotherapy for BRCA mutation-positive HER2-negative breast cancer with a high risk of recurrence

8. The efficacy and safety of olaparib have not been established in combination use with other antineoplastic drugs.

9. A decision on the necessity of concomitant endocrine therapy must be made based on a full understanding of the information in the "Clinical Studies" section, taking into account the expression of hormone receptors, etc.

Treatment of BRCA mutation-positive, metastatic castration-resistant prostate cancer

10. The efficacy and safety of olaparib alone have not been established in patients with no history of treatment with abiraterone acetate or enzalutamide.

~~8~~~~10~~11. The efficacy and safety of olaparib have not been established in combination use with other antineoplastic drugs.

~~9~~~~11~~12. The efficacy and safety of olaparib have not been established in the absence of surgical or medical castration.

Appendix

List of Abbreviations

Abiraterone	abiraterone acetate
ADT	androgen deprivation therapy
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
ATM	ATM serine/threonine kinase
BARD1	BRCA1 associated RING domain 1
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
BRIP1	BRCA1 interacting protein C-terminal helicase 1
BV	bevacizumab (genetical recombination)
CDK12	cyclin dependent kinase 12
CHEK1	checkpoint kinase 1
CHEK2	checkpoint kinase 2
CI	confidence interval
COVID-19	coronavirus disease
CRPC	castration-resistant prostate cancer
CT	computed tomography
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
Docetaxel	docetaxel hydrate
DSB	double strand break
FANCL	FA complementation group L
g*BRCA* mutation	germline *BRCA* mutation
HER2	human epidermal growth factor receptor 2
HRR	homologous recombination repair
IL	interleukin
ILD	interstitial lung disease
ITT	intention-to-treat
KLK3	kallikrein 3
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Prostate Cancer
NOD/SCID mouse	non-obese diabetic/severe combined immunodeficient mouse
Olaparib/abiraterone	a combination of olaparib and abiraterone
Olaparib/BV	a combination of olaparib and BV
OS	overall survival
PALB2	partner and localizer of BRCA2
PAR	poly (ADP-ribose)
PARP	poly (ADP-ribose) polymerase
Partial change application	application for partial change approval
PCWG-2	Prostate Cancer Working Group Criteria 2
Placebo/BV	a combination of placebo and BV
PMDA	Pharmaceuticals and Medical Devices Agency

PK	pharmacokinetics
PSA	prostate-specific antigen
PT	preferred term
QD	quaque die
QOL	quality of life
RAD51AP1	RAD51 associated protein 1
RAD51B	RAD51 paralog B
RAD51C	RAD51 paralog C
RAD51D	RAD51 paralog D
RAD54L	RAD54 like
RECIST	Response Evaluation Criteria in Solid Tumors
RMI2	RecQ mediated genome instability 2
rPFS	radiological progression-free survival
SMQ	standardized MedDRA queries
SOC	system organ class
Study 08	Study D081DC00008
Study 19	Study D0810C00019
The OlympiA study	Study D081CC00006
The OlympiAD study	Study D0819C00003
The PAOLA-1 study	Study D0817C00003
The PROfound study	Study D081DC00007
The POLO study	Study D081FC00001
The PROpel study	Study D081SC00001
The SOLO1 study	Study D0818C00001
The SOLO2 study	Study D0816C00002
The SOLO3 study	Study D0816C00010
TMPRSS2	transmembrane protease serine 2