The **R**eal world **E**fficacy and sa**F**ety of n**I**rapa**R**ib in Korean women with pri**M**ary and recurrent epithelial ovarian cancer

(REFIRM)

Protocol

NCT number : NCT06086665

Seoul Asan Medical Center

Jeong-Yeol Park

PROTOCOL SUMMARY

Study Title	The real world efficacy and safety of niraparib in Korean women with primary and recurrent epithelial ovarian cancer(REFIRM)
Principal Investigator	Jeong-Yeol Park, MD, PhD Professor, Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea
Study funding institution	Takeda Pharmaceuticals Korea co., Ltd

Objectives	• To evaluate the efficacy and safety of niraparib in Korean women with primary and recurrent epithelial ovarian cancer who underwent niraparib maintenance therapy • To evaluate the efficacy and safety of salvage niraparib therapy in Korean women with heavily pretreated epithelial ovarian cancer.
Study Design	Multicenter, retrospective cohort and chart-review study
Duration of study	2023.04.01 – 2024.06.30
Study drug	Niraparib
Study subjects (study drug, and etc)	• Study population: Patients with epithelial ovarian cancer of any histological type ➢ Cohorts • Observation cohort (Cohort A) : All patients who did not receive any kind of maintenance therapy for primary epithelial ovarian cancer from Dec 2019 to Oct 2022 • Treatment cohort (Cohort B-D) : Epithelial ovarian cancer patients who treated with niraparib from Dec 2019 to Oct 2022 ■ Cohort B: All patients who received or who are receiving niraparib maintenance therapy for primary epithelial ovarian cancer in 1st line setting. ■ Cohort C: All patients who received or who are receiving niraparib maintenance therapy for recurrent epithelial ovarian cancer in 2nd or 3rd line setting. ■ Cohort D: All patients who received or who are receiving salvage niraparib therapy for recurrent epithelial ovarian cancer in 4th line or more line setting.
Vulnerable subjects	Not applicable
Study methods	This study is a multicenter, retrospective cohort and comparative study in Korea.

	Clinical information will be collected and analyzed through medical records of 12 centers.
Efficacy evaluation	Progression-free survival analysis - Obtain a survival curve using the Kaplan-Meir method, and compare the survival rates between groups using the log-rank test. Multivariate survival analysis is performed using Cox's proportional hazard model.
Safety evaluation	The fraction that adverse events occurred, the fraction that dose modification occurred, the fraction that dose delay occurred, and the fraction that treatment discontinuation occurred w*ill be* calculated, respectively. comparison of the fractions between groups w*ill be* done by the chi-square test or the Fisher exact test *according to the fraction and sample size of data*. Comparison of means between groups w*ill be* done by Student t test or Mann-Whitney U test. Also Student T test or Mann Whitney U test will be used to compare the means between groups according to the fraction and sample size of data.
Expected outcomes	Throughout this study, we expect to confirm the real world efficacy and safety of Niraparib in maintenance and salvage therapy for Korean ovarian cancer patients. In addition, this study is a multicenter study in Korea, so we aim to obtain clinical information of 700 primary and recurrent epithelial ovarian cancer patients. This is a first large size of Korea study for ovarian cancer patients.

dy Protocol

1. Title

The real world efficacy and safety of niraparib in Korean women with primary and recurrent epithelial ovarian cancer(REFIRM)

2. e of sites

- Total 12 sitesAsan Medical Center, Seoul (Jeong-yeol* Park)
- Samsung Medical Center (Byunggi Kim*)
- Seoul National University Hospital (Kim Jae-won*)
- National Cancer Center (Myong Cheol Lim)
- Severance Hospital (Lee Jeong-yoon)
- Keimyung University Hospital (Shin Sojin)
- Kyungpook national university Chilgok Hospital (Dae Gy Hong)
- Seoul St. Mary's Hospital (Keun Ho Lee)
- Pusan National University Yangsan Hospital.(Yong Jung Song)
- Inje University haeundae paik hospital (Yong Il Ji)
- Pusan National University hospital (Ki Hyung Kim)
- Inje University Busan Paik Hospital (Dae Hoon Jeong)

3. Principal investigator and co-investigators

1) Principal investigator

Jeong-Yeol Park, MD, PhD

Professor, Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

e-mail : *catgut1-0@hanamil.nat* / *obgyjypark@amc.seoul.kr* / *obgyjypark@gmail.com*

Tel : +82-2-3010-3646

2) Investigators

- Samsung Medical Center (Byunggi Kim*)
- Seoul National University Hospital (Kim Jae-won*)

- National Cancer Center (Myong Cheol Lim)
- Severance Hospital (Lee Jeong-yoon)
- Keimyung University Hospital (Shin Sojin)
- Kyungpook national university Chilgok Hospital (Dae Gy Hong)
- Seoul St. Mary's Hospital (Keun Ho Lee)
- Pusan National University Yangsan Hospital.(Yong Jung Song)
- Inje University haeundae paik hospital (Yong Il Ji)
- Pusan National University hospital (Ki Hyung Kim)
- Inje University Busan Paik Hospital (Dae Hoon Jeong)

3) Main study researcher

Dr. Ok-Ju Kang

Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

lalala1301@gmail.com

02-3010-0011

4. Name and location of study funding institution

Takeda Pharmaceuticals Korea co., Ltd
37F, Lotte World Tower, Olympic-Ro 300, Songpa-gu, Seoul 0551, Korea (05551)

5. Duration of study

2023.04.01 – 2024.06.30

6. Target disease

Primary and recurrent epithelial ovarian cancer

7. Study background and rationale

1) Background

It has been three years since niraparib was introduced into Korea, and about 600 Korean patients with epithelial ovarian cancer have been treated with this drug. The efficacy and safety of niraparib in primary and recurrent epithelial ovarian cancer were well demonstrated in the NOVA trial and the PRIMA trial, and the efficacy and safety of niraparib in heavily pretreated epithelial ovarian cancer patients were confirmed in the -QUADRA trial. However, safety and efficacy data in Korean women are still scanty. The

purpose of this study was to evaluate the safety and efficacy of niraparib in Korean women with primary and recurrent epithelial ovarian cancer.

2) Study rationale

The pivotal clinical trials of niraparib in primary and recurrent epithelial ovarian cancer, PRIMA, NOVA, and -QUADRA trials, did not include Korean women with epithelial ovarian cancer. Therefore, the efficacy and safety of niraparib in Korean women with epithelial ovarian cancer have not yet been properly evaluated or reported. However, the use of niraparib in Korean women with epithelial ovarian cancer is rapidly increasing, and a lot of experience in drug use is accumulating. To confirm that the efficacy and safety of niraparib used in the actual treatment process in Korean women are similar to the clinical trial results, and to prepare a plan to maximize niraparib compliance by effectively controlling the dosing schedule change and side effects in Korean women, it is very important to analyze the clinical results of Korean women with epithelial ovarian cancer using niraparib.

8. Study method

1) Inclusion and Exclusion criteria

■ Inclusion criteria:

- Patients were diagnosed with all histologic type of epithelial ovarian cancer
- Observation cohort (Cohort A): All patients who did not receive any kind of maintenance therapy for primary epithelial ovarian cancer from Dec 2019 to Oct 2022
- Treatment cohort: Epithelial ovarian cancer patients who treated with niraparib as maintenance treatment in any line from Dec 2019 to Oct 2022
  - Cohort B: All patients who received or who are receiving niraparib maintenance therapy for primary epithelial ovarian cancer in 1st line setting
  - Cohort C: All patients who received or who are receiving niraparib maintenance therapy for recurrent epithelial ovarian cancer in 2nd or 3rd line setting
  - Cohort D: All patients who received or who are receiving salvage niraparib therapy for recurrent epithelial ovarian cancer in 4th line or more line setting

■ Exclusion criteria:

- Borderline ovarian tumor
- Malignant ovarian germ cell tumor
- Malignant sex-cord stroma tumor
- Other malignancy within 5 years of diagnosis of epithelial ovarian cancer excluding carcinoma in situ of uterine cervix, endometrium, bladder, stomach, papillary thyroid cancer, and non-melanoma skin cancer

2) Total # of Subjects *:*

- Sample size of target population from real practice is not known a priori. All eligible patient records available in sites meeting the inclusion criteria will be analysed.
- Estimated numbers of patients in each cohort are below.
    - Observation cohort/Cohort A : approximately 350 patients
    - Cohort B: approximately 350 patients
    - Cohort C: approximately 150 patients
    - Cohort D: approximately 15 patients
- Total target number of subjects in Asan medical center: approximately 200 patients

3) Sample size determination

Considering the nature of retrospective study, sample size cannot be calculated based on reference. We have a plan to collect the patient data as much as possible from multi-centers.

4) Informed Consent

As this is a retrospective cohort study using medical records, we plan to get approval on consent exemption.

5) Study process

(1) IRB approval from each site

(2) In each site, investigator and study team will investigate the medical records from patients diagnosed with primary and recurrent epithelial ovarian cancers based on inclusion/exclusion criteria and collect the clinical information and result of laboratory, pathology, imaging and treatment records including response, retrospectively.

(3) (Expected period of medical records: 1st December 2019 – October 2022)

(4) Each site will assign a subject number for each patient. Patient number will consist with site number and number of patient's order. Site number will be used with abbreviation of hospital name in English. Subject sequence numbers are assigned sequentially, starting with 001.

(5) Each site will secure the files related to the subject number and information confidentially.

(6) Each site will transmit the data to Seoul Asan Medical Center.

(7) Asan medical center will analyze data.

Our data will not be exported outside the AMC, instead AMC will collect and analyze the data while other institutions will only be involved in data collection. Takeda Product will only use statistical results from the data. Data collection

Clinical demographics of patients will be collected, which include biochemical test results,

histologic results, imaging test results, treatment, recurrence status, and survival/death follow-up. All data will be collected based on medical cords

(1) Basic information

Age at diagnosis, date at diagnosis, height, body weight, BMI

(2) Stage and pathological test

Primary/recurrent, tissue type, stage, pelvic lamp node metastasis, aortic lymph node metastasis

(3)  etic test (if implemented)

Germline BRCA1/2 mutation status

Somatic BRCA1/2 mutation status

(4) Treatment history

Advanced chemotherapy, previous history of chemotherapy, date of 1st cytoreductive surgery, blood loss during surgery, residual tumor status, CA-125 before treatment, residual tumor status after treatment, total number of chemotherapy cycles, duration of treatment, date of discontinuation, reason for discontinuation

(5) Recurrence history

Date of recurrence (confirmed with image-based RECIST version1.1)
age at recurrence, performance status, CA-125, ascites status, location and size of recurrent lesions

(6) Treatment with niraparib as maintenance treatment

Type of anti-cancer drug, number of chemotherapy cycles, initial dose of Niraparib, dose modification schedule, number of days of administration, date of discontinuation, reason for discontinuation, image is discontinued due to disease progression

(7) Treatment with niraparib as salvage therapy

Initial dose of Niraparib, dose modification schedule, number of days of administration, date of discontinuation, reason for discontinuation

(8) Follow-up

Survival/death, last visit date, date of death

patients' deaths will be collected through medical records

6) Management and Reporting of adverse events

(1) **Definitions**

1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally

associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the healthcare provider considers to be clinically significant

1.2. Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Healthcare provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the Healthcare provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

1.3. Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

1.4. Product Quality Complaints

A Product Quality Complaint is any written, electronic, or oral communication that alleges

deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product or device and combination product after it is released for distribution.

1.5. Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse, or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product
- Use of counterfeit medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE
- Unintended benefit

An SSR should be reported even if there is no associated AE.

1.6 Relationship of an AE to studied drug(s)

- **Related (Yes):** An AE that follows a reasonable temporal sequence from administration of the medication, vaccine or device (including the course after withdrawal of the medication), and for which a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the medication, vaccine or device, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also have contributed.
- **Not related (No):** An AE that does not follow a reasonable temporal sequence from administration of the medication, vaccine or device and/or that can reasonably be explained by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments.

The assessment of the relationship of an AE to the studied drug(s) should be based on the Investigator’s consideration of all available information about the event, including temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative etiology (e.g. underlying illness, concurrent conditions, concomitant treatments).

(2) Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Complaints to Takeda Pharmacovigilance

• SAEs, AEs, ADRs, SSRs and PQCs in the healthcare record or other applicable source data that are part of the study objectives or endpoints. Events/complaints which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of any interim analysis and in the final study report.
Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

• SAEs, AEs, SSRs and PQCs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints.
Events/complaints which are not part of the study objectives and endpoints will not be abstracted or collected from medical records or other applicable source records.

(3) Reporting of adverse drug reactions and special situation reports to regulatory agencies.

•The Institution/Investigator is solely responsible for reporting all Adverse Events and Serious Adverse Events to regulatory authorities, investigators, IRBs or IECs and Takeda, as applicable, in accordance with national regulations in the countries where the study is conducted.

9. Data and Statistical analysis method

1) Progression-free survival

Obtain a survival curve using the Kaplan-Meir method in all cohorts, and compare the survival rates between cohort A vs cohort B in total patients, BRCA WT and mutation patients using the log-rank test. Multivariate survival analysis will be performed using Cox's proportional hazard model.

2) Safety analysis

The fraction that adverse events occurred, the fraction that dose modification occurred, the fraction that dose delay occurred, and the fraction that treatment discontinuation occurred were calculated, respectively. The comparison of the fractions between groups will be done by the Chi-square test or the Fisher exact test. The comparison of means between groups will be done by Student t test or Mann-Whitney U test.

- The data for SAEs, AEs with grade>=3, and AEs with fatal outcome will be analyzed

-The important risks (eg, hematological toxicities, second primary malignancies will be particularly evaluated/analyzed

3) Overall survival analysis

Obtain a survival curve using the Kaplan-Meir method in all cohorts, and compare the survival rates between cohort A vs cohort B in total patients, BRCA WT and mutation patients using the log-rank test. Multivariate survival analysis is performed using Cox's proportional hazard model.

➢ Statistical analysis will be performed using IBM SPSS version 21, and $p < 0.05$ (two-sided test) will be recognized as a statistically significant difference.

- In Multivariate survival analysis, we will consider the factors including germline BRCA mutational status, tumor HRD status, previous neoadjuvant chemotherapy, and response to first-line platinum chemotherapy, residual disease status following cytoreductive surgery, stage at diagnosis, and whether a patient received neoadjuvant chemo with IDS or PDS followed by adjuvant chemo, if possible.

10. Expected outcomes

Throughout this study, we expect to confirm the real world efficacy and safety of Niraparib in maintenance and salvage therapy for Korean ovarian cancer patients.

In addition, this study is a multicenter study in Korea, so we aim to obtain clinical information of 700 primary and recurrent epithelial ovarian cancer patients. This is a first large size of Korea study for ovarian cancer patients.

11. Subject Data and Safety Protection

1) Ethical principles of the study

This study will be adopted by the principles of the 18th World Medical Assembly (the declaration of Helsinki) and conducted in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH) guidelines, and the applicable country's regulatory requirements and laws. In addition, this study will be initiated after IRB approval.

2) Personal information protection

The patients' medical number and pathology number will be stored as a separate file under the responsibility of Principal investigator, and will be coded and managed so that personal identification cannot be verified through research data.

All data will be stored with a password protected file and stored in a locked laboratory. Only a single computer will be used for data collection and analysis, and this hardware will be under surveillance controlled by institution's web security program.

Only the registered research personnel are allowed to view the data, and these files will not be open to anyone other than listed in our study documents

According to article 15 of the Bioethics and Safety act, medical records and data related to the research will be kept for 3 years from the time the study is completed. Documents including personal information will be disposed after storge period in accordance with article 16 of the Enforcement Decree of the Personal Information Protection Act.

12. Archiving of study documents and Disposal

The estimated research period is around 1 year from the date of IRB approval. The collected data of subjects will be stored as separate file under the responsibility of Principal investigator, coded, managed so that personal identification cannot be verified through research data, stored and used, and research data will be stored with password and in a locked laboratory.

According to article 15 of the Bioethics and Safety act, records related to the research will be kept for 3 years from the time the study is completed. Privacy information(ex. E-CRF, any documented

information about the patients) will be destroyed thereafter according to the study site destruction process in accordance with article 16 of the Enforcement Decree of the Personal Information Protection Act. The instructions about data destruction will be stored as a file signed by both the principal- and co-investigators.

13. Preservation and Discarding of Human Materials

Not applicable

14. References

1. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M, Ledermann JA, Lorusso D, Vergote I, Ben-Baruch NE, Marth C, Mądry R, Christensen RD, Berek JS, Dørum A, Tinker AV, du Bois A, González-Martín A, Follana P, Benigno B, Rosenberg P, Gilbert L, Rimel BJ, Buscema J, Balser JP, Agarwal S, Matulonis UA; ENGOT-OV16/NOVA Investigators. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164. doi: 10.1056/NEJMoa1611310. Epub 2016 Oct 7. PMID:27717299.

2. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Pérez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, Monk BJ; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed AdvancedOvarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402. doi:10.1056/NEJMoa1910962. Epub 2019 Sep 28. PMID: 31562799.

3. Wu XH, Zhu JQ, Yin RT, Yang JX, Liu JH, Wang J, Wu LY, Liu ZL, Gao YN, Wang DB, Lou G, Yang HY, Zhou Q, Kong BH, Huang Y, Chen LP, Li GL, An RF, Wang K, Zhang Y, Yan XJ, Lu X, Lu WG, Hao M, Wang L, Cui H, Chen QH, Abulizi G, Huang XH, Tian XF, Wen H, Zhang C, Hou JM, Mirza MR. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2021 Apr;32(4):512-521. doi:10.1016/j.annonc.2020.12.018. Epub 2021 Jan 14. PMID: 33453391.

4. Moore KN, Secord AA, Geller MA, Miller DS, Cloven N, Fleming GF, Wahner Hendrickson AE, Azodi M, DiSilvestro P, Oza AM, Cristea M, Berek JS, Chan JK, Rimel BJ, Matei DE, Li Y, Sun K, Luptakova K, Matulonis UA, Monk BJ. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2019 May;20(5):636-648. doi: 10.1016/S1470-2045(19)30029-4. Epub 2019 Apr 1. Erratum in: Lancet Oncol. 2019 May;20(5):e242. PMID: 30948273.

5. Del Campo JM, Matulonis UA, Malander S, Provencher D, Mahner S, Follana P, Waters J, Berek JS, Woie K, Oza AM, Canzler U, Gil-Martin M, Lesoin A, Monk BJ, Lund B, Gilbert L, Wenham RM, Benigno B, Arora S, Hazard SJ, Mirza MR. Niraparib Maintenance Therapy in Patients With Recurrent Ovarian Cancer After a Partial Response to the Last Platinum-Based Chemotherapy in the ENGOT-OV16/NOVA Trial. J Clin Oncol. 2019 Nov 10;37(32):2968-2973. doi: 10.1200/JCO.18.02238. Epub 2019 Jun 7. PMID: 31173551; PMCID: PMC6839909.