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A randomized phase II study of secondary cytoreductive surgery in patients with relapsed ovarian cancer who have progressed on a PARP inhibitor as first-line maintenance therapy: the SOCCER-P study (KGOG 3067/ JGOG 3036/APGOT-OV11)

Hyun-Woong Cho ,[1] Hee-Seung Kim ,[2] Jeong-Yeol Park ,[3] Yoo Young Lee ,[4] Myong Cheol Lim,[5] Sung-Jong Lee,[6] Kyung-Jin Min,[7] Kyung Jin Eoh,[8] Kwang Beom Lee,[9] Min Kyu Kim,[10] Jae Yun Song,[11] Seung-Hyuk Shim ,[12] Yong Il Ji,[13] Yong-Joong Song,[14] Suk-Joon Chang ,[15] Mi Kyung Kim ,[16] Akiko Abe,[17] Yusuke Kobayashi ,[18] Hiroaki Kajiyama ,[19] Muneaki Shimada,[20,21] Aikou Okamoto,[22] Joseph S Ng ,[23,24] Jung-Yun Lee[25]

For numbered affiliations see end of article.

Correspondence to
Dr Jung-Yun Lee, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seodaemun-gu, Korea (the Republic of); JUNGYUNLEE@yuhs.ac

Accepted 26 June 2024

To cite: Cho H-W, Kim H-S, Park J-Y, *et al. Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2024-005838

ABSTRACT

Background Although two recent phase III randomized controlled trials showed survival benefits of undergoing secondary cytoreductive surgery for an initial relapse of ovarian cancer, patients who received a poly-ADP ribose polymerase inhibitor (PARPi) as the first-line maintenance treatment, which is currently the standard treatment for advanced ovarian cancer, were not included in those trials. Therefore, determining an optimal treatment strategy, including secondary cytoreductive surgery, in patients whose cancer progresses even with PARPi treatment, is needed.

Primary Objective To determine whether secondary cytoreductive surgery is beneficial in patients who have progressed on PARPi maintenance treatment.

Study Hypothesis Secondary cytoreductive surgery followed by chemotherapy is superior to chemotherapy alone for patients who have progressed on PARPi maintenance treatment.

Trial Design The SOCCER-P study is a multicenter randomized phase II clinical trial. Patients who meet the eligibility criteria will be randomized to either undergo secondary cytoreductive surgery and subsequent platinum-based chemotherapy plus or minus bevacizumab, or to receive platinum-based chemotherapy plus or minus bevacizumab alone. Patients randomly allocated to the surgery group will undergo secondary cytoreductive surgery followed by six cycles of a physician's choice of platinum-based chemotherapy once they have recovered from surgery.

Major Inclusion/Exclusion Criteria The major inclusion criteria are as follows: first recurrence of disease with treatment-free interval from last platinum dose (TFIp) ≥6 months and progression during PARPi maintenance or treatment-free interval from last PARPi therapy (TFI_{PARPi}) <3 months. The major exclusion criteria are as follows: >1 line of prior chemotherapy, TFIp <6 months, and radiological signs suggesting metastases not accessible to surgical removal (complete resection is deemed not possible).

Primary Endpoint Progression-free survival.

Sample Size 124 patients.

Estimated Dates for Completing Accrual and Presenting Results Accrual completion approximately the end of 2026 and the results are expected after 2 years of follow-up in 2029.

Trial Registration NCT05704621.

INTRODUCTION

Ovarian cancer remains one of the leading causes of cancer-related deaths in the USA and worldwide, with an estimated 19 710 new cases and 13 270 new deaths in 2023 in the USA[1] and 313 959 new cases and 207 252 deaths worldwide in 2020.[2] Most patients with ovarian cancer receive platinum-based chemotherapy; however, despite aggressive treatment, approximately 80% of patients at an advanced stage ultimately experience relapse and die from the treatment-resistant disease.

The frontline therapy for women with relapsed ovarian cancer has long been systemic treatment; however, only a few trials have shown a significant overall survival benefit from chemotherapy in relapsed ovarian cancer.[3–5] Recent prospective randomized studies, however, have shown benefits from secondary cytoreductive surgery with respect to progression-free survival (PFS) in selected patients.[6 7] Although these trials showed a benefit of surgery with respect to PFS, they do have some limitations. Patients' BRCA statuses are unknown and very few patients received a subsequent poly-adenosine diphosphate ribose polymerase inhibitor (PARPi) and bevacizumab. Most importantly, the aforementioned

studies did not include patients who received PARPi as first-line maintenance, which is currently considered to be the standard treatment for advanced ovarian cancer.

The success of PARPi has led to the approval of three different PARPis for the treatment of ovarian cancer. Several clinical trials have demonstrated the clear benefit of PARPis in terms of PFS for first-line maintenance in advanced ovarian cancer, although most patients will inevitably develop treatment resistance.[5 8–10] Following progression from PARPi maintenance, the response to subsequent chemotherapy seems to be reduced in patients with ovarian cancer compared with patients who did not previously receive PARPi treatment.[11–13] Therefore, optimal strategies, including secondary cytoreductive surgery, in the treatment of patients whose cancer progresses on PARPi treatment is needed.

We aim to evaluate, in a prospectively randomized multicenter setting, whether maximum effort cytoreductive surgery followed by platinum-based combination chemotherapy can improve PFS when compared with platinum-based combination chemotherapy alone in patients who had a first relapse and have progressed on PARPi treatment.

METHODS

Trial Design

The SOCCER-P study is a multicenter, investigator-initiated, randomized phase II trial of secondary cytoreductive surgery in patients with relapsed ovarian cancer who have progressed on PARPi as first-line maintenance therapy. Patients who meet the eligibility criteria will be randomized to either undergo secondary cytoreductive surgery and subsequent platinum-based chemotherapy plus or minus bevacizumab, or to receive platinum-based chemotherapy plus or minus bevacizumab alone. Patients randomly allocated to the surgery group will undergo secondary cytoreductive surgery followed by six cycles of a physician's choice of platinum-based chemotherapy, to commence once they have recovered from surgery. Patients in the no surgery group will be given six cycles of a physician's choice of platinum-based chemotherapy. Recommended systemic treatments are as follows:

1. Six cycles of pegylated liposomal doxorubicin (30 mg/m^2, day 1) and carboplatin (AUC 5, day 1) ± bevacizumab (10 mg/kg, days 1 and 15) every 4 weeks followed by bevacizumab maintenance (15 mg/kg, every 3 weeks)
2. Six cycles of gemcitabine (1000 mg/m^2, days 1 and 8) and carboplatin (AUC 4, day 1) ± bevacizumab (15 mg/kg, day 1) every 3 weeks followed by bevacizumab maintenance (15 mg/kg, every 3 weeks)
3. Six cycles of paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC 5–6, day 1) ± bevacizumab (15 mg/kg, day 1) every 3 weeks followed by bevacizumab maintenance (15 mg/kg, every 3 weeks)

Randomization is stratified according to the center and treatment-free interval from the last platinum chemotherapy dose (TFIp; an interval of 6–12 months or an interval of ≥12 months), BRCA status (BRCA pathologic variant or no BRCA pathologic variant), and use of bevacizumab. Figure 1 shows the trial schema.

The protocol for the present study was approved by national and local research ethics committees and written informed consent was obtained from all patients. Sixteen, five, and one sites planned to recruit patients for the SOCCER-P trial in Korea, Japan, and Singapore, respectively.

Participants

The inclusion criteria are as follows: first recurrence of invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer of any initial stage; TFIp ≥6 months (180 days); progression during PARPi maintenance or treatment-free interval from last PARPi therapy (TFI_{PARPi}) <3 months (90 days); age ≥19 years; written informed consent provided; potentially complete gross resection of all recurrent tumor by secondary cytoreductive surgery (1: positive AGO score; 2: positive iMODEL + positron emission tomography-computed tomography (PET-CT); and 3: patients who are likely to have a complete resection by consensus between the surgeon and designated radiologist even if negative AGO score or iMODEL + PET-CT).

The major exclusion criteria are as follows: non-epithelial and borderline tumors; planned second-look surgery or debulking surgery after completion of chemotherapy or palliative surgery;

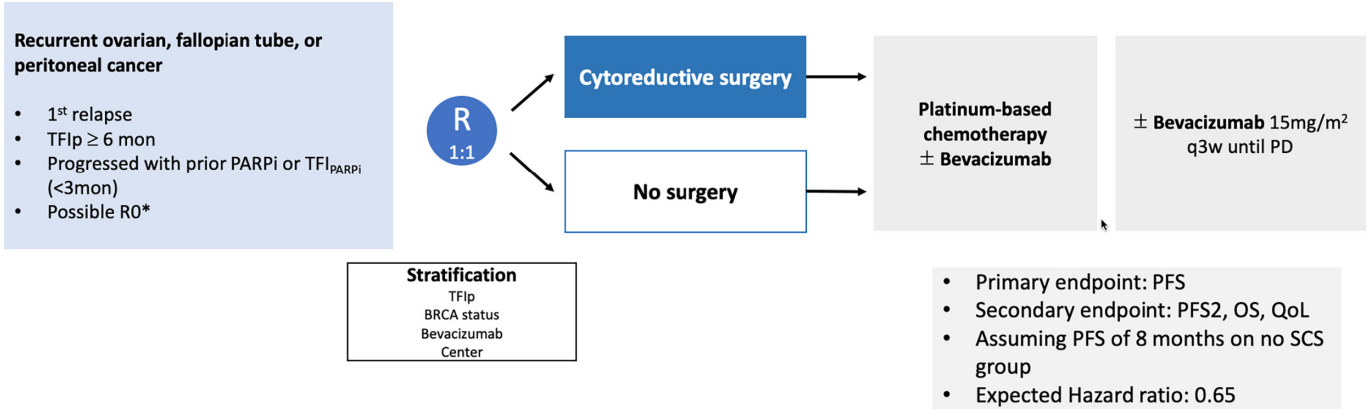

Figure 1 Study schema of SOCCER-P trial. *Patients who are considered likely to undergo a complete resection according to the international model (AGO or iMODEL) or based on a consensus between the surgeon and designated radiologist are eligible for the present study. OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PFS, progression-free survival; QoL, quality of life; TFIp, treatment-free interval from the last platinum chemotherapy dose; TFI_{PARPi}, treatment-free interval from last PARPi therapy.

prior treatment with >1 line of prior chemotherapy; second, third, or subsequent recurrence; second malignancies treated by laparotomy as well as other neoplasms if the treatment might interfere with the treatment of relapsed ovarian cancer, or if a major impact on the prognosis is expected; TFIp <6 months; radiographic signs suggesting metastases not accessible for surgical removal (complete resection deemed not possible); any concomitant disease not allowing surgery and/or chemotherapy; any medical history indicating excessive peri-operative risk; any current medication inducing considerable surgical risk (bleeding due to oral anticoagulating agents, bevacizumab); and no assessable archival tumor tissue.

Primary Endpoint

The primary objective of the present study is to assess the efficacy of secondary cytoreductive surgery on PFS compared with no surgery in patients with relapsed ovarian cancer who have progressed on PARPi as first-line maintenance therapy. The secondary objectives are the effects of secondary cytoreductive surgery on overall survival, PFS2 (defined as the time from the date of randomization to tumor progression on a next-line treatment or death), quality of life, and surgical morbidity. To monitor patient safety and supervise the progress of the SOCCER-P trial, an independent data monitoring committee has been established.

Sample Size

For power and sample size calculation, an HR of 0.65 corresponding to a prolongation of the median PFS from 8 months in the no surgery group based on previous studies[11 12 14] in favor of secondary cytoreductive surgery is considered clinically relevant.[6] With a planned accrual period of 3 years, a subsequent 2-year follow-up period, and accounting for a dropout rate of 10%, 124 patients would be needed to ensure 80% power using a type I error rate of 0.1 (one-sided) to reject the null hypothesis.

Randomization and Blinding

Randomization is performed via list randomization with variable block lengths and is stratified by center, TFIp (6–12 months vs ≥12 months), bevacizumab treatment (bevacizumab vs no bevacizumab), and BRCA status (BRCA pathologic variant or no BRCA pathologic variant). After verifying eligibility criteria, patients will be randomized to either secondary cytoreductive surgery or no surgery at a 1:1 ratio. The data of the patients will be documented remotely with an electronic data capture system hosted at the Korea Gynecologic Oncology Group (KGOG).

Statistical Methods

The primary endpoint of the present study is PFS, while the secondary endpoints are overall survival, PFS2, quality of life as measured by EORTC QLQ-C30, OV28, and EQ-5D-5L results and safety. All time-to-event endpoints will be calculated from the date of randomization until the event of interest.

For the primary analysis we will compare the PFS between the two groups using a stratified log-rank test on an intention-to-treat basis at a time point 2 years after the recruitment of the last participant. If the proportional hazards assumption is not satisfied, a stratified Wilcoxon test will be used for the comparison. The Kaplan–Meier method will be used to estimate the survival functions for PFS in each treatment group. Additionally, a stratified Cox regression model will be used to estimate the adjusted HR effect, adjusting for systemic therapy, age, International Federation of Gynecology and Obstetrics (FIGO) stage, and residual disease after surgery due to recurrence. One-sided tests will be conducted at a significance level of 10%.

The analysis for overall survival and PFS2 will be performed in the same manner as for PFS. HR estimates and corresponding 95% confidence intervals will be provided. Kaplan–Meier estimates for the median overall survival and PFS2 and corresponding 95% confidence intervals will also be presented. Additional Cox regression models will be performed to assess the impact of important baseline covariates on overall survival and PFS2. Sub-groups such as BRCA status and TFIp status will also be descriptively explored. All secondary efficacy analyses will be purely descriptive or exploratory in nature.

DISCUSSION

As PARPis become standard care for patients with advanced ovarian cancer, new clinical challenges regarding treatment options after patients experience cancer progression on PARPi treatment are emerging. In PARPi-naïve patients with platinum-sensitive relapsed ovarian cancer, secondary cytoreductive surgery in those who have the potential for a complete resection provided a statistically significant PFS benefit.[6 7] However, whether patients who have experienced progression during PARPi treatment will benefit from secondary cytoreductive surgery on relapse is unknown. In several previous studies, the efficacy of platinum-based chemotherapy following progression after PARPi maintenance was found to be reduced in patients with platinum-sensitive relapsed ovarian cancer compared with PARPi-naïve patients.[11 12 14] The emergence of PARPi resistance raises the question of how best to treat patients who have progressed on PARPi treatment.

The hypothesis supporting the usefulness of secondary cytoreductive surgery in patients who experience progression during PARPi is the survival benefit in PARPi-naïve patients with platinum-sensitive relapsed ovarian cancer who undergo surgical resection,[6 7] and modest PFS benefits of surgery in oligometastatic recurrent ovarian cancer during PARPi maintenance from small retrospective studies.[15 16] Additionally, in theory, secondary cytoreductive surgery could reduce tumor burden and eliminate resistant clones.

The authors hypothesize that secondary cytoreductive surgery may overcome treatment resistance after a patient experiences progression during a PARPi. SOCCER-P is the first phase II trial to address the question of whether secondary cytoreductive surgery provides benefits to patients with platinum-sensitive relapsed ovarian cancer who have previously progressed on PARPi treatment.

Author affiliations
[1]Department of Obstetrics and Gynecology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, South Korea
[2]Department of Obstetrics and Gynecology, Seoul National University, Seoul, South Korea
[3]Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea
[4]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

[5]Gynecologic Cancer Branch & Center for Uterine Cancer, National Cancer Center, Goyang, South Korea
[6]Department of Obstetrics and Gynecology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[7]Department of Obstetrics and Gynecology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, South Korea
[8]Department of Obstetrics and Gynecology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, South Korea
[9]Department of Obstetrics and Gynecology, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea
[10]Department of Obstetrics and Gynecology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea
[11]Department of Obstetrics and Gynecology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea
[12]Department of Obstetrics and Gynecology, Research Institute of Medical Science, Konkuk University School of Medicine, Seoul, South Korea
[13]Department of Obstetrics and Gynecology, Haeundae Paik Hospital, Inje University College of Medicine, Busan, South Korea
[14]Department of Obstetrics and Gynecology, Pusan National University College of Medicine, Busan, South Korea
[15]Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, South Korea
[16]Department of Obstetrics and Gynecology, Ewha Womans University College of Medicine, Seoul, South Korea
[17]Department of Gynecologic Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan
[18]Department of Obstetrics and Gynecology, Institute of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
[19]Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
[20]Department of Gynecology, Tohoku University Hospital, Sendai, Miyagi, Japan
[21]Department of Clinical Biobank, Advanced Research Center for Innovations in Next-Generation Medicine, Tohoku University, Sendai, Miyagi, Japan
[22]Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan
[23]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, National University of Singapore, Singapore
[24]Gyn Cancer Program, National University Cancer Institute Singapore, Singapore
[25]Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, South Korea

X Joseph S Ng @drjoeng

Contributors Concept and design: HWC, JYL. Acquisition of data: HWC, JYL. Analysis and interpretation of data: HWC, JYL, H-SK, J-YP, YYL, MCL, S-JL, K-JM, KJE, KBL, MKK, JYS, S-HS, YIlJ, YJS, S-JC, M-KK, AA, YK, HK, MS, AO, JSN. Drafting of the manuscript: HWC, JYL. Critical revision of the manuscript for important intellectual content: H-SK, J-YP, YYL, MCL, S-JL, K-JM, KJE, KBL, MKK, JYS, S-HS, YIlJ, YJS, S-JC, M-KK, AA, YK, HK, MS, AO, JSN. Statistical analysis: HWC, JYL. Administrative, technical, or material support: H-SK, J-YP, YYL, MCL, S-JL, K-JM, KJE, KBL, MKK, JYS, S-HS, YIlJ, YJS, S-JC, M-KK, AA, YK, HK, MS, AO, JSN. Supervision: JYL. Guarantors: JYL.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available in a public, open access repository. The data of the patients are documented remotely with an electronic data capture system hosted at the Korea Gynecologic Oncology Group (KGOG).

ORCID iDs
Hyun-Woong Cho http://orcid.org/0000-0002-0724-9971
Hee-Seung Kim http://orcid.org/0000-0001-6876-8671
Jeong-Yeol Park http://orcid.org/0000-0003-2475-7123
Yoo Young Lee http://orcid.org/0000-0001-5902-9877
Seung-Hyuk Shim http://orcid.org/0000-0001-8043-2257
Suk-Joon Chang http://orcid.org/0000-0002-0558-0038
Mi Kyung Kim http://orcid.org/0000-0001-6829-332X
Yusuke Kobayashi http://orcid.org/0000-0002-4503-2845
Hiroaki Kajiyama http://orcid.org/0000-0003-0493-1825
Joseph S Ng http://orcid.org/0000-0002-8901-9212

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