A phase II trial of cytoreductive surgery combined with niraparib maintenance in platinum-sensitive, secondary recurrent ovarian cancer: SGOG SOC-3 study

Tingyan Shi,1 Sheng Yin,1 Jianqing Zhu,2 Ping Zhang,2 Jihong Liu,3 Libing Xiang,1 Yaping Zhu,4 Sufang Wu,4 Xiaojun Chen,1 Xieng Wang,6 Yincheng Teng,7 Tao Zhu,2 Aijun Yu,2 Yingli Zhang,2 Yanling Feng,2 He Huang,2 Wei Bao,4 Yanli Li,4 Wei Jiang,5 Ping Zhang,6 Jiarui Li,6 Zhihong Ai,1 Wei Zhang,6 Huixun Jia,2 Yuqin Zhang,1 Rong Jiang,1 Jiejie Zhang,2 Wen Gao,2 Yuting Luan,1 Rongyu Zang1

1Ovarian Cancer Program, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Zhongshan Hospital, Fudan University, Shanghai, China
2Department of Gynecologic Oncology, Zhejiang Cancer Hospital, Hangzhou, China
3Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China
4Department of Obstetrics and Gynecology, Shanghai General Hospital, Shanghai, China
5Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China
6Department of Gynecology and Obstetrics, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
7Department of Gynecology and Obstetrics, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China
8Department of Biostatistics, Fudan University, Shanghai, China
9Clinical Statistics Center, Shanghai General Hospital, Shanghai, China

ABSTRACT

Background: In China, secondary cytoreductive surgery (SCR) has been widely used in ovarian cancer (OC) over the past two decades. Although Gynecologic Oncology Group-0213 trial did not show its overall survival benefit in first relapsed patients, the questions on patient selection and effect of subsequent targeting therapy are still open. The preliminary data from our pre-SOC1 phase II study showed that selected patients with second relapse who never received SCR at recurrence may still benefit from surgery. Moreover, poly(ADP-ribose) polymerase inhibitors (PARPi) maintenance now has been a standard care for platinum sensitive relapsed OC. To our knowledge, no published or ongoing trial is trying to answer the question if patient can benefit from a potentially complete resection combined with PARPi maintenance in OC patients with secondary recurrence.

Methods: SOC-3 is a multi-center, open, randomized, controlled, phase II trial of SCR followed by chemotherapy and niraparib maintenance vs chemotherapy and niraparib maintenance in patients with platinum-sensitive second relapsed OC who never received SCR at recurrence. To guarantee surgical quality, if the sites had no experience of participating in any OC-related surgical trials, the number of recurrent lesions evaluated by central-reviewed positron emission tomography–computed tomography image shouldn’t be more than 3. Eligible patients are randomly assigned in a 1:1 ratio to receive either SCR followed by 6 cycles
Surgery and PARPi in 2nd recurrent ovarian cancer

Xiaojun Chen  
https://orcid.org/0000-0002-5493-1500  
Xipeng Wang  
https://orcid.org/0000-0002-7555-4185  
Yincheng Teng  
https://orcid.org/0000-0002-6451-4479  
Tao Zhu  
https://orcid.org/0000-0002-2991-4067  
Aijun Yu  
https://orcid.org/0000-0003-0472-7858  
Yingli Zhang  
https://orcid.org/0000-0001-6929-8480  
Yanling Feng  
https://orcid.org/0000-0002-3485-1490  
He Huang  
https://orcid.org/0000-0002-6223-4799  
Wei Bao  
https://orcid.org/0000-0002-3942-7218  
Yanli Li  
https://orcid.org/0000-0003-0133-2261  
Wei Jiang  
https://orcid.org/0000-0002-9998-0066  
Ping Zhang  
https://orcid.org/0000-0003-1428-692X  
Jianli Li  
https://orcid.org/0000-0003-2246-1302  
Zhong Ai  
https://orcid.org/0000-0002-8920-8192  
Wei Zhang  
https://orcid.org/0000-0002-9601-4823  
Huixun Jia  
https://orcid.org/0000-0001-9341-5587  
Yuqin Zhang  
https://orcid.org/0000-0003-0078-8574  
Rong Jiang  
https://orcid.org/0000-0002-2138-167X  
Jiejie Zhang  
https://orcid.org/0000-0001-8114-1988  
Wen Gao  
https://orcid.org/0000-0002-7404-5485  
Yuting Luan  
https://orcid.org/0000-0002-4494-6167  
Rongyu Zhang  
https://orcid.org/0000-0002-1334-2398  

Funding  
The study is supported by Clinical Trial Project of Zhongshan Hospital, Fudan University (No. 2018ZSLC33). We would like to thank Zai Lab Co., Ltd for the funding of this investigator-initiated study, including financial support and niraparib tablets. The funders had no role in the design, conduct, analysis and interpretation of the data and decision to publish.  

INTRODUCITON  
Epithelial ovarian cancer (EOC) is one of the leading fatal gynecologic malignant tumors, resulting in 184,799 cancer deaths worldwide 2018 [1]. More than 70% of EOC patients are diagnosed with advanced diseases. Despite most of the patients have initially good response to platinum-based chemotherapy, majority will be suffered with continuous recurrences unfortunately and the 5-year overall survival (OS) of EOC remains poor. Chemotherapy is usually offered to recurrent patients, with a palliative intent. For platinum-sensitive recurrence with treatment-free interval ≥6 months, carboplatin in combination with paclitaxel, gemcitabine or pegylated liposomal doxorubicin represents the main treatment regimen, being repeated as long as the patients remain platinum-sensitive.

Secondary cytoreductive surgery (SCR) is a practical, but controversial option for platinum-sensitive recurrence. Mountains of retrospective and pooled studies have shown that SCR superiorly improves OS in platinum-sensitive recurrent patients, compared with chemotherapy alone [2], and complete resection is the strongest prognostic factor [3]. There are 3 randomized phase III trials focused on the survival benefit of SCR in platinum-sensitive recurrent ovarian cancer (OC) [Gynecologic Oncology Group [GOG]–0213 trial, Arbeitsgemeinschaft Gynäkologische Onkologie [AGO] Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent ovarian cancer III [DESKTOP III] and Shanghai Gynecologic Oncology Group SOC-1 [SGOG SOC-1] trial) [4]. Recently, GOG-0213 did not show a survival benefit of SCR followed by chemotherapy compared with chemotherapy alone [5]. However, the patient selection criteria are different from the other 2 trials, which is only deemed by the investigator to be amenable to complete gross resection [6]. While, DESKTOP III trial selects possibly resectable patients by using the AGO model that includes 3 factors: 1) complete resection at first surgery, 2) good performance status, and 3) absence of ascites. The interim analysis of DESKTOP III reported a significantly increased progression-free survival (PFS) in favor of SCR followed by chemotherapy, with the complete resection rate of 67% [7]. SGOG SOC-1 is a multicenter, randomized phase III study of SCR followed by chemotherapy (surgery group) versus chemotherapy alone (no-surgery group) in patients with platinum-sensitive recurrent OC in China, in which a pooled study-validated iMODEL score of less than 4.7 is considered as low-risk for complete resection [8]. Censored on 1st March 2018, 32% of the patients in no-surgery group received debulking surgery at recurrence and impossible to complete resection. The sample size is 96 patients. Primary endpoint is 12-month non-progression rate.

Trial Registration: ClinicalTrials.gov Identifier: NCT03983226  
Keywords: Ovarian Neoplasms; Cytoreductive Surgery; Chemotherapy; Poly(ADP-ribose) Polymerase Inhibitors; Clinical Trial

https://ejgo.org  
https://doi.org/10.3802/jgo.2020.31.e61  
2/8
interpretation of data.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: S.T., Y.S., Z.J., Z.P.1, L.J., Z.Y., W.S., C.X., W.X., T.Y., T.Y.A., Z.Y., F.Y., H.H., B.W., L.Y., J.W., Z.P.1, L.J., A.Z., Z.W., J.H., Z.Y., J.R., Z.J., G.W., L.Y., J.R.; Supervision: Z.R.; Writing - original draft: S.T.; Writing - review & editing: S.T., Y.S., Z.J., Z.P.1, L.J., Z.Y., W.S., C.X., W.X., T.Y., T.Y.A., Z.Y., F.Y., H.H., B.W., L.Y., J.W., Z.P.1, L.J., A.Z., Z.W., J.H., Z.Y., J.R., Z.J., G.W., L.Y., Z.R. 1Z.P., Ping Zhang from Zhejiang Cancer Hospital; 2Z.P., Ping Zhang from Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

the secondary recurrent disease in the ongoing SOC-1 trial. In China, SCR has been standard of care for OC in some high-volume cancer centers and most patients prefer surgery over the past two decades. The Data Monitoring Committee of SOC-1 concerned about the high rate of treatment switching that might be an important confounder for the final analysis of efficacy, and recommended a further exploration on it. Therefore, in the subsequent SOC-3 trial, we aim to validate whether those patients who did not receive SCR can still benefit from the next surgery when the secondary recurrence happened. To our knowledge, there were no any published or ongoing studies to address this issue.

Polyadenosine 5′-diphosphoribose (poly[ADP-ribose]) polymerase (PARP) inhibition is a novel approach to targeting tumor with deficiencies in DNA repair mechanisms. PARP inhibition treatment takes more and more important roles in recurrent OC clinical practice. Niraparib is a potent PARP inhibitors (PARPi; PARP-1 and -2) that has been developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with other anti-cancer agents. National Comprehensive Cancer Network guideline recommends niraparib as a maintenance therapy for persistent disease or recurrence if partial or complete response after chemotherapy. Therefore, we added niraparib maintenance in both treatment arms to balance the possible bias of targeting therapy. On the other hand, SOLO1 study showed that the survival benefit of olaparib was more prominent in patients with complete resection in first-line setting [9]. We suspected that PARPi might result in a similar effect on recurrent patients with complete resection. In addition, NOV A study demonstrated that niraparib maintenance significantly prolonged the PFS compared with placebo in platinum-sensitive relapsed patients with partial or complete response after chemotherapy, among which 40% were secondary recurrence and more [10]. We hypothesize that patients with stable disease after third-line chemotherapy can benefit from niraparib maintenance as well, but the safety and quality of life (QoL) should be carefully assessed. Data from Caucasian ethnics suggested that high-risk patients with baseline body weight <77 kg or platelet count <150×10^9/L have a higher incidence of platelet count decreased when receiving a starting dose of 300 mg once daily [10]. The pharmacokinetics profile of niraparib in Chinese patients is consistent with that in Caucasian patients [11]. In this trial, we use 200 mg once daily as a starting dose for majority of patients, while 300 mg once daily for those whose weight was ≥77 kg.

Therefore, we firstly start the SOC-3 trial in platinum-sensitive secondary recurrent patients who did not receive SCR when recurrence and complete resection seems feasible, to evaluate the efficacy of cytoreductive surgery combined with niraparib maintenance.

METHODS

1. Trial design
SGOG SOC-3 is a multi-center, open, randomized, controlled, phase II trial of secondary cytoreduction followed by chemotherapy and niraparib maintenance (surgery group) versus chemotherapy and niraparib maintenance (no-surgery group) in patients with platinum-sensitive secondary recurrent OC. Eligible patients with platinum-sensitive, secondary relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer are randomly assigned in a 1:1 ratio to receive either cytoreductive surgery followed by 6 cycles of chemotherapy and niraparib maintenance (surgery group) or 6 cycles of chemotherapy and niraparib maintenance alone (no-surgery group) (Fig. 1).
Recommended third-line chemotherapeutic regimens are as follows.

1. Carboplatin area under the curve 5/paclitaxel 175 mg/m² every 21 days, 6 cycles.
2. Carboplatin area under the curve 5/docetaxel 60–75 mg/m² every 21 days, 6 cycles.
3. Carboplatin area under the curve 4 day 1/gemcitabine 1g/m² day 1, 8 every 21 days, 6 cycles.
4. Carboplatin area under the curve 5/pegylated liposomal doxorubicin 30 mg/m² every 28 days, 6 cycles.

Patients who complete at least 4 cycles of chemotherapy and must be, in the opinion of the investigator, without disease progression (complete or partial response, or stable disease according to response evaluation criteria in solid tumors (RECIST) 1.1 or Gynecological Cancer Intergroup (GCIG) criteria [12]) will be assigned niraparib tablets p.o. 300 or 200 mg daily. The starting dose of niraparib needs to be set according to the patient’s baseline data of weight and platelet count. If the baseline body weight is ≥ 77 kg and platelet count at baseline is ≥ 150,000/µL, the patient will be given niraparib tablets p.o. 300 mg once daily; otherwise 200 mg once daily will be provided until disease progression. All the patients should initiate niraparib treatment within 8 weeks after their last dose of platinum-containing chemotherapy (last dose is the day of the last infusion).

This study is initiated by SGOG, with currently 7 centers from China. The trial has been approved by the ethics committee of Zhongshan Hospital Fudan University and registered at ClinicalTrials.gov (NCT03983226).

**2. Patients**

Major inclusion criteria are platinum-sensitive, secondary relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer (EOC, primary peritoneal cancer, fallopian tube cancer), which is defined as those with platinum-free interval of 6 months or more; age ≥18 years; written informed consent provided; Eastern Cooperative Oncology Group performance status 0–2.
status 0 to 2; never received SCR when recurrence; a possible complete gross resection of all recurrent disease, as assessed by an experienced surgeon or investigator. It can be included if single lesion outside the peritoneal cavity can be resected. Previously received maintenance therapy is available. Positron emission tomography–computed tomography (PET/CT) was highly recommended to evaluate the possibility of resection. No more than 3 disease lesions were detected by the central-reviewed PET/CT if the participated center never participated in any surgical trials on OC before.

Major exclusion criteria are borderline tumors and non-epithelial ovarian malignancies; complete secondary debulking surgery when recurrence; planned interval-debulking, or second-look surgery, or palliative surgery; impossible to achieve complete resection or impossible to assess resectability; received more than 2 chemotherapeutic regimens, regardless of maintenance therapy; third recurrence or more; secondary invasive neoplasms who have been treated by surgery, if the treatment might interfere with the treatment of relapsed OC or if major impact on prognosis is expected; progression during chemotherapy or recurrence within 6 months after second-line platinum-based therapy; any contradiction not allowing surgery or chemotherapy or niraparib; any significant medical comorbidities that will increase perioperative risk (estimation of investigator); any medication induced considerable risk of surgery; ≥3 grade anemia, neutropenia or thrombocytopenia due to chemotherapy, and lasted for more than 4 weeks; a known hypersensitivity to niraparib or any of the excipients of the product.

All patients with platinum-sensitive secondary recurrent OC will be screened for this study after a written informed consent has been obtained. The process of screening should be documented.

3. Outcomes

The primary objective is to assess the efficacy for 12-month non-progression rate of cytoreductive surgery followed by chemotherapy and niraparib maintenance compared with chemotherapy and niraparib maintenance in platinum-sensitive secondary recurrent OC patients who never received secondary cytoreduction when recurrent. The 12-month non-progression rate is defined as the non-progression rate within 12-months since randomization. Progression is defined as follow: 1) general condition deteriorates, or 2) increased level of serum CA125 according to GCIG criteria [12], or 3) new sign of lesions by clinical signs, imaging or histopathological diagnosis, or 4) new or re-emerging pleural effusion and ascites, or significantly increased volume of pleural effusion or ascites, or 5) increased measurable or non-measurable lesions diagnosed as disease progression according to RECIST 1.1 criteria [12]. Follow-up is that patients should receive regular follow-up once quarterly for the first 5 years, then every 6 months.

Secondary objectives are PFS, OS, treatment-free interval, safety and QoL. PFS is defined as the time from the date of randomization to disease progression/recurrence or death from any reason or last follow-up, whichever comes first. OS is defined as interval between date of randomization and date of death from any reason or last follow-up, whichever comes first. Treatment-free survival is defined as the time from the date of randomization to death from any reason or last follow-up, whichever comes first, minus each treatment period after randomization, including surgery and chemotherapy. Safety includes postoperative 30-day complications and adverse events of chemotherapy and niraparib according to the Common Terminology Criteria for Adverse Events version 5.0 [13]. QoL will be assessed by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
The exploratory objectives are the efficacy of niraparib in those patients who are evaluated with stable disease after chemotherapy, in those who previously received PARPi, in those who have no residual disease after secondary cytoreduction, and in those patients with single recurrent lesion. Data Monitoring Committee has been established to monitor patient safety and control the quality of trial.

4. Sample size
Based on the previous data on NOV A trial [10] and the third-line chemotherapy of OC [15,16], we estimated 12-month non-progression rate in no-surgery group as 45%. Given to the interim analysis report of DESKTOP III trial [7] and the exploratory analysis in our published AICE trial [17], we conservatively estimate the 12-month non-progression rate in surgery group can improve 25% compared with that in no-surgery group.

Therefore, assuming an anticipated 25% increase (from 45% to 70%) of the 12-month non-progression rate in favour of the surgery group, with an accrual time of 2 years, approximately 96 subjects will be randomized to surgery group and no-surgery group at a 1:1 ratio to ensure 80% power using a type I error rate of 0.1 (2-sided) to reject the null hypothesis. Considering 5% of drop rate, the sample size will be 102 patients.

5. Randomization and blinding
Randomization was performed according to a randomization code generated by computer and by a centralized office with patient data screened by the principal investigator. The patients will be randomized to surgery group and no-surgery group at a 1:1 ratio by the stratified blocked method with block length of 6. The stratification factor is whether patient was enrolled in the SOC-1 trial (Evaluation of Secondary Cytoreductive Surgery in Platinum-Sensitive Recurrent Ovarian Cancer: A Phase III, Multicenter, Randomized Trial, NCT01611766) or not.

Blinding is not feasible since the surgical intervention can not be withheld from the patients and doctors.

6. Statistical methods
The primary endpoint is 12-month non-progression rate. Secondary endpoints are PFS, OS, treatment-free intervals, 30-day post-operative complications, and QoL.

The primary analysis will use the intention-to-treat population. The 12-month non-progression rate will be compared between treatment groups by using the \( \chi^2 \) test. The trial was also structured, a priori, to assess progression-free and OS, with the significance level of 0.1. Progression-free and OS and treatment-free intervals will be compared by a 2-sided Log-Rank test. Kaplan-Meier method will be used for the survival distribution in each treatment group. Rates at fixed time points (e.g. 12 months) will be derived from the Life Table estimate. The Cox proportional hazard method will be used to calculate the hazard ratios and 95% confidence interval.

Exploratory analysis will be performed in the subgroup populations as follows, 1) recurrent lesions: single, localized and multiple lesions; 2) whether patient was enrolled in the SOC-1 trial; and 3) whether patient was treated with chemotherapeutics.
trial or not; 3) whether patient was regularly followed up by gynecologic oncologist or not; 4) response to the third-line chemotherapy: complete, partial response and stable disease; 5) whether patient was received PARPi or not before randomization; 6) the residual disease after secondary cytoreduction.

**DISCUSSION**

To date, there is no standard care for platinum-sensitive recurrent OC. The debate on efficacy of secondary cytoreduction is still open. In China, SCR is widely used in clinical practice of recurrent setting management for decades of years. Most of recurrent patients and their families in China tend to choose surgical treatment. Thus, more than 30% of patients in no-surgery group received secondary debulking surgery after randomization in SOC-1 trial. Among them, nearly 60% were diagnosed with secondary recurrence. The high percentage of treatment switching from control group to surgery could not reflect the efficacy of surgery. Therefore, we designed this SOC-3 trial and hypothesize that patients with secondary recurrence can still benefit from SCR. Assuming some of eligible secondary recurrent participants might be from the no-surgery group (control arm) in the SOC-1 trial, whether patients were enrolled in the SOC-1 trial has been considered as randomization strata (enrolled in SOC-1 or not). This is the first randomized trial, to our knowledge, to answer an important open question about SCR combined with niraparib maintenance in OC patients with platinum-sensitive secondary recurrence.

**REFERENCES**

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

2. Gockley A, Melamed A, Cronin A, Bookman MA, Burger RA, Cristae MC, et al. Outcomes of secondary cytoreductive surgery for patients with platinum-sensitive recurrent ovarian cancer. Am J Obstet Gynecol 2019;221:625.e1-625.e14.

3. Zang RY, Harter P, Chi DS, Sehouli J, Jiang R, Tropé CG, et al. Predictors of survival in patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery based on the pooled analysis of an international collaborative cohort. Br J Cancer 2011;105:890-6.

4. Herzog TJ, Armstrong DK, Brady MF, Coleman RL, Einstein MH, Monk BJ, et al. Ovarian cancer clinical trial endpoints: Society of Gynecologic Oncology white paper. Gynecol Oncol 2014;132:8-17.

5. Coleman RL, Spirtos NM, Enserro D, Herzog TJ, Sabbatini P, Armstrong DK, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. N Engl J Med 2019;381:1929-39.

6. Zang R, Zhu J. Which patients benefit from secondary cytoreductive surgery in recurrent ovarian cancer? J Gynecol Oncol 2019;30:e116.

7. Du Bois A, Vergote I, Ferron G, Reuss A, Meier W, Greggi S, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20. J Clin Oncol 2017;35:abstr5501.

8. Tian WJ, Chi DS, Sehouli J, Tropé CG, Jiang R, Ayhan A, et al. A risk model for secondary cytoreductive surgery in recurrent ovarian cancer: an evidence-based proposal for patient selection. Ann Surg Oncol 2012;19:597-604.
9. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495-505.

10. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154-64.

11. Zhang J, Zheng H, Gao Y, Lou G, Yin R, Ji D, et al. Phase I pharmacokinetic study of niraparib in Chinese patients with epithelial ovarian cancer. Oncologist 2020;25:19-e10.

12. Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 2011;21:419-23.

13. U.S. Department of Health and Human Services. NCI common terminology criteria for adverse events (CTCAE) version 5.0 [Internet]. Washington, D.C.: U.S. Department of Health and Human Services; c2017 [cited cited 2017 Nov 27]. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/.

14. Wenzel L, Huang HQ, Cella D, Walker JL, Armstrong DK; Gynecologic Oncology Group. Validation of FACT/GOG-AD subscale for ovarian cancer-related abdominal discomfort: a Gynecologic Oncology Group study. Gynecol Oncol 2008;110:60-4.

15. Nishio S, Katsumata N, Matsumoto K, Tanabe H, Yonemori K, Kouno T, et al. Usefulness of third-line chemotherapy for women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who receive platinum/taxane regimens as first-line therapy. J Cancer Res Clin Onc 2009;135:551-7.

16. Yoshihama T, Chiyoda T, Katoaka F, Nomura H, Iguchi Y, Hashimoto S, et al. Effectiveness of third-line chemotherapy in recurrent ovarian cancer patients. Eur J Gynaecol Oncol 2015;36:424-7.

17. Shi T, Jiang R, Pu H, Yang H, Tu D, Dai Z, et al. Survival benefits of dose-dense early postoperative intraperitoneal chemotherapy in front-line therapy for advanced ovarian cancer: a randomised controlled study. Br J Cancer 2019;121:425-8.